Respiratory CHAPTER
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Table of contents

- **Section 1**: Overview ............................................ 4
- **Section 2**: Upper Respiratory Tract ............ 93
- **Section 3**: Lower Respiratory Tract ........... 171
- **Section 4**: Miscellaneous ...................... 430

**Appendix** :

1. **Mind Map** .................................................. 502
2. **MedComics** .................................................. 513
3. **First Aid for USMLE STEP 1 2019** ........ 526
4. **First Aid for (ORGAN SYSTEMS)** ............ 555
5. **Q-Bank** ..................................................... 633

- **References** ..................................................
SECTION 1:
OVERVIEW

1. PHYSIOLOGY:
   Functional organization of the respiratory system
32. PHYSIOLOGY:
    Gas transport

5. ANATOMY:
   Muscles involved in respiration
39. PHYSIOLOGY:
    Hypoxia and Cyanosis

10. PHYSIOLOGY:
    Mechanism of breathing
47. PHYSIOLOGY:
    Control of Breathing

18. PHYSIOLOGY:
    Respiratory ventilation

25. PHYSIOLOGY:
    Gas transfer
53. BIOCHEMISTRY:
    Globular proteins
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.

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 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.
- **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.
- **Regulating the acid-base status of the body by washing out extra carbon dioxide from the blood.**
- **Secretion of important substances like surfactant.**
Respiratory passages airways can be divided into:

- **Conductive Zone**
  - Starts from nose to the end of terminal bronchioles.
  - Helps 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.

### 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.

### 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: (4) During forced respiration we use more muscles than normal respiration.
**SECTION I | Functional organization of the respiratory system**

**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.

**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.

**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.
- 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.
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.

### 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.
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)
Respiratory Movements:

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

<table>
<thead>
<tr>
<th>DIAPHRAGM</th>
<th>RIBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiration (in breath)</td>
<td>Expiration (out breath)</td>
</tr>
<tr>
<td>Contraction, descent (down) Of diaphragm</td>
<td>Relaxation, ascent (up)</td>
</tr>
<tr>
<td>Increase of vertical diameter of thoracic cavity</td>
<td>Decrease of vertical diameter of thoracic cavity</td>
</tr>
</tbody>
</table>

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)
3. **Sternal:** Posterior surface of xiphoid process

**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

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

**Openings of diaphragm (apertures)**
- **Caval apertures,** at level of T8
- **Esophageal apertures,** at level of T10
- **Aortic apertures,** at level of T12

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

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

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

### Accessory muscles of Inspiration

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Scalene muscles</th>
<th>Pectoralis major</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Cervical vertebrae</td>
<td>clavicle + sternum + costal cartilages</td>
</tr>
<tr>
<td><strong>Insertion</strong></td>
<td>1st rib (scalenus anterior and Medius) 2nd rib (scalenus posterior)</td>
<td>Bicipital grooveof humerus</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Elevate 1st &amp; 2nd ribs</td>
<td>Increases antero-posterior diameter of thoracic cavity, when arm is fixed</td>
</tr>
</tbody>
</table>

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

#### A- Ribs depressors

<table>
<thead>
<tr>
<th>Muscle</th>
<th>subcostal</th>
<th>Transversus thoracic</th>
<th>Internal intercostal</th>
<th>Innermost intercostal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direction</strong></td>
<td>Backward and Laterally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nerve</strong></td>
<td>Intercostal nerve ventral rami from T1 to T11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Depression of the Ribs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
B- Anterior abdominal wall muscles.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>External oblique</th>
<th>Internal oblique</th>
<th>Rectus abdominis</th>
<th>Transversus abdominis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction</td>
<td>Downward &amp; medially</td>
<td>Upward &amp; medially</td>
<td>Vertical</td>
<td>Transverse</td>
</tr>
<tr>
<td>Nerve</td>
<td>lower 5 intercostal nerves (T7-T11), subcostal nerve (T12) and first lumbar nerve.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>(during forced expiration): Compression of abdominal viscera to help in ascent of diaphragm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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:
  o The septum transversum gives rise to the central tendon of the diaphragm.
  o The pleuroperitoneal membranes give rise to parts of the tendinous portion of the diaphragm.
  o The dorsal mesentery of the esophagus gives rise to the crura of the diaphragm.
  o 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.
Objective 1

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

Mechanism of Breathing | SECTION I

Respiratory muscles:

olian 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.

olian Expiratory muscles:
- **During RestingExpiration**: 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.
**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.

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**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).

---

**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:

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.
### Section 1 | Mechanism of Breathing

#### 3- Transpulmonary pressure (TPp) (Extending Pressure)
- The difference between the alveolar pressure (P_{alv}) and the pleural pressure (P_{ppl}). (TPp = P_{alv} - P_{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)
  
  - P_{alv} = 0 \text{ mmHg}
  - P_{ppl} = -5 \text{ mmHg}
  
  
  TPp = 0 - (-5) = +5 \text{ mmHg}

  During inspiration
  - P_{alv} = -1 \text{ mmHg}
  - P_{ppl} = -7.5 \text{ mmHg}
  
  TPp = -1 - (-7.5) = +6.5 \text{ 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

<table>
<thead>
<tr>
<th>Pressure</th>
<th>During rest</th>
<th>During inspiration</th>
<th>During expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-alveolar pressure</td>
<td>(0 mmHg) 760 mmHg</td>
<td>(-1 mmHg) 759 mmHg</td>
<td>(+1 mmHg) 761 mmHg</td>
</tr>
<tr>
<td>Intrapleural pressure</td>
<td>(-5 mmHg) 755 mmHg</td>
<td>(-7.5 mmHg) 752.5 mmHg</td>
<td>(just for your information) -6.5 mmHg according to Linda</td>
</tr>
<tr>
<td>Transpulmonary pressure TPp</td>
<td>TPp = 0 - (-5) = +5 mmHg</td>
<td>TPp = -1 - (-7.5) = +6.5 mmHg</td>
<td>(just for your information) TPp = +1 -(-6.5) = +7.5 mmHg</td>
</tr>
</tbody>
</table>

---

**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.

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**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.
Compliance of the lung (CL)

- 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. \((CL= \Delta V / \Delta P)\)
- 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.

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)

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.
Diseases that affect compliance of lung:

- **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

- **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)

Note: Fibrosis is not as flexible as elastin, so the compliance will decrease.
Forces Acting on The Lung System

In respiratory physiology, units of pressure are usually given as cm H$_2$O. 1 cm H$_2$O = 0.74 mm Hg (1 mm Hg = 1.36 cm H$_2$O)

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 properties of alveoli.
     o As the lung expands, recoil increases; as the lung gets smaller, recoil decreases.
     o Recoil, as a force, always acts to collapse the lung.
   • Chest wall recoil represents the outward force of the chest wall.
     o FRC represents the point where this outward recoil of the chest wall is counterbalanced 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.
     o The outward recoil of the chest and inward recoil of the lung create a negative (sub atmospheric) IPP.
     o 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.
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, about 500 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 H₂O
  - This decreases IPP back to its original level of -5 cm H₂O, 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.
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.

### 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 = $\Delta V/\Delta P$

**Problem**

- Tidal volume = 0.6 liters
- Intrapleural pressure before inspiration = -5 cm H$_2$O
- Intrapleural pressure after inspiration = -8 cm H$_2$O
- Lung compliance 0.6 liters/3 cm H$_2$O = 0.200 liters/cm H$_2$O
- The preceding calculation simply means that for every 1 cm H$_2$O 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., -5 to -6 cm H$_2$O) or out of the system if surrounding pressure becomes more positive (e.g., -5 to -4 cm H$_2$O).
  - 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.
Respiratory Chapter

SECTION I | Respiratory ventilation

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

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

- 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 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.

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 the 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.

Dead Space: Understanding the Physiology Behind it by 100lyric

“all values are based on an average 70 kg male”
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 = 300 ml.
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 = 1100 ml.
4. **Residual volume (RV):** is the volume of air that still remain in the lungs after the most forceful expiration = 1200 ml. It is not measured by spirometer.

**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.

---

**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.

**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.
Respiratory ventilation

**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

**Example**

\[ C_1 \times V_1 = C_2 \times V_2 \]

- \( C_1 \): concentration of H, in spirometry.
- \( V_1 \): volume of air in the spirometry.
- \( C_2 \): final concentration of helium.
- \( V_2 \): volume of spirometry + FRC.

\[
FRC = \left( \frac{C_1 \times HE (C_1)}{C_2 \times HE (C_2)} \right) - 1 \times V_1 / V_2
\]

**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.
Respiratory Chapter

Respiratory ventilation

<table>
<thead>
<tr>
<th>Restrictive lung diseases</th>
<th>Obstructive lung diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio</td>
<td></td>
</tr>
<tr>
<td>Normal – increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>FEV1</td>
<td>Decreased – normal</td>
</tr>
<tr>
<td>FVC</td>
<td>Decreased a lot</td>
</tr>
<tr>
<td>TLC</td>
<td>Decreased</td>
</tr>
<tr>
<td>RV</td>
<td>Decreased</td>
</tr>
<tr>
<td>Examples</td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
</tbody>
</table>

**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 the restrictive person.

**Restrictive lung diseases**
- Interstitial pulmonary fibrosis

**Obstructive lung diseases**
- Bronchial asthma, emphysema

---

**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 occurs, 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:**
Respiratory 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 $\rightarrow$ 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 $\rightarrow$ (500 – 150) X 12 = 350 X 12 = 4200 ml/min.

- **The differences between the (MRV) & alveolar ventilation:**
  
<table>
<thead>
<tr>
<th>Minute Respiratory Volume</th>
<th>Alveolar Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>New air moves into the respiratory passages</td>
<td>New air into the alveoli and adjacent gas exchange</td>
</tr>
<tr>
<td>MRV= TV X RR</td>
<td>AV= (TV – dead space volume) X RR</td>
</tr>
<tr>
<td>It is equal to the tidal volume times the respiratory rate/min.</td>
<td>It is equal to the respiratory rate times the amount of new air that enters these areas with/breath.</td>
</tr>
</tbody>
</table>

**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 compliance also occurs with aging and with a saline-filled 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 not a 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 relationship between the surface tension and the pressure inside a bubble is given by the Law of Laplace.
   - \( \text{Pressure} \propto \frac{\text{tension}}{\text{radius}} \)

**Figure V-1-11. Surface Tension**
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 lowers lung 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).

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 H2O.
- 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
**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 epithelium 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**

**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 = \( \frac{1}{radius^4} \)
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.

Ventilation

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

Dead Space
Regions of the respiratory system that contain air but are not exchanging \( \text{O}_2 \) and \( \text{CO}_2 \) with blood are considered dead space.

Anatomic Dead Space
Airway regions that, because of inherent structure, are not capable of \( \text{O}_2 \) and \( \text{CO}_2 \) exchange with the blood. Anatomic dead space (anatVd) includes the conducting zone, which ends at the level of the terminal bronchioles. Significant gas exchange (\( \text{O}_2 \) uptake and \( \text{CO}_2 \) 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.
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.

**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 physioIVd 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**

\[ V = VT \]
\[ (f) = 500 \text{ (15)} \]
\[ = 7,500 \text{ mL/minMinute} \]

ventilation (\( V^* \)) is the total volume of air entering the lungs per minute.
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.
- $V_A = (VT - VD) f = (500 \text{ mL} - 150 \text{ mL}) 15 = 5250 \text{ mL/min}$ ($V_A$: 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?

<table>
<thead>
<tr>
<th></th>
<th>Tidal volume</th>
<th>rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person A</td>
<td>600 ML</td>
<td>10/MIN</td>
</tr>
<tr>
<td>Person B</td>
<td>300 ML</td>
<td>20/MIN</td>
</tr>
</tbody>
</table>

Answer: Person A. Person B has rapid, shallow breathing. This person has a large component 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.
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).
- 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.
Ventilation

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 respiratory 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](image)

**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](image)
**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**

- 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.
  - CO₂ 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 0.2 mm. The extremely thin walls of these alveoli form part of the respiratory membrane, whose thickness inversely affects the rate of gas diffusion.

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 = \( \frac{S}{\sqrt{MW}} \) directly proportional.
   - Inversely proportional to The thickness of the respiratory membrane.
   So \( \rightarrow \) 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(\(\Delta P\)):
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\(_2\)
     \( \rightarrow \) 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\(_2\)
     \( \rightarrow \) net diffusion from the blood into the alveoli occurs.
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.

---

### Partial pressure of gases (in a mixture)

#### Composition of respiratory air:

<table>
<thead>
<tr>
<th>Component</th>
<th>Inhaled air</th>
<th>Exhaled air</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>Oxygen</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>Trace</td>
<td>4%</td>
</tr>
</tbody>
</table>
Partial pressure of gases (in a mixture):
- In respiratory physiology, there is a mixture of gases mainly of O₂, N₂, and CO₂.
- 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.

The partial pressure of gases in a mixture 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 pressure of 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 + . . .

Henry's Law:
Gas solubility is proportional to the gas partial pressure. If the temperature stays constant increasing the pressure will increase the amount of dissolved gas. Gases diffuse from high pressure to low pressure.

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

<table>
<thead>
<tr>
<th></th>
<th>Atmospheric Air* (mm Hg)</th>
<th>Humidified Air in Dead Space (mm Hg)</th>
<th>Alveolar Air (mm Hg)</th>
<th>Expired Air (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂</td>
<td>597.0</td>
<td>563.4</td>
<td>593.0</td>
<td>566.0</td>
</tr>
<tr>
<td>O₂</td>
<td>155.0 (20.84%)</td>
<td>149.3 (19.61%)</td>
<td>104.0</td>
<td>120.0</td>
</tr>
<tr>
<td>CO₂</td>
<td>0.3 (0.04%)</td>
<td>0.3</td>
<td>40.0</td>
<td>27.0</td>
</tr>
<tr>
<td>H₂O</td>
<td>3.7 (0.50%)</td>
<td>4.7</td>
<td>47.0</td>
<td>47.0</td>
</tr>
</tbody>
</table>

- **Oxygen** concentration in the atmosphere is 21%
  - So partial O₂ pressure (PO₂) in atmosphere = 760 mmHg (1 ATM) x 21% = 160 mmHg.
  - This mixes with old air already present in alveolus to arrive at PO₂ of 104 mmHg in alveoli.

- **Carbon dioxide** concentration in the atmosphere is 0.04%
  - So PCO₂ in atmosphere = 760 mmHg x 0.04% = 0.3 mmHg
  - This mixes with high CO₂ levels from residual volume in the alveoli to arrive at PCO₂ of 40 mmHg in the alveoli.

**Explanation of 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.
Gas exchange and gas transfer

**PO2 and PCO2 in air, lungs and tissue:**

**PO2 and PCO2 in air, lungs and tissue:**

Cells use oxygen in metabolic activities all the time, which means that the PO₂ 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 O₂ into the interstitial fluid. This deoxygenated blood circulates back into the heart and into the lungs, where the PO₂ of alveolar air causes O₂ to diffuse into the pulmonary capillaries.

The same mechanism happens with CO₂ but in the opposite direction, because cells produce CO₂ instead of consuming it like it does with O₂.

---

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

---

*The PO₂ will enter the alveoli = 104(Alv.Z) + 149(Con.Z) = 253 mmHg*
**SECTION 1 | Gas exchange and gas transfer**

- **To summaries:**

<table>
<thead>
<tr>
<th></th>
<th>PO2</th>
<th>PCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveoli</td>
<td>104 mmHg</td>
<td>40 mmHg</td>
</tr>
<tr>
<td>Pulmonary capillaries</td>
<td>40 mmHg</td>
<td>45 mmHg</td>
</tr>
<tr>
<td>Tissue capillaries</td>
<td>95 mmHg</td>
<td>40 mmHg</td>
</tr>
<tr>
<td>Interstitial fluid</td>
<td>40 mmHg</td>
<td>45 mmHg</td>
</tr>
<tr>
<td>Calls</td>
<td>23 mmHg</td>
<td>46 mmHg</td>
</tr>
</tbody>
</table>

**Gas concentrations in the alveoli:**

- **Oxygen**
  
<table>
<thead>
<tr>
<th>At resting condition</th>
<th>During exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator rate</td>
<td>4.2 L/min</td>
</tr>
<tr>
<td>Volume enter the pulmonary capillaries</td>
<td>250 ml/min</td>
</tr>
<tr>
<td></td>
<td>1000 ml/min (x4 normal volume)</td>
</tr>
</tbody>
</table>

**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.

**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.

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

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

The normal lung

Partial Pressure of a Gas in Ambient Air

- \( P_{\text{gas}} = F_{\text{gas}} \times P_{\text{atm}} \) (\( P_{\text{atm}} \): atmospheric pressure, \( F_{\text{gas}} \): 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: \( P_{O2} = 0.21 \times 760 = 160 \) 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 H2O (\( P_{H2O} \)) is dependent only on temperature and at 37°C is 47 mm Hg. Humidifying the air reduces the partial pressure of the other gases present.
- For example, the PO2 of inspired air is: \( P_{O2} = 0.21 \times (760 - 47) = 150 \) mm Hg

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.

Factors Affecting Alveolar PCO2

- Only 2 factors affect alveolar PCO2: metabolic rate and alveolar ventilation.
- \( \text{PACO2} \sim \text{metabolic CO2 production/alveolar ventilation} \)
- At rest, unless there is fever or hypothermia, CO2 production is relatively constant; so you can use changes of PACO2 to evaluate alveolar ventilation.
Gas Exchange and Gas Transfer

Alveolar Ventilation
There is an inverse relationship between PACO\textsubscript{2} and alveolar ventilation. This is the main factor affecting alveolar PCO\textsubscript{2}. Therefore, if ventilation increases, PACO\textsubscript{2} decreases; if ventilation decreases, PACO\textsubscript{2} increases.

- **Hyperventilation**
  During hyperventilation, there is an inappropriately elevated level of alveolar ventilation, and PACO\textsubscript{2} is depressed.
  If V•A is doubled, then PACO\textsubscript{2} is decreased by half.
  For example, PACO\textsubscript{2} = 40 mm Hg
  \[ 2 \times V\cdot A; \text{PACO}_2 = 20 \text{ mm Hg} \]

- **Hypoventilation**
  During hypoventilation, there is an inappropriately depressed level of alveolar ventilation, and PACO\textsubscript{2} is elevated.
  If V•A is halved, then PACO\textsubscript{2} is doubled.
  For example, PACO\textsubscript{2} = 40 mm Hg
  \[ \frac{1}{2} V\cdot A; \text{PACO}_2 = 80 \text{ mm Hg} \]

- **Metabolic Rate**
  There is a direct relationship between alveolar PCO\textsubscript{2} and body metabolism. For PaCO\textsubscript{2} to remain constant, changes in body metabolism must be matched with equivalent changes in alveolar ventilation.
  - If V•A matches metabolism, then PACO\textsubscript{2} remains constant.
  - For example, during exercise, if body metabolism doubles, then V•A must double if PaCO\textsubscript{2} is to remain constant.
  - If body temperature decreases and there is no change in ventilation, PaCO\textsubscript{2} decreases, and the individual can be considered to be hyperventilating.

Factors Affecting Alveolar PO\textsubscript{2}
The alveolar air equation includes all the factors that can affect alveolar PO\textsubscript{2}.

\[ PAO_2 = (patm - 47) \times \text{FiO}_2 - \text{PACO}_2 / \text{RQ} \]

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\textsubscript{2}:
1. **Patm** = atmospheric pressure, at sea level 760 mm Hg
   An increase in atmospheric pressure (hyperbaric chamber) increases alveolar PO\textsubscript{2}, and a decrease (high altitude) decreases alveolar PO\textsubscript{2}.
2. **FiO\textsubscript{2}** = fractional concentration of oxygen, room air 0.21
   An increase in inspired oxygen concentration increases alveolar PO\textsubscript{2}.
3. **PaCO\textsubscript{2}** = alveolar pressure of carbon dioxide, normally 40 mm Hg
   An increase in alveolar PCO\textsubscript{2} decreases alveolar PO\textsubscript{2}, and a decrease in alveolar PCO\textsubscript{2} increases alveolar PO\textsubscript{2}. For most purposes, you can use arterial carbon dioxide (PaCO\textsubscript{2}) in the calculation.
4. The fourth variable is RQ.
   \[ \text{RQ} \text{ respiratory exchange ratio} = \frac{\text{CO}_2 \text{ produced ml/min}}{\text{O}_2 \text{ consumed ml/min}} = \text{normally 0.8} \]

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

\[ PAO_2 = (760 - 47) \times 0.21 - 40/0.8 = 100 \text{ mm Hg} \]
Gas Exchange and Gas Transfer

**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)**
  
  \[\text{PaO}_2 = \text{PiO}_2 - \text{PaCO}_2\] (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.)

\[V \cdot \text{gas} = \frac{A}{T} \times D \times (P_1 - P_2)\] (\(V \cdot \text{gas}\) = rate of gas diffusion)

**Structural Features That Affect the Rate of Diffusion**

There are 2 structural factors and 2 gas factors that 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 surface 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 oxygen 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 of \(CO_2\) 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 O2 is: $100 - 40 = 60 \text{ mm Hg}$

- An increase in the PO2 gradient across the lung membranes helps compensate for a structural problem. If supplemental O2 is administered, alveolar PO2 increases, because of the elevated gradient. However, supplemental O2 does not improve the ability of the lungs to remove CO2 from blood. This increased gradient helps re-turn the rate of O2 diffusion toward normal. The greater the structural problem, the greater the gradient necessary for a normal rate of O2 diffusion.

- The gradient for CO2 is $47 - 40 = 7 \text{ mm Hg}$.

- Even though the gradient for CO2 is less than for O2, CO2 still diffuses faster because of its greater solubility.

Recall Question: Which of the following factors increases alveolar PCO2, assuming no compensation?
A. Decrease in atmospheric pressure ($\text{Patm}$)
B. Increase in fractional concentration of oxygen ($\text{FiO}_2$)
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 substances between the interstitium and the capillary:

1. If the substance equilibrates between the capillary and interstitium, it is 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 dissolved 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 simply $P1$ (alveolar partial pressure), since $P2$ is considered to be zero.
- Understand the forms of oxygen transport in the blood, and the importance of each.
- Differentiate between O2 capacity, O2 content and O2 saturation.
- Describe the oxygen-hemoglobin dissociation curve.
- Define the P50 and its significance.
- How DPG, temperature, H+ ions and PCO2 affect affinity of O2 for hemoglobin and the physiological importance of these effects.
- 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**

<table>
<thead>
<tr>
<th>Oxyhemoglobin</th>
<th>Deoxyhemoglobin</th>
<th>Methemoglobin</th>
<th>Carboxyhemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal heme contains iron in the reduced form (Fe2+). Fe2+ shares electrons and bonds with oxygen.</td>
<td>When oxyhemoglobin dissociates to release oxygen, the heme iron is still in the reduced form.</td>
<td>Has iron in the oxidized form (Fe3+). Lacks electrons and cannot bind with O2. Blood normally contains a small amount.</td>
<td>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.</td>
</tr>
</tbody>
</table>
Transport of O₂

- 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.

- 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

  \[ \text{Hb} + 4\text{O}_2 \rightarrow \text{Hb(O}_2\text{)}_4 \]

Transport of O₂ 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.
  \[ \text{Hb} + \text{O}_2 \rightarrow \text{HbO}_2 \]

- 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 O₂ (Po₂) in Alveoli
2. Low Po₂ in Capillary

- Transport O₂:
  - Diffusion Difference- Very Short \(\rightarrow\) O₂ Diffusion- Very Rapid \(\rightarrow\) O₂ Diffuses from Alveoli into RBC \(\rightarrow\) (Attaches to Heme Molecule) \(\rightarrow\) Carried To Tissues
  - Concentration Gradient
    - High Concentration of O₂ in Alveoli
    - Low Concentration of O₂ in Capillary O₂
Transport of oxygen in arterial blood:

<table>
<thead>
<tr>
<th>Notes</th>
<th>Calculations</th>
<th>In venous blood</th>
<th>During strenuous exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of oxygen released from the hemoglobin to the tissues is 5ml O2 per each 100ml blood.</td>
<td>O2 content in 97% saturation — oxygen released to tissue during strenuous exercise = O2 content in 97% saturation — oxygen released to tissue (5ml x 3 folds = 15 ml O2 is given /100 ml blood)</td>
<td>19.4 ml.</td>
<td>4.4 ml.</td>
</tr>
</tbody>
</table>

O2 capacity, content and saturation:

<table>
<thead>
<tr>
<th>O2 content</th>
<th>O2-binding capacity</th>
<th>Percent saturation</th>
<th>Dissolved O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of O2 in blood (ml O2/100 ml blood)</td>
<td>Maximum amount of O2 bound to hemoglobin (ml O2/100 ml blood) measured at 100% saturation</td>
<td>100 % of heme groups bound to O2</td>
<td>Unbound O2 in blood (ml O2/100 ml blood)</td>
</tr>
</tbody>
</table>

Transport of oxygen in the dissolved state:

1. At normal arterial PO2= 95 mmHg.
   - 95 x 0.003 (The solubility of O2 in blood is 0.003 mL O2/100 mL/mm Hg (SOLUBILITY factor)).
   o 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.
   o 0.12 of oxygen remains dissolved.
   ➔ Calculation: from henry’s law

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

\[
\text{Concentration of dissolved gas} = \text{partial pressure} \times \text{solubility factor}
\]

o 0.17 ml of oxygen is normally transported in the dissolved state to the tissues per each 100 ml of blood.
Oxygen and carbon dioxide transport

**CO₂ transport**
- Large amount of CO₂ is continuously produced in the body.
- In the resting state, 4 ml CO₂ is 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 CO₂ 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 H₂O 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 form HHb) and bicarbonate ions.
4. Bicarbonate ions go 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 CO₂ and H₂O within the RBC.

**Transport of CO₂ 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 CO₂
\[ \text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3 \quad \text{H}^+ + \text{HCO}_3^- \]
- At the tissues, CO₂ diffuses into the RBC; shifts the reaction to the right.
- Increased [HCO₃⁻] produced in RBC → HCO₃⁻ diffuses into the blood.
- RBC becomes more + → Cl⁻ attracted in (Cl⁻ shift).
- H⁺ released buffered by combining with deoxyhemoglobin.
- HbCO₂ formed → Unloading of O₂.

At pulmonary capillaries
\[ \text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3 \quad \text{H}^+ + \text{HCO}_3^- \]
- At the alveoli, CO₂ diffuses into the alveoli; reaction shifts to the left.
- Decreased [HCO₃⁻] in RBC → HCO₃⁻ diffuses into the RBC.
- RBC becomes more - → Cl⁻ diffuses out (reverse Cl⁻ shift).
- Deoxyhemoglobin converted to oxyhemoglobin
- Has weak affinity for H⁺ → Gives off HbCO₂.

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 PO₂ in the blood (X-axis).
- PO₂ = 95mmhg due to 97% saturation → in arterial blood
- PO₂ = 40mmhg due to 75% saturation → in venous blood
Factors affecting oxygen-haemoglobin dissociation curve:

<table>
<thead>
<tr>
<th>Right shift</th>
<th>Left shift</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meaning</strong></td>
<td>the oxygen is unloaded to the tissues from Hb</td>
</tr>
<tr>
<td><strong>pH</strong> (H⁺ conc)</td>
<td>↓ pH (↑(H⁺ conc))</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>↑</td>
</tr>
<tr>
<td><strong>(2,3-DPG)</strong></td>
<td>↑ (Bohr effect)</td>
</tr>
<tr>
<td><strong>PCO₂</strong></td>
<td>↑</td>
</tr>
<tr>
<td><strong>P50</strong></td>
<td>↑ (lower affinity for O₂)</td>
</tr>
</tbody>
</table>

Fetal haemoglobin

---

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.

---

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 2α+2β. Unlike in children, it consists of 2α + 2α. 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
Bohr effect

At lung:
- Movement of CO₂ from blood to alveoli.
- Decrease blood CO₂ & H⁺.
- Increase O₂ affinity of Hb.
- More O₂ transport to tissue.

At tissue:
- Movement of CO₂ from tissues to blood.
- Increase CO₂ & H⁺ in blood.
- Decrease O₂ affinity of Hb.
- More O₂ 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 O₂ (affinity of Hb to CO is very high that to O₂).
  ➔ It causes Left shift of the O₂-Hb curve.

Utilization Coefficient

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

Utilization Coefficient = \( \frac{O₂ \text{ delivered to the tissues}}{O₂ \text{ content of arterial blood}} \)

- 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.
  
  \[ V^{\text{gas}} = \frac{A}{T} \times D \times (P_1 - P_2) \]
  
  \[ V^{\text{CO}} = \frac{A}{T} \times D \times PaCO \]

- 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 oxygen 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](image)
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.

<table>
<thead>
<tr>
<th>Site 4 - O₂</th>
<th>Systemic arterial blood = 97% saturated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attached when the minimal PO₂ ≈ 100 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site 3 - O₂</th>
<th>Systemic venous blood = 75% saturated (resting state)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attached when the minimal PO₂ ≈ 40 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site 2 - O₂</th>
<th>P50 for arterial blood. P50 is the PO₂ required for 50% saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attached when the minimal PO₂ ≈ 26 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site 1 - O₂ usually remains attached under physiologic conditions.</th>
<th>Under physiologic conditions, only sites 2,3, and 4 need to be considered.</th>
</tr>
</thead>
</table>

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

Hemoglobin O₂ 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 O₂.
- If the [Hb] is 15 g/100 mL (15 g%), then the maximal amount of O₂ 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, PO₂ 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 PaO₂ 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 PaO₂ but has little effect on total oxygen content. For example:

<table>
<thead>
<tr>
<th>Dissolved O₂</th>
<th>HbO₂</th>
<th>Total O₂ Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>If PaO₂ = 100 mm Hg</td>
<td>0.3</td>
<td>≈ 19.4</td>
</tr>
<tr>
<td>If PaO₂ = 130 mm Hg (hyperventilation)</td>
<td>0.4</td>
<td>≈ 19.4</td>
</tr>
</tbody>
</table>

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)

- The opposite chemical changes shift the curve to the left.

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.
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.

![Graph showing effects of Hb concentration changes](image)

Carbon Monoxide
Carbon monoxide (CO) has a greater affinity for Hb than does oxygen (240x greater). The figure below shows that with CO, the O2-Hb dissociation curve is shifted to the left (CO increases the affinity of Hb for O2) and HbO2 content is reduced.

![Graph showing effects of carbon monoxide](image)
Oxygen and Carbon Dioxide Transport

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

- **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 PO₂ 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 PCO₂ of only 40–47 mm Hg, about 5% of the total CO₂ is carried in the dissolved form.

**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 CO₂ is carried as carbamino compounds. The attachment sites that bind CO₂ are different from the sites that bind O₂.

**Bicarbonate**

About 90% of the CO₂ is carried as plasma bicarbonate. In order to convert CO₂ into bicarbonate or the reverse, carbonic anhydrase (CA) must be present.

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-
\]

The steps in the conversion of CO₂ into bicarbonate in a systemic capillary are seen below.
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%).

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 H$_2$O. 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. \( P = \text{height} \times \text{gravity} \times \text{density} \)
- Thus, IPP is higher (less negative) at the base (bottom) of the lung compared to the apex (top).
Oxygen and Carbon Dioxide Transport

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 O₂ and CO₂ in alveoli are determined by the combination of ventilation (adding O₂, removing CO₂) and perfusion (removing O₂ and adding CO₂). 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 PO₂ falls, PCO₂ rises, and blood pH falls (remember that CO₂ generates H⁺).
  - Thus, PaO₂ at the base is <100 mm Hg and PaCO₂ is >40 mm Hg.
Oxygen and Carbon Dioxide Transport

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, PCO₂ falls, 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 PO₂, and high PCO₂; 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 PaO₂ and PaCO₂ = 0; X-axis intercept in figure below).

To summarize:
• As V•A/Q falls, PO₂ falls and PCO₂ rises. The extreme is a shunt.
  o 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, PO₂ rises and PCO₂ 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.
Oxygen and Carbon Dioxide Transport

Problem
The following ratios represent lung units under resting conditions:

\[ V_A/Q \]

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:

- \( \text{PACO}_2 \), end capillary \( \text{PCO}_2 \)? (Answer: A)
- \( \text{PAO}_2 \), end capillary \( \text{PO}_2 \)? (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 \( \text{PO}_2 \), 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?

- \( \text{PACO}_2 \) (increase)
- \( \text{PAO}_2 \) (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?

- \( \text{PACO}_2 \) (decrease)
- \( \text{PAO}_2 \) (increase)
- Pulmonary end capillary pH (increase)

All answers here are based on the fact that the thrombus increases the \( V_A/Q \) ratio. This produces lung units that act as dead space.
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
• $P_{O_2} = 100$ mm Hg and $P_{CO_2} = 40$ 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 $P_{O_2} = 95$ mm Hg and $P_{CO_2} = 40$ 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: $(age + 4)/4$

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.
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 PCO$_2$ are reduced.

2. Diffusion Impairment
• Diffusion impairment means a structural problem in the lung. As described earlier in this book, this can be produced by a decreased surface area and/or increased thickness of lung membranes.
• 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 normal by supplemental oxygen, there is still an abnormally large A–a gradient.
• In summary:
  o There is an increase in A–a oxygen gradient.
  o Supplemental oxygen can relieve the hypoxemia.
  o End-tidal air does not reflect the arterial values.
  o It is characterized by a decrease in DLCO.

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-Barré, Lambert-Eaton, and myasthenia gravis.
• Diffusional problems of the lung result in pulmonary diseases, such as 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.
Oxygen and Carbon Dioxide Transport

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 alveolar, resulting in an elevated \( A-a \) 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 administration 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:
  o Increase in \( A-a \) oxygen gradient
  o Supplemental oxygen ineffective at returning arterial \( PO_2 \) to normal
  o 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 \( PO_2 \) values in the left below. Note from the descriptions that follow where the first increase in \( PO_2 \) 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.
Oxygen and Carbon Dioxide Transport

Table V-4.1. Consequences of 3 Left-to-Right Shunts

<table>
<thead>
<tr>
<th></th>
<th>Atrial Septal Defect</th>
<th>Ventricular Septal Defect</th>
<th>Patent Ductus (newborn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial PO2</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Right atrial PO2</td>
<td>↑</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Right atrial PO2</td>
<td>↑</td>
<td>↑</td>
<td>No change</td>
</tr>
<tr>
<td>Pulmonary arterial PO2</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pulmonary arterial PO2</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

- 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.
Objective

- Define hypoxia and list its various physiological and pathological causes
- Define hypo and hyper-ventilation in terms of arterial PCO2 and PO2.
- Define cyanosis and its clinical presentation
- Define ventilation/perfusion (V/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 than perfused and the base is more perfused than ventilated due to gravity force.
- During exercise the V/Q ratio becomes more homogenous among different parts of the lung.

<table>
<thead>
<tr>
<th>Increased V/Q Ratio</th>
<th>Decreased V/Q Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Increased PO2</td>
<td>Decreased PO2</td>
</tr>
<tr>
<td>Decreased PCO2</td>
<td>Increased PCO2</td>
</tr>
<tr>
<td>PCO2 &lt; 40</td>
<td>PCO2 &gt; 40</td>
</tr>
</tbody>
</table>
### Regional Blood Flow and Distribution

<table>
<thead>
<tr>
<th>Zone 1: Apex</th>
<th>Zone 2</th>
<th>Zone 3: Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation is higher than Perfusion. There is more Alveolar Oxygen. Because Alveolar pressure is higher than arterial pressure so it compresses the vessels.</td>
<td>Ventilation and Perfusion are similar</td>
<td>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</td>
</tr>
</tbody>
</table>

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**.
SECTION I | Hypoxia and cyanosis

**Causes of V/Q Mismatching**

- **Causes of non uniform ventilation**:
  - Uneven resistance to airflow
  - Collapsed airways (Emphysema)
  - Bronchoconstriction (Asthma)
  - Inflammation (Bronchitis)

- **Non-uniform compliance throughout the lung**:
  - Fibrosis
  - Pulmonary vascular congestion
  - Atelectasis

**Dead space:**

No gas exchange is possible in dead space, because there is no blood flow to receive O₂ from alveolar gas or add CO₂ 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 PO₂ and a low PCO₂.

**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 O₂ to the blood or carry away CO₂ 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 PO₂ and high PCO₂.
Hypoxia and cyanosis

SECTION I

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
- 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 Fe2+ state), it is called methemoglobin. Methemoglobin does not bind to O2.
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 O2.)
This is useful in hypoxic hypoxia, but of less value in other types of hypoxia. Histotoxic hypoxia will not benefit from O2 therapy.
Hypoxia and cyanosis

**Hypercapnia:**

Excess of CO₂ in body fluids, it *usually occurs with hypoxia*. PCO₂ increases above 52 mmHg, it decreases the PH
→ recall from the 1st lecture: CO₂ 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
Respiratory Chapter

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.

SECTION 1 | Hypoxia and cyanosis

Central cyanosis:
Generalized impairment of circulation. Can occur in hypoxic hypoxia.
- Cyanotic congenital heart-disease
- Fallot tetralogy
- 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**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanism</th>
<th>( \text{Pa}_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Cardiac output</td>
<td>↓ Blood flow</td>
<td>—</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>↓ ( \text{Pa}_2 )</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>↓ ( O_2 ) saturation of hemoglobin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ ( O_2 ) content of blood</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>↓ Hemoglobin concentration</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>↓ ( O_2 ) content of blood</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td>↓ ( O_2 ) content of blood</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Left shift of ( O_2 )-hemoglobin curve</td>
<td></td>
</tr>
<tr>
<td>Cyanide poisoning</td>
<td>↓ ( O_2 ) utilization by tissues</td>
<td>—</td>
</tr>
</tbody>
</table>
Control of breathing

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:

1. Control Of Respiration (regulation of breathing) by Armando Hasudungan
2. The respiratory center | Respiratory system physiology | NCLEX-RN | Khan Academy by khanacademymedicine
3. Central chemoreceptors | Respiratory system physiology | NCLEX-RN | Khan Academy by khanacademymedicine
4. Peripheral chemoreceptors | Respiratory system physiology | NCLEX-RN | Khan Academy by khanacademymedicine
5. Control of Ventilation by CalitZube

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 CO2 20 time more soluble than O2.

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.
**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 cross the BBB and but $H^+$ cannot.

**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 $PO_2$.

**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.
Control of breathing

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 PCO₂ **increases**, so does the PCO₂ of both the interstitial fluid of the medulla and the CSF. (CO₂ passes this barrier very easily) In these fluids, the CO₂ 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 CO₂ concentration increases than when the blood H+ ion increases. For this reason, respiratory center activity is increased very strongly by changes in blood CO₂, a fact that we subsequently discuss quantitatively.

o Comparing between ↑CO₂ and ↑ hydrogen, who’s affecting more?

**The CO₂**

o 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.

o A change in blood CO₂ concentration has a potent acute effect on controlling respiratory drive but only a weak chronic effect after a few days’ adaptation.³

o Excitation of the respiratory center by CO₂ is great after the blood CO₂ 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 CO₂ first increase.
2. The kidneys increasing the blood HCO₃⁻, which binds with H+ ions in the blood and CSF to reduce their concentrations.
3. The HCO₃⁻ 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.
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.

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.

<table>
<thead>
<tr>
<th>Respiratory Acidosis</th>
<th>Respiratory Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoventilation</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Accumulation of CO₂ in the tissues.</td>
<td>Excessive loss of CO₂.</td>
</tr>
<tr>
<td>$\uparrow$ PCO₂</td>
<td>$\downarrow$ PCO₂ (35 mmHg).</td>
</tr>
<tr>
<td>$\downarrow$ pH (Normal= 7.3)</td>
<td>$\uparrow$ pH</td>
</tr>
</tbody>
</table>

**Metabolic Acidosis**

- Ingestion, infusion or Production of a fixed acid.
- $\downarrow$ renal excretion of hydrogen ion.
- Loss of HCO₃ or other bases from the EC compartment.

**Metabolic Alkalosis**

- Ingestion, infusion or excessive renal reabsorption of bases such as HCO₃.
- $\uparrow$ pH

**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 CO₂. The stimulatory effect of increased CO₂ may be due to the local production of H⁺ from CO₂.
- Because the blood–brain barrier is freely permeable to CO₂, the activity of these receptors changes with increased or decreased systemic arterial PCO₂.
- H⁺ does not easily penetrate the blood-brain barrier. Thus, an acute rise in arterial H⁺, not of CO₂ 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 CO₂ (H⁺) on the central chemoreceptors. The relationship between the central chemoreceptors and systemic arterial blood can be seen below.

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 CO₂, mainly via the central chemoreceptors but with a small contribution via the peripheral chemoreceptors.

2. **PO₂ receptors**
   - The factor monitored by these receptors is PO₂, not oxygen content.
   - Because they respond to PO₂, they are actually monitoring dissolved oxygen and not oxygen on Hb.
   - When systemic arterial PO₂ is close to normal (≅100 mm Hg) or above normal, there is little any stimulation of these receptors.
Control of breathing

- They are strongly stimulated only by a dramatic decrease in systemic arterial PO2.
- Sensitivity to hypoxia increases with CO2 retention.
- These receptors do not adapt.

Bridge to Pathology/Pharmacology
The normal CO2 drive to breathe is suppressed in COPD patients, and by narcotics and general anesthetics.

Clinical Correlate
Although oxygen content is reduced in anemia, the PaO2 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.

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 between 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.
Globular proteins

**Objective 1**
- Describe the globular proteins using common examples → Hemoglobin & myoglobin.

**Objective 2**
- Study the structure and functions of globular proteins:
  - Hemoglobin (a major globular protein)
  - Myoglobin
  - γ-globulins (immunoglobulins)

**Objective 3**
- Know the different types of hemoglobin and difference between normal and abnormal hemoglobin.

**Objective 4**
- Understand the diseases associated with globular proteins.

**Types of proteins**

- **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)**

**Type of Globular proteins**

<table>
<thead>
<tr>
<th>Types</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>( O_2 ) transport</td>
</tr>
<tr>
<td></td>
<td>All over the body</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>( O_2 ) storage/supply</td>
</tr>
<tr>
<td></td>
<td>only in heart and muscle</td>
</tr>
<tr>
<td>( a_1, a_2, \beta )-globulins</td>
<td>various functions</td>
</tr>
<tr>
<td>( \gamma )-globulins</td>
<td>immune function</td>
</tr>
<tr>
<td>(immunoglobulins)</td>
<td>catalysis of biochemical reactions</td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
</tr>
</tbody>
</table>

**Hemoglobin**

- **Functions:**
  1. Carries \( O_2 \) from lungs to tissues.
  2. Carries \( CO_2 \) from tissues to lungs.

- **Normal level (g/dL):**

- **Abnormal Form of hemoglobin:**
  - Carboxy Hb (bound to CO)
  - Met Hb
  - Sulfur 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
- $4 \times 2 = 8$ Oxygen atoms

**Types of Hemoglobin**

<table>
<thead>
<tr>
<th>(HbF)</th>
<th>HbA₂</th>
<th>HbA₁C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetal Hemoglobin</strong></td>
<td>Major hemoglobin found in the fetus and newborn.</td>
<td>Appears shortly before birth (~8th month)</td>
</tr>
<tr>
<td><strong>Importance</strong></td>
<td>Transfers O₂ from maternal to fetal circulation across placenta.</td>
<td>Constitutes ~2% of total Hb.</td>
</tr>
<tr>
<td></td>
<td>* Due to: Higher affinity for O₂ than HbA</td>
<td></td>
</tr>
</tbody>
</table>
| **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)

- **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.

- **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.

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:
  - NADH-cytochrome b5 reductase deficiency
  - Certain drugs
  - Reactive oxygen species
Globular proteins

**Myoglobin**

A globular hemeprotein in heart and skeletal muscle

**Structure:**
Contains a single polypeptide chain forming a single subunit with eight α-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 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

**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
- IgG
- IgA
- IgE
- IgD

**In summary:**
SECTION 1 | Globular proteins

Take home message

- 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

**Histology:**
The upper respiratory tract.

**ANATOMY:**
Nose, nasal cavity, paranasal sinuses and pharynx

**Microbiology:**
Viruses Causing Respiratory Infections I

**Microbiology:**
Bacteria causing upper respiratory tract infection

**Microbiology:**
Viruses Causing Respiratory Infections II

**Pharmacology:**
Rhinitis and cough
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:

- Upper
  - Nasal cavity
  - Paranasal sinuses
  - Larynx
  - Trachea
  - Bronchi
  - Bronchioles
  - Lung

- Lower
  - Nasal cavity
  - Nasopharynx
  - Larynx
  - Trachea
  - Primary bronchi
    - (extrapulmonary bronchi)
  - Intrapulmonary bronchi
  - Primary bronchioles
    - (preterminal bronchi)
  - Terminal bronchioles
  - Respiratory bronchioles
  - Alveolar ducts
  - Alveolar sacs
  - Pulmonary alveoli
**Nasal cavity**

- 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

**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.
- 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.
Histology of the upper respiratory tract

**olfactory region (area) of nasal cavity:**

- **olfactory mucosa:**
  - **site:**
    1. roof of nasal cavity.
    2. upper part of nasal septum.
    3. over superior concha.

- **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

---

**Clinical Correlate:**

Sinusitis is an inflammation or 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.

**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- Hyaline cartilages: e.g. Thyroid cartilage.
    - 2- Elastic cartilages: e.g. Epiglottis.

  - Extrinsic and intrinsic muscles: all are skeletal.

  - Ligaments.
SECTION 2 | Anatomy of nasal cavity, paranasal sinuses and pharynx

Objective

- Describe the boundaries of the nasal cavity.
- Describe the nasal conchae and meati.
- Demonstrate the openings in each meatus.
- Describe the paranasal sinuses and their functions.
- Describe the pharynx and its parts.

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 sphenopalatine 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:

<table>
<thead>
<tr>
<th>Drainage in Nasal Cavity</th>
<th>Sinuses and Duct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphenoid recess</td>
<td>Sphenoidal sinus</td>
</tr>
<tr>
<td>Superior meatus</td>
<td>Posterior ethmoidal sinus</td>
</tr>
<tr>
<td>Middle meatus</td>
<td>The Maxillary sinuses</td>
</tr>
<tr>
<td></td>
<td>The Frontal sinuses</td>
</tr>
<tr>
<td></td>
<td>The anterior ethmoidal sinuses</td>
</tr>
<tr>
<td></td>
<td>The middle ethmoidal sinuses</td>
</tr>
<tr>
<td>Inferior meatus</td>
<td>Nasolacrimal duct</td>
</tr>
</tbody>
</table>

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.
SECTION 2 | Anatomy of nasal cavity, paranasal sinuses and pharynx

**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 (Adenoids) 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 text 1
- 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.
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.**

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

**Differentiate Rhinitis and Nasal polyp.**

<table>
<thead>
<tr>
<th></th>
<th>Rhinitis</th>
<th>Nasal polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Rhinovirus no 1 cause</td>
<td>• Secondary to repeated rhinitis (HY)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CF (if you see child with nasal polyp, suspect CF) - HY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Asprin intolerant asthma (HY)</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Runny nose, sneezing, congestion</td>
<td>Protrusion of edematous, inflamed nasal mucosa</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Laryngeal papilloma</th>
<th>Laryngeal carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Benign papillary tumor of vocal cord</td>
<td>SCC of epithelial lining of vocal cord</td>
</tr>
<tr>
<td>Cause</td>
<td>HPV 6 and 11; EtOH and smoking (papilloma rarely progress to carcinoma)</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>• Hoarseness of voice&lt;br&gt;• Usually single in adults and multiple in children (HY)</td>
<td>• Hoarseness of voice&lt;br&gt;• Cough and stridor</td>
</tr>
</tbody>
</table>

Laryngeal papilloma

Laryngeal carcinoma
Nasopharynx, Larynx

Differentiate acute epiglottitis and laryngotracheobronchitis (croup).

<table>
<thead>
<tr>
<th></th>
<th>Acute epiglottitis</th>
<th>Laryngotracheobronchitis (croup)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>H. Influenzae type b most common cause (in immunized or non-immunized kids.)</td>
<td>Parainfluenza virus most common cause</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Too much drooling, dysphagia, sore throat, fever, muffled voice, inspiratory stridor</td>
<td>Barking cough and inspiratory stridor</td>
</tr>
<tr>
<td><strong>Risk of acute airway obstruction</strong></td>
<td>(medical emergency)</td>
<td></td>
</tr>
<tr>
<td><strong>X-ray</strong></td>
<td>Thumb sign on X-ray</td>
<td>Steeple sign on X-ray</td>
</tr>
</tbody>
</table>

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

![vocal cord nodule](image)

Fig: vocal cord nodule (usually bilateral and seen on true vocal cord)
**SECTION 2 | Bacterial Upper Respiratory Tract Infections**

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

**Objective**

**Introduction**

**Upper respiratory tract infection (URTI)**

- **Pharyngitis**
- **Pertussis**
- **Sinusitis**
- **Epiglottis**
- **Otitis Media**
- **Deep neck space infections**

**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).

**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.
**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.

**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

**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.
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

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)

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

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 IV 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?
  - 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

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.

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/nerve/epithelium.

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

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.

**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.

**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 (Bordet-Gengou)

**Treatment:**
- Prevented by vaccination.
- Erythromycin.

**Note:**
- Pertussis in infants less than 6 months will present with cyanosis because these 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.
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.

<table>
<thead>
<tr>
<th><strong>Epidemiology</strong></th>
<th>More common in children.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>BACTERIAL:</td>
</tr>
<tr>
<td></td>
<td>- Streptococcus pneumoniae</td>
</tr>
<tr>
<td></td>
<td>- H. influenzae</td>
</tr>
<tr>
<td></td>
<td>- Moraxella catarrhalis</td>
</tr>
<tr>
<td></td>
<td>- Group A streptococcus, Staph aureus, and Anaerobic bacteria also can cause both of otitis &amp; sinusitis.</td>
</tr>
<tr>
<td></td>
<td>VIRAL:</td>
</tr>
<tr>
<td></td>
<td>Can be alone or with bacteria. E.g. RVS, Rhinovirus.</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>tympanic membrane will look erythematous</td>
</tr>
<tr>
<td><strong>Diagnostic</strong></td>
<td>Mainly clinical diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Tymanocentesis: Sometimes is needed and Middle ear fluid can be sent for culture.</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Mainly clinical diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Imaging (CT/MRI) when there is suspension of complications.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Amoxicillin or Amoxicillin with Clavulanic acid</td>
</tr>
<tr>
<td><strong>General Note</strong></td>
<td>There is Fluid and inflammation of the mucosal lining of the middle ear.</td>
</tr>
<tr>
<td></td>
<td>Can be acute or chronic</td>
</tr>
<tr>
<td></td>
<td>complication:</td>
</tr>
<tr>
<td></td>
<td>- Periorbital cellulitis.</td>
</tr>
<tr>
<td></td>
<td>- Brain abscess &amp; meningitis</td>
</tr>
</tbody>
</table>
### In Summary

<table>
<thead>
<tr>
<th>Infection</th>
<th>Gastro-Pharyngitis</th>
<th>Diphtheria</th>
<th>Epiglottitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Group A streptococcus (streptococcus pyogenes)</td>
<td>Corynebacterium diphtheriae</td>
<td>H. influenzae Type b (mainly)</td>
</tr>
</tbody>
</table>
| **Diagnosis** | o Throat swab  
 o Rapid Bacterial antigen detection  
 o Culture on blood agar  
 o Antistreptolysin O | o ELEK’s Test  
 o Culture on special media containing tellurite (e.g. Tinsdale media)  
 | o Blood cultures  
 o Culture of epiglottic surface (under controlled setting) |
| **Clinical features** | o Exudate of tonsils  
 o Enlarged, tender of lymph nodes  
 o Edema & Erythema  
 o Fever 38.4 to 39.4°C | o Formation of pseudomembranous  
 o Diphtheria toxin  
 o undeveloped countries | o Dysphagia  
 o Drooling  
 o respiratory distress. |
| **Management** | Penicillin x 10 days  
 **Allergy** = Clindamycin or macroide | Antitoxin + antibiotic  
 (Penicillin or erythromycin)  
 Vaccination with diphtheria toxoid containing vaccine. | Ceftriaxone & Vancomycin  
 Prevention: HiB vaccination |

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pertussis</th>
<th>Acute Otitis Media</th>
<th>Acute Bacterial Sinusitis</th>
</tr>
</thead>
</table>
| **Etiology** | Bordetella pertussis (GNB). | o S. pneumoniae  
 o H. influenzae (non-typable)  
 o Viral | S. pneumoniae  
 H. influenzae (non-typable)  
 M. catarrhalis  
 Anaerobes  
 Viral |
| **Diagnosis** | o Nasopharyngeal (NP) swabs  
 o Charcoal blood or Bordet-Gengou media | o Mainly clinical diagnosis  
 o Typanocentesis sometimes needed | o Mainly clinical diagnosis.  
 o Imaging (CT/MRI) when there is suspension of complications |
| **Clinical features** | o Severe coughing  
 o Vomiting  
 o Divided into phases | o Fever  
 o Tympnic membrane (TM) will look erythematous/red | o Nasal discharge  
 o Sinus pain  
 o Patient have viral URTI |
| **Management** | Macrolide (erythromycin) preventative  
 **Note** : Acellular pertussis-containing vaccine | Amoxicillin or Amoxicillin Clavulanic acid | Amoxicillin Clavulanic acid for 1 to 2 weeks |
## Ear, Nose, Throat, Upper Respiratory System Infections

<table>
<thead>
<tr>
<th>Type infection</th>
<th>Cause vignette/key clues</th>
<th>Common causal agents</th>
</tr>
</thead>
</table>
| 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 threatening                                               | *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) |
| Sore throat                  | Some mouth with thick white coating (painful red base under); increased risk: premature infants, AIDS, IC pts, pts on antibiotics, vitamin C deficiency | *Candida* |
|                              | 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 severe fatigue, lymphadenopathy, fever, rash; heterophile (+); Downey type II cell | Epstein-Barr virus |

*NF = normal flora*
Ear, Nose, Throat, Upper Respiratory System Infections

<table>
<thead>
<tr>
<th>Type infection</th>
<th>Cause vignette/key clues</th>
<th>Common causal agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold</td>
<td>Rhinitis, sneezing, coughing; list CA with seasonal peaks</td>
<td>Rhinoviruses (summer-fall) Coronavirus (winter-spring) Human metapneumovirus Adenovirus, many other</td>
</tr>
</tbody>
</table>

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. galloyticus (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)
  o Phage-coded (i.e., the cells are lysogenized by a phage)
  o Cause fever and rash of scarlet fever: superantigens

Diseases: look at tables

Acute suppurative group A streptococcal infection*

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

Acute suppurative group A streptococcal infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Sequelea of</th>
<th>Mechanism/symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever</td>
<td>Pharyngitis with group A strep</td>
<td>Antibodies to heart tissue/ 2weeks post pharyngitis, fever, joint inflammation, carditis, erythema marginatum (chorea later) type II hypersensitivity</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>Pharyngitis or skin infection</td>
<td>Immune complexes bound to glomeruli/pulmonary edema and hypertension, “smoky” urine (type III hypersensitivity)</td>
</tr>
</tbody>
</table>

• 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 lactam 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 Loeffler 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

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

**Prevention**: toxoid vaccine (formaldehyde-modified toxin is still immunogenic but with reduced toxicity), part of DTaP, DTP, or Td, boosters 10-year intervals
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. influenzae 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. influenzae was major causal agent

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

**Treatment:** cefotaxime or ceftriaxone 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
**Moraxella catarrhalis**

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

**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 cephalosporin 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 cyclase) 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 (pertussis) vs. results of bacterial culture

<table>
<thead>
<tr>
<th></th>
<th>Incubation</th>
<th>Catarrhal</th>
<th>Paroxysmal</th>
<th>Convalescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>7-10 days</td>
<td>1-2 days</td>
<td>2-4 weeks</td>
<td>3-4 weeks (or longer)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None</td>
<td>Rhinorrhea, malaise, sneezing, anorexia</td>
<td>Repetitive cough with whoops, vomiting, leukocytosis</td>
<td>Diminished paroxysmal cough, development of secondary complications (pneumonia, seizures, encephalopathy)</td>
</tr>
<tr>
<td>Bacterial culture</td>
<td><a href="image1">Image</a></td>
<td><a href="image2">Image</a></td>
<td><a href="image3">Image</a></td>
<td><a href="image4">Image</a></td>
</tr>
</tbody>
</table>

#### 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 fluorescence (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 inflammatory in CNS; CSF reveals high WBCs (neutrophils) 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; ceftriaxone 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
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pie in glass Capsule – Group A Strep is encapsulated</td>
</tr>
<tr>
<td>2.</td>
<td>Hot Apple – Capsule made out of Hyaluronic Acid</td>
</tr>
<tr>
<td>3.</td>
<td>Heating Lamp w/ &quot;B&quot; Light – Beta Hemolytic</td>
</tr>
</tbody>
</table>
| 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. |
| 5. | 2nd Baker w/ Cape – represents Strep Toxins 3 issues  
   a. Scarlet Fever  
      i. Strawberry Tongue  
      ii. Red Handkerchief - Pharyngitis,  
      iii. Red Gingerbread Man - widespread rash that spares the face.  
   b. Cape w/Bolt - Toxic Shock Like Syndrome mediated by a super antigen – SpeA, SpeC  
   c. Burnt Gingerbread man - Necrotizing Fasciitis = Sperl  
   d. 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  
   e. Chef Swatting away other chef – Antiphagocytic action  
   f. Miter hat - Very antigenic and elicits a humoral response, creating an antibodies to myosin in cardiac muscle (Molecular mimicry), damages mitral valves  
   g. Red Handkerchief – Pharyngitis precipitates RF, NOT IMPETIGO  
   h. Cupcakes w/ JONES on them  
      i. J = Joints  
      ii. "Heart" = Heart Problems  
      iii. Nodules on exterior surfaces  
      iv. Erythema marginalum  
      v. Sydenham's Chorea  
   i. 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  
   j. 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 - DNAases, depolymerize DNA  
   k. Bassett hound – Bacitracin sensitive  
   l. Lady checking a box of donuts – Tongs are antibodies, check ASO titers to see if there was a Group A Strep Infection. |
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 laughlers 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**
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. Dipped 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
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
### 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 Mezzanine, **Children** on the Ground - 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.
SECTION 2
Viruses Causing Respiratory Infections

Objective

- 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)
- Describe their epidemiology and pathogenesis
- Identify the respiratory infections and the clinical features of URTI and LRTI.
- Describe their epidemiology and pathogenesis
- Know the laboratory diagnosis, and treatment of these infections.
- 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.

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::

<table>
<thead>
<tr>
<th>Name of the virus</th>
<th>Family</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Influenza virus</td>
<td>Orthomyxoviridae</td>
<td>URTI and LRTI</td>
</tr>
<tr>
<td>2) Parainfluenza virus</td>
<td>Paramyxoviridae</td>
<td>LRTI</td>
</tr>
<tr>
<td>3) Respiratory syncytial virus</td>
<td>Coronaviridae</td>
<td>URTI and LRTI</td>
</tr>
<tr>
<td>4 Rhinovirus</td>
<td>Picornaviridae</td>
<td>URTI</td>
</tr>
<tr>
<td>5 Coronavirus</td>
<td>Coronaviridae</td>
<td>URTI and LRTI</td>
</tr>
<tr>
<td>6 Adenovirus</td>
<td>Adenoviridae</td>
<td>URTI and eye infections</td>
</tr>
<tr>
<td>7 Human metapneumovirus</td>
<td>Paramyxoviridae</td>
<td>LRTI</td>
</tr>
</tbody>
</table>

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

Arabic Translation:
Croup = مرض الحلق

Arabic Translation:
Note: (2) Lower respiratory tract infections

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.

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

Orthomyxoviridae Family
- Influenza virus, Avian flu and Swine flu -

I: Influenza virus:

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

- Haemagglutinin proteins:
  
<table>
<thead>
<tr>
<th>Haemagglutinin (H)</th>
<th>Neuraminidase (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attachment to the host cell surface receptors.</td>
<td>Responsible for release of the progeny viral particles from the infected cell.</td>
</tr>
<tr>
<td>No Attachment = No infection</td>
<td></td>
</tr>
<tr>
<td>Antibodies to the HA is responsible for immunity.</td>
<td></td>
</tr>
<tr>
<td>our immune system use it as an antigen.</td>
<td></td>
</tr>
<tr>
<td>Human associated H antigenic type are H1, H2, H3</td>
<td>Human associated N antigenic type are N1, N2. Other N for animals, though it can infect human 1</td>
</tr>
<tr>
<td>Other H for animals, though it can infect human</td>
<td></td>
</tr>
</tbody>
</table>

- 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:
<table>
<thead>
<tr>
<th>Influenza Virus Types</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infect</td>
<td>Human and Animal.</td>
<td>Human only.</td>
<td>Human only.</td>
</tr>
<tr>
<td>Antigenic changes</td>
<td>- Antigenic drift</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Antigenic shift = Reassortment = rearrangement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antigenic drift only.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Extra Explanation:
Antigenic drift (minor change)
- A mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibody binding 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 2 | Viruses Causing Respiratory Infections

**Pathogenesis:**
Infests 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.
- Secondary bacterial pneumonia.
- Reye’s syndrome.

**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.

**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.
Viruses Causing Respiratory Infections I | SECTION 2

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)

   **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.

**Paramyxoviridae Family**

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

1: Parainfluenza Virus:

Enveloped virus with -ve polarity ssRNA genome with 5 serotypes.

**Transmission:** Inhalation of infectious aerosol droplets mainly in winter

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

**Clinical syndromes:**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Syndrome Croup or acute laryngotracheobronchitis</th>
<th>Bronchiolitis and Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infecting type</td>
<td>PIV Type-I, II</td>
<td>PIV Type-III</td>
</tr>
<tr>
<td>Host</td>
<td>infants and young children</td>
<td>young children</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Fever, harsh cough, difficult inspiration can lead to airway obstruction which may require hospitalization and tracheostomy</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment and prevention:**
Supportive treatment, No specific treatment or vaccine available
SECTION 2 | Viruses Causing Respiratory Infections I

2- Respiratory Syncytial Virus (RSV) and Human metapneumovirus!

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

**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:** 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.

**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.
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:**
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

- 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)

- Describe their epidemiology and pathogenesis

- Identify the Target group and modes of transmission and Clinical manifestations.

- Describe their epidemiology and pathogenesis

- Know the laboratory diagnosis, and treatment of these infections.

- 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. 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.
1- Rhinovirus:

- **Structural features:**
  Nonenveloped virus with (+ve polarity) ssRNA 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. Pharyngitis 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:

<table>
<thead>
<tr>
<th>Immunocompetent host</th>
<th>Immunocompromised host</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Asymptomatic (in young children)</td>
<td>Can cause:</td>
</tr>
<tr>
<td>o Infectious mononucleosis (in adolescence) [or glandular fever]</td>
<td>o Lymphoproliferative disease (LD).</td>
</tr>
<tr>
<td>o Incubation period = 4-7 weeks</td>
<td>o oral hairy leukoplakia (OHL)</td>
</tr>
<tr>
<td>o Can present with Fever, sore throat, tonsillitis, malaise, pharyngitis, hepatitis, hepatosplenomegaly &amp; abnormal LF.</td>
<td>o Nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>o Complications: {acute airway obstruction, splenic rupture, CNS inf}</td>
<td>o Burkitt’s lymphoma</td>
</tr>
</tbody>
</table>

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 influenza 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
Viral infections of the respiratory system

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
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

#### 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
Viral infections of the respiratory system

**Malignancies**
- Burkitt lymphoma: cancer of the maxilla, mandible, abdomen; Africa; malaria cofactor; AIDS patients; translocation juxtaposes c-myc oncogene 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

<table>
<thead>
<tr>
<th>Virus</th>
<th>Transmission</th>
<th>Pathogenesis</th>
<th>Diseases</th>
<th>Diagnosis</th>
<th>Treatment/prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteroviruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piolo</td>
<td>Fecal-oral</td>
<td>Virus target anterior horn motor neuron</td>
<td>Asymptomatic to fever of unknown origin; aseptic meningitis; paralytic piolo (flaccid asymmetric paralysis, no sensory loss)</td>
<td>Serology (virus absent from CSF)</td>
<td>No specific Antiviral/live vaccine (Sabin); killed vaccine (Salk)</td>
</tr>
</tbody>
</table>
## Viral infections of the respiratory system

<table>
<thead>
<tr>
<th>Virus</th>
<th>Transmission</th>
<th>Pathogenesis</th>
<th>Diseases</th>
<th>Diagnosis</th>
<th>Treatment/prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteroviruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neural fatigue</td>
<td>Post-piolo syndrome</td>
<td>Patient with piolo decades earlier, progressive muscle atrophy</td>
<td></td>
</tr>
<tr>
<td>Coxasackie A</td>
<td>Fecal oral</td>
<td>Fecal-oral spread with potential for dissemination to other organs; often asymmetric with viral sheeding</td>
<td>Hand, foot, and mouth (A16); herpangina; aseptic meningitis; acute lymphoglandular pharyngitis; common cold</td>
<td>Virus isolation from throat, stool, or CSF</td>
<td></td>
</tr>
<tr>
<td>Coxasackie B</td>
<td>fecal oral</td>
<td>As above</td>
<td>Bornholm disease (devil’s grip); aseptic meningitis; severe systematic disease of newborns; <strong>myocarditis</strong></td>
<td>As above</td>
<td>No specific/handwashing</td>
</tr>
<tr>
<td>D68</td>
<td>Fecal-oral, respiratory</td>
<td>Invade mucosa, lymphatics; potential spread to CNS</td>
<td>Motor-neuron disease, respiratory disease</td>
<td>Serology/RT-PCR</td>
<td>No specific/IVIG/handwashing</td>
</tr>
<tr>
<td>Echoviruses</td>
<td>Fecal-oral</td>
<td>As above</td>
<td>Fever and rash of unknown origin; aseptic meningitis</td>
<td>As above</td>
<td>No specific/handwashing</td>
</tr>
</tbody>
</table>
## Viral infections of the respiratory system

<table>
<thead>
<tr>
<th>Virus</th>
<th>Transmission</th>
<th>Pathogenesis</th>
<th>Diseases</th>
<th>Diagnosis</th>
<th>Treatment/prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>Respiratory</td>
<td>Acid labile; grows at 33 C (91.4 F); over 100 serotypes</td>
<td>Common cold; #1 cause, peak summer/fall</td>
<td>Clinical</td>
<td>No specific/handwashing</td>
</tr>
<tr>
<td>HAV</td>
<td>Fecal-oral</td>
<td>Virus targets hepatocytes; liver function is impaired</td>
<td>Infectious hepatitis</td>
<td>IgM to HAV serology</td>
<td>No specific/killed vaccine and hyperimmune serum</td>
</tr>
</tbody>
</table>
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 chest – 4 C’s to diagnose measles, Cough, Conjunctivitis, Kopik Signs, Coryza
8. Coughing, dripping nose, red eyes on weasel
9. Bowl of blue marbles – Kopik 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 later, starts on the head and works down
12. Solid dress – confluenza 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 SSPE = SSPE
16. Tentacles w/ berries stuck together – HA (causes RBC’s to stick together), and
17. Hand stuck together - fusion proteins cause 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 – Ribavirin can be used to treat in adults
30. Extra Pale w/ IgG rattle covered in fusion slime – Palivizumab – monoclonal antibody.
31. Seals in the background – Parainfluenza – seal bark cough
32. 3 wolves – all 3 virulence factors, NA, HA, Fusion
33. Church w/ steeples – steeple radiographic sign on xray, Grouper – inspiratory stridor a howling noise (church door open) - laryngeotracheobronchitis
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
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. H 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 CD21, that is a receptor for complement component CD3, to infect B Cells
13. Man’s mouth w/tonsillar exudates – Pharyngitis
14. Diffrs 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 nasopharyngeal 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
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
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 coxsackie 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. Coxsackie 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
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
18. Mud on rhino face to symbolize a URI
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>
<thead>
<tr>
<th>1st generation</th>
<th>2nd generation</th>
<th>3rd generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylamine: Chlorpheniramine (Chlorphenamine)</td>
<td>Levocetirizine</td>
<td>Levocetirizine</td>
</tr>
<tr>
<td>Ethanolamine: Dimenhydrinate</td>
<td>Cetirizine</td>
<td>Levocetirizine</td>
</tr>
<tr>
<td>Ethanolamine: Diphenhydramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylenediamine: Antazoline</td>
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<td></td>
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<tr>
<td>Phenothiazine: Promethazine</td>
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<tr>
<td>Piperazine: Cyclizine</td>
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<td></td>
</tr>
<tr>
<td>Piperidine: Azatidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketotifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous: Cyproheptadine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1st generation**
- Interactions with enzyme inhibitors (macrolides, antifungal, calcium antagonists)
- Additive pharmacodynamic ADRs

**2nd generation**
- No drug interaction
- Minimal ADRs since they are more specific for H1 receptors

**3rd generation**
- Long duration (better control)

- The older 1st generation drugs are still widely used because they are effective and inexpensive.
- These drugs penetrate the BBB and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects.

- 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

*All are used systemically or topically*
SECTION 2 | Treatment of Acute and Chronic Rhinitis and Cough

H1 Blockers Have:
- Rhinitis
- Conjunctivitis
- Urticaria
- Flu

Indication:

Good control of:
- Asthma
- Otitis
- Anaphylaxis
- Sinusitis
- Atopic dermatitis

Poor control of:
- Allergies
- Itching (Even if non allergic)
- Others:
  - Insomnia
  - Sleep aid
  - Vertigo
  - Anxiety
  - Cough

Indications Linked to H1 Block

Antihistamines

Indications not linked to H1 block
- Cholinergic
  - Dry mouth
  - Urinary retention
  - Sinus tachycardia
- Adrenergic
  - Hypotension
  - Dizziness
  - Reflex tachycardia
- Serotonin
  - Appetite
- Histamine H1
- Histamine H2
  - Allergic inflammation, itching, sneezing, rhinorrhea
  - Neurotransmission in CNS
  - Sedation
  - Cognitive & psychomotor performance
  - Appetite

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.
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 preventing symptoms 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
### Drugs: Anti-allergic

#### 2- Anti-allergics

<table>
<thead>
<tr>
<th>Type</th>
<th>Mast cell stabilizers</th>
<th>Leukotriene receptor antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Cromolyn (another name for cromoglycate) and Nedocromyl</td>
<td>Montelukast</td>
</tr>
<tr>
<td>M.O.A</td>
<td>Histamine release (mast cell stabilizers by inhibiting Cl channels), i.e. can act only as a prophylactic; it does not antagonize releases histamine.</td>
<td>Block leukotriene action</td>
</tr>
<tr>
<td>Uses</td>
<td>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</td>
<td>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)</td>
</tr>
<tr>
<td>ADRs</td>
<td>Can induce cough, wheezes, headache, rash, ...etc.</td>
<td>As in asthma</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th>Example</th>
<th>Beclomethasone, budesonide and fluticasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.O.A</td>
<td>It has Anti-inflammatory effect by blocking phospholipase A2 and arachidonic acid synthesis which lead to inhibit prostaglandins &amp; leukotrienes synthesis that's why corticosteroids are important in asthma? inhibits the synthesis of leukotrienes.</td>
</tr>
<tr>
<td>Uses</td>
<td>Administered topically (inhaled) as steroid spray</td>
</tr>
<tr>
<td></td>
<td>Given if severe intermittent or moderate persistent symptoms</td>
</tr>
<tr>
<td></td>
<td>Local corticosteroids are preferably used more than systemic ones.</td>
</tr>
<tr>
<td></td>
<td>Why? To reduce the side effects.</td>
</tr>
<tr>
<td>ADRs</td>
<td>Nasal irritation, fungal infection, hoarseness of voice</td>
</tr>
</tbody>
</table>

**Note:** Effectiveness of different drug groups in controlling symptoms of Rhinitis:
## Drugs: Decongestants

### 4- Decongestants

<table>
<thead>
<tr>
<th>Type</th>
<th>Systemic</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Pseudoephedrine</td>
<td>1-Phenylethylamines:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Phenylephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Methoxamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-Imidazoline:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Naphazoline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Oxymetazoline HCL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Xylometazoline HCL</td>
</tr>
</tbody>
</table>

**α-adrenergic agonists.** They make vasoconstriction of blood vessels in nasal mucosa & reduce the rhinorrhea.

**Treatment of nasal stuffiness**

**Uses**

- nervous, insomnia, tremors, palpitations, and hypertension.

**ADRs**

- Can cause Rebound nasal stuffiness (repeated administration 10 days -2 weeks)

**CI**

- hypertension, heart failure, angina pectoris, hyperthyroidism and glaucoma.

### Note:

Pseudoephedrine has many side effects because of the ephedrine which is a sympathomimetic.

## Drugs: Anticholinergics

### 5- Anticholinergics

<table>
<thead>
<tr>
<th>Example</th>
<th>Ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses</td>
<td>o Nasal drops to control rhinorrhea (excess nasal secretions &amp; discharge), so very effective in vasomotor rhinitis (watery hyper-secretion).</td>
</tr>
<tr>
<td></td>
<td>o Bronchodilator in asthma.</td>
</tr>
<tr>
<td>ADRs</td>
<td>Minimal systemic side effects (wheezing, bladder pain, cough producing mucus).</td>
</tr>
</tbody>
</table>

### Note:

Effectiveness of different drug groups in controlling symptoms of Rhinitis:

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-allergy</td>
<td>++</td>
</tr>
<tr>
<td>Antihistaminic</td>
<td>++</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>++</td>
</tr>
<tr>
<td>Decongestant</td>
<td>++</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>-- ++</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Reflex Stimulation</th>
<th>Direct Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritate GIT ↓ stimulate gastropulmonary vagal reflex ↓ loosening and thinning of secretions</td>
<td>Stimulate secretory glands ↓ Increase respiratory fluids production</td>
</tr>
<tr>
<td>M.O.A</td>
<td></td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>Iodinated glycerol, Na or K iodide/acetate, Ammonium chloride, Ipecacuahna.</td>
</tr>
<tr>
<td>Example</td>
<td></td>
</tr>
<tr>
<td>Dry mouth, chapped lips, risk of kidney stones (increases uric acid excretion).</td>
<td>Unpleasant metallic taste, hypersensitivity, hypothyroidism, swollen salivary glands (overstimulation of salivary secretion), &amp; flare of old TB.</td>
</tr>
<tr>
<td>ADRs</td>
<td></td>
</tr>
<tr>
<td>*It is useful for patients with gout because it increases uric acid excretion.</td>
<td></td>
</tr>
<tr>
<td>Uses</td>
<td></td>
</tr>
<tr>
<td>o Common cold</td>
<td></td>
</tr>
<tr>
<td>o Bronchitis</td>
<td></td>
</tr>
<tr>
<td>o Pharyngitis</td>
<td></td>
</tr>
<tr>
<td>o Chronic paranasal sinusitis</td>
<td></td>
</tr>
<tr>
<td>The ultimate outcome is that cough is indirectly diminished</td>
<td></td>
</tr>
</tbody>
</table>
Drugs: Mucolytics

Used to dissolve or breakdown mucus in the respiratory tract → mucus is less viscous → coughed up easily.

<table>
<thead>
<tr>
<th>N-Acetyl Cysteine</th>
<th>Bromhexine &amp; Ambroxol (Ambroxol is a metabolite of Bromhexine)</th>
<th>Pulmozyme Dornase Alpha or rhDNAase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overview</strong></td>
<td>It helps to:</td>
<td>A recombinant human-deoxyribonuclease-1 enzyme which is genetically engineered that is nebulized + Full benefit appears within 3-7 days</td>
</tr>
<tr>
<td></td>
<td>- Increase Immune defense.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Decrease antibiotics usage.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Decrease pain in acute sore throat.</td>
<td></td>
</tr>
<tr>
<td><strong>M.O.A</strong></td>
<td>Increase Breakdown of S-S bonds in glycoprotein in mucous → which lead to less viscid mucous.</td>
<td>Increase Synthesize of serous mucus o Increase activate ciliary clearance</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
<td>Bronchospasm, stomatitis, rhinorrhea, rash, nausea &amp; vomiting</td>
<td>Rhinorrhea, lacrymation, gastric irritations, hypersensitivity</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td></td>
<td>Voice changes, pharyngitis, laryngitis, rhinitis, chest pain, fever, rash</td>
</tr>
</tbody>
</table>

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.
### 1- Inhibitors of airway stretch receptors

<table>
<thead>
<tr>
<th>Location</th>
<th>In Pharynx</th>
<th>In Larynx</th>
<th>In Tracheobronchial Airway</th>
<th>During bronchoscopy or bronchography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses</td>
<td>Demulcents forms a protective coating (Soothing)</td>
<td>Emollients forms a protective coating.</td>
<td>Aerosols or inhalation of hot steam</td>
<td>local anesthetic aerosols</td>
</tr>
<tr>
<td>Drugs</td>
<td>o Lozenges o Gargles</td>
<td>o Menthol o Eucalyptus</td>
<td>o Tincture benzoin compound. o Eucalyptus</td>
<td>o Lidocaine o Benzocaine o Tetracaine</td>
</tr>
</tbody>
</table>

### 2- Inhibitors of pulmonary stretch receptors in alveoli

<table>
<thead>
<tr>
<th>Drug</th>
<th>Benzonatate</th>
</tr>
</thead>
</table>

**M.O.A.**

Sensitivity (numbing) of receptors by local anesthetic action.

**ADRs**

- Drowsiness, dizziness, dysphagia, allergic reactions.
- Overdose → mental confusion, hallucination, restlessness & tremors
### Treatment of Acute and Chronic Rhinitis and Cough

**Drugs: Antitussive**

Stop or reduce cough by acting either:

#### Centrally:

It acts on the cough center itself.

<table>
<thead>
<tr>
<th>Drug</th>
<th>OPIOIDS</th>
<th>NON-OPIOIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>OPIOIDS</td>
<td>Antihistamines (&gt;sedating)</td>
</tr>
<tr>
<td>Pholcodine</td>
<td>OPIOIDS</td>
<td>Dextromethorphan</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M.O.A</th>
<th>activating µ opioid receptors</th>
<th>Dextromethorphan increases threshold at cough center.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>It has benefits over opioids in being:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o As potent as codeine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Less constipating.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o No respiratory depression.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o No inhibition of mucociliary clearance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o No addiction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADRs</th>
<th></th>
<th>Normal dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O Nausea, vomiting, dizziness, rash &amp; pruritus.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O High dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O Hallucinations + opiate like side effects on respiration &amp; GIT</td>
</tr>
</tbody>
</table>

- Normal dose:
- 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)

<table>
<thead>
<tr>
<th>Drug</th>
<th>M block</th>
<th>Sedation</th>
<th>Animation</th>
<th>Other characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Widely used OTC drug</td>
</tr>
<tr>
<td>Promethazine</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>Some α block and local anesthetic action</td>
</tr>
<tr>
<td>Chlortetrime</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Possible CNS stimulation</td>
</tr>
<tr>
<td>Meclizine</td>
<td>++</td>
<td>++</td>
<td>++++</td>
<td>Highly effective in motion sickness</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>+/-</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Loratidine</td>
<td>+/-</td>
<td>0</td>
<td>0</td>
<td>No CNS entry</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>+/-</td>
<td>0</td>
<td>0</td>
<td>No CNS entry</td>
</tr>
</tbody>
</table>
**SECTION 2 | Viruses Causing Respiratory Infections I**

- 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)

- Describe their epidemiology and pathogenesis

- Identify the respiratory infections and the clinical features of URTI and LRTI.

- Describe their epidemiology and pathogenesis

- Know the laboratory diagnosis, and treatment of these infections.

- 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.

**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::**

<table>
<thead>
<tr>
<th>Name of the virus</th>
<th>Family</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Influenza virus</td>
<td>Orthomyxoviridae</td>
<td>URTI and LRTI</td>
</tr>
<tr>
<td>2) Parainfluenza virus</td>
<td>Paramyxoviridae</td>
<td>LRTI</td>
</tr>
<tr>
<td>3) Respiratory syncytial virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Rhinovirus</td>
<td>Picornaviridae</td>
<td>URTI</td>
</tr>
<tr>
<td>5 Coronavirus</td>
<td>Coronaviridae</td>
<td>URTI and LRTI</td>
</tr>
<tr>
<td>6 Adenovirus</td>
<td>Adenoviridae</td>
<td>URTI and eye infections</td>
</tr>
<tr>
<td>7 Human metapneumovirus</td>
<td>Paramyxoviridae</td>
<td>LRTI</td>
</tr>
</tbody>
</table>
Viruses Causing Respiratory Infections

SECTION 2

1: Influenza virus, Avian flu and Swine flu

Orthomyxoviridae Family

- Influenza virus

Structural virus:

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

Influenza viral proteins:

<table>
<thead>
<tr>
<th>Haemagglutinin (H)</th>
<th>Neuraminidase (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attachment to the host cell surface receptors.</td>
<td>Responsible for release of the progeny viral particles from the infected cell.</td>
</tr>
<tr>
<td>No Attachment = No infection</td>
<td></td>
</tr>
<tr>
<td>Antibodies to the HA is responsible for immunity. Our immune system use it as an antigen.</td>
<td></td>
</tr>
</tbody>
</table>

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 (*).

1: Influenza virus:

- Haemagglutinin (H)
  - Responsible for attachment to the host cell surface receptors.
- Neuraminidase (N)
  - Responsible for release of the progeny viral particles from the infected cell.
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9 neuraminidase antigenic type, (N1 – N9).

Human associated H antigenic type are H1, H2, H3
Other H for animals, though it can infect human (*).

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:

<table>
<thead>
<tr>
<th>Influenza Virus Types</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infect</td>
<td>Human and Animal.</td>
<td>Human only.</td>
<td>Human only.</td>
</tr>
<tr>
<td>Antigenic changes</td>
<td>- Antigenic drift</td>
<td>- Antigenic shift = Reassortment = rearrangement</td>
<td>Antigenic drift only.</td>
</tr>
</tbody>
</table>

Extra Explanation:

Antigenic drift (minor change)

- A mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibody binding 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.

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 of 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.

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SECTION 3:
LOWER RESPIRATORY TRACT

PATHOLOGY:
Microbiology:
Immunology:
Tuberculosis (TB)

Pharmacology:
Drugs used in TB

Pathology:
Lobar AND Broncho pneumonia

Microbiology:
Hospital Acquired pneumonia

Microbiology:
Community Acquired pneumonia

Pharmacology:
Respiratory tract infections

Microbiology:
Respiratory fungal infection and aspergillosis

Pathology:
Lung Tumors

Anatomy:
Mediastinum

Anatomy:
Radiological anatomy of the thorax.
Objective 1.1.2.3.4.5.6

- Identify the development of the laryngotracheal (respiratory) diverticulum.
- Identify the development of the larynx.
- Identify the development of the trachea.
- Identify the development of the bronchi & Lungs.
- Describe the periods of the maturation of the lung.
- 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 the 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 infant.

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.

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.

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)
   o Regurgitation of milk
   o Gagging and cyanosis after feeding
   o Abdominal distention after crying
   o 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.
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.

Objective

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 & Type II Pneumocytes
- Interstitium.
Histology of the Lower Respiratory Tract

**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:
  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 exhalation 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 8-2-11. Respiratory Pathways](image)
Histology of the lower respiratory tract

<table>
<thead>
<tr>
<th></th>
<th>Trachea</th>
<th>Bronchi</th>
<th>Bronchioles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelia</td>
<td>Pseudostratified ciliated columnar (PCC) cells, goblet cells</td>
<td>PCC to simple columnar cells</td>
<td>Ciliated, some goblet cells, Clara cells in terminal bronchioles</td>
</tr>
<tr>
<td>Cartilage</td>
<td>16-20 C-shaped cartilaginous rings</td>
<td>Irregular plates</td>
<td>None</td>
</tr>
<tr>
<td>Glands</td>
<td>Seromucous glands</td>
<td>Fewer seromucous glands</td>
<td>None</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Between open ends of C-shaped cartilage</td>
<td>Prominent</td>
<td>Highest proportion of smooth muscle in the bronchial tree</td>
</tr>
<tr>
<td>Elastic fibers</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

- 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.

- The trachea is composed of concentric rings of cartilage, 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.

**Tracheal Epithelial Cell Types**
- **Columnar cells** extend from the basal membrane to the luminal surface. These cells contain 200–300 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 (Amino-Precursor-Uptake-Decarboxylase), DNES cells (Diffuse NeuroEndocrine System), 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.
**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.

**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.
Histology of the lower respiratory tract

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.

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
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 phagocyted dust or cigarette particles, and heart failure cells because they have phagocyted blood cells that have escaped into the alveolar space during congestive heart failure.
Describe the Extent, structure and functions of the larynx.

Describe the Extent, structure and functions of the trachea.

Describe the bronchi and branching of the bronchial tree.

Describe the functions of bronchi and their divisions.

Objective

- 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
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 vagina 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
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 of 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
**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.

Structures of the Respiratory Zone
**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.

**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:**

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**Normal airway**

- Epithelium
- Basement membrane
- Lamina propria
- Smooth muscle
- Glands
- Cartilage

**Airway in asthma**

- Epithelium
- Basement membrane
- Lamina propria
- Smooth muscle
- Glands
- Cartilage

- Mucus accumulation
- Eosinophils
- Macrophages
- Smooth muscle
- Hypertrophy and hyperplasia
- Chronic inflammation (due to eosinophils, macrophages, and other inflammatory cells)
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:

<table>
<thead>
<tr>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
</tr>
<tr>
<td>IL-5</td>
</tr>
<tr>
<td>IL-9</td>
</tr>
<tr>
<td>IL-13</td>
</tr>
</tbody>
</table>

Repeted 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).
Pathology of Bronchial Asthma

**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 COPD
- 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.
**Pathology of Bronchial Asthma** | SECTION 3

- **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:**
  - 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 rhinitis, 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:

<table>
<thead>
<tr>
<th>IL-4</th>
<th>Induces class switching to IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td>Attracts eosinophils</td>
</tr>
<tr>
<td>IL-10</td>
<td>Stimulates TH2 and inhibits TH1</td>
</tr>
</tbody>
</table>

- IgE coats mast cells and next time same allergen is encountered, massive mast cell degranulation occurs.
  - Histamines (arteriolar vasodilation and increased 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)

What are nonallergic causes of asthma?
- Exercise
- Viral infection
- Aspirin (HY)
- Occupational exposure

What is presentation of aspirin intolerant asthma?
- Nasal polyps (nasal polyp in kids highly associated with CF)
- Bronchospasm with aspirin
Lung Pathology

1.2 - Asthma & Bronchectasis

1. Asthma

2. General:
   a. In asthma, obstruction prevents air from leaving the lungs (trapped in distal airways): (Kid obstructing exit)
   b. Asthma is a disease characterized by bronchial hyperactivity (HYPERACTIVE TO RES) or diagnosed bronchial hyperreactivity (HYPERACTIVE TO RES)
   c. Asthma In comparison to COPD is a transient reversible process, caused by hyperreactive airways that leads to airway inflammation and obstructive symptoms (BACKWARDS CAP)
   d. Asthma is characterized by chronic bronchial inflammation with eosinophils (Flame with a slant)
   e. Asthma is characterized by smooth muscle hypertrophy and hyperactivity and increase mucous secretion (MUCUS DRIPPING and GRIP ON LIMB)
   f. Asthmatic involves a type 1 hypersensitive reaction, with common triggers being animal dander, pollen, dust, and other environmental agents (ANTIGENIC SQUIRREL)

3. Mechanism of Action:
   a. The antigen is picked up by a T helper cell and then presented to a T helper cell where it gets too activated
   b. Interleukins 4, 5, 10 are activated
   c. Interleukins 4, 10 will activate B cells that will make a lot of IgE
   d. This signals the B cells to produce IgE which make mast cells degranulate (1 finger in the air)
   e. Blotting out - Mast cell
   f. IgE antigen is remobilized it binds to the cell and crosslinks the IgE which leads to degranulation (SQUIRREL CROSS LINKING BEHIND)

4. Phases of Asthma:
   a. Early Phase:
      i. Pro-inflammatory molecules released by mast cells induce bronchoconstriction, mucous production and vasodilation in large airways (GRIPPING DROOLING, DILATED SLEEVES)
   b. Late Phase:
      i. Inflammation consisting of eosinophils, neutrophils and T-cells occurs 4-6 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 from eosinophilic inflammation is release of major basic protein, an antihelminthic toxin that causes epithelial damage, basement release and further eosinophil chemotaxis (DAMAGED MAJOR BASE SKIN)
      v. Chronic inflammation from repeated attacks causes permanent structural changes to bronchial wall (CHRONIC FLAME CAPE)
   c. Histology:
      i. Macrophages in bronchus and bronchiola (Can plugged with mucus)
      ii. Eosinophilic infiltration of the airways is one of the hallmark of atopic asthma (eosinophils in spum and eosinoplasia)
      iii. Mucoid plugging of epithelial cells can lead to the formation of Kuschmann spicule, which are whorled deposits of epithelial cells (Curly wiring from plugged can)
      iv. Charcoal-Laden crystals are then, needle like concretions of eosinophilic proteins seen in the spum of asthmatics (PINK JACKS)

5. Clinical Presentation:
   a. Expiratory wheezing from bronchoconstriction is common in asthma exacerbations (KID WITH PARY BLOWER)
   b. Acute dyspnea is a common symptom of asthma exacerbation (KID PUFFING OUT AIR)
   c. Chronic cough especially nocturnal cough, in children may be the only symptom (Kid waking up form cough)
   d. Asthma is highly associated with obesity, so a family history of allergies is common (FAMILY PHOTO)
   e. Severe asthma attacks can lead to pulsus paradoxus, a drop in systolic BP > 10 mmHg on inspiration (PULSUS PARADOXOUS)
   f. Imaging:
      i. Air trapping in acute exacerbation can be seen on chest x ray as a hyper inflated lung (flattened diaphragm, and lengthening of the cardiac silhouette) (KID with SWAY)

6. Pulmonary Function Tests:
   a. Classic spirometry findings in asthma are a FEV1/FVC < 70 and an FEV1 < 80% predicted (FALLING FEV1/FVC)
   b. In between attacks these attacks are probably normal

7. Laboratory Tests:
   a. Patients with acute asthma exacerbations will have an initial respiratory alkalosis form hyperventilation (can progress to acidosis as severity increases BLOWING H8 bubbles that end up popping)
   b. Chronic bronchectasis is caused by chronic recurrent bacterial infections
   c. Tumors causing obstruction can lead to distal infarction, thus obstructing the cycle of infection/inflammation & bronchoectasis
   d. Chronic Phthisis is the most common cause of bronchoectasis in the US (thick secretions cause obstruction leading to infection/inflammation) (two up)
   e. Primary cilia dysfunction is another possible cause of bronchoectasis (secretions are not cleared due to dysfunctional cilia)

8. Bronchoectasis primarily affects the lower lobes (failure on CXR and CT as CROWDED bronchial markings extending to the edge of the lung periphery (CROWDED LUNG PERIPHERY)

9. Bronchoectasis is characterized by copious spum production, often described as "cup falls"
   a. Can have hemoptysis
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

<table>
<thead>
<tr>
<th></th>
<th>Non-atopic asthma (intrinsic)</th>
<th>Atopic asthma (extrinsic)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td>Very severe</td>
<td>Less severe</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>Older patients (10-33% of asthmatics)</td>
<td>60-90% children 50% of adults</td>
</tr>
<tr>
<td><strong>History of allergy</strong></td>
<td>Not needed</td>
<td>Needed</td>
</tr>
<tr>
<td><strong>Serum IgE</strong></td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td><strong>Skin test</strong></td>
<td>Negative</td>
<td>Positive (in 70-85%)</td>
</tr>
</tbody>
</table>
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.

**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
**Asthma treatment + COPD treatment**

- Different types of drugs used for treatment of asthma and COPD.
- Differentiate between treatment and prophylactic therapy for asthma.
- Recognize the different types of bronchodilators regarding pharmacokinetics, pharmacodynamics, uses and side effects.
- 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.

**Triggers of asthma:**

- Exogenous chemicals or irritants
- Chest infections
- Stress
- Exercise (in cold air)
- Pets
- Seasonal changes
- Emotional conditions
- Some drugs (as aspirin, β-boosters)

---

**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.
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

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Prophylactic</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is a <strong>quick relief</strong> → Treat acute episodic attack of Asthma.</td>
<td>It is for <strong>control</strong> (Anti-inflammatory) → Reduce the frequency of attacks and nocturnal night awakenings.</td>
</tr>
<tr>
<td>- Antimuscarinics</td>
<td>- Corticosteroids</td>
</tr>
<tr>
<td>- Short acting (\beta_2)-agonists</td>
<td>- Mast cell stabilizers</td>
</tr>
<tr>
<td>- Xanthine preparations</td>
<td>- Leukotrienes antagonists</td>
</tr>
</tbody>
</table>

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 adenylyl 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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Epinephrine (Adrenaline), Isoprenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Given S.C, I.M (Not effective orally).</td>
</tr>
<tr>
<td></td>
<td>Rapid onset of action (maximum effect within 15 min).</td>
</tr>
<tr>
<td></td>
<td>Has short duration of action (60-90 min).</td>
</tr>
<tr>
<td><strong>Clinical uses</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epinephrine: Non-selective adrenergic agonist (α1, α2, β1, β2).</td>
</tr>
<tr>
<td></td>
<td>Potent bronchodilator.</td>
</tr>
<tr>
<td></td>
<td>Adrenaline is the drug of choice for acute anaphylaxis (hypersensitivity reaction).</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia.</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle tremor.</td>
</tr>
<tr>
<td></td>
<td>CVS side effects (β1 actions): tachycardia, arrhythmia, hypertension.</td>
</tr>
<tr>
<td><strong>CI</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVS patients :hypertension, heart failure.</td>
</tr>
<tr>
<td></td>
<td>Diabetic patients.</td>
</tr>
<tr>
<td></td>
<td>Asthmatic patient with hypertension.</td>
</tr>
</tbody>
</table>
### B. Short acting β2 agonist

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Salbutamol, terbutaline.</th>
</tr>
</thead>
</table>
| 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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Salbutamol</th>
</tr>
</thead>
</table>
| 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 β1 stimulation.
### Muscarinic antagonists

<table>
<thead>
<tr>
<th><strong>Drugs</strong></th>
<th>o Ipratropium, Tiotropium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>o Act by blocking muscarinic receptors (non-selective)</td>
</tr>
</tbody>
</table>
| **Pharmacodynamics** | o Inhibit bronchoconstriction and mucus secretion with no anti-inflammatory action.  
 o Less effective than β2 agonists.  
 o Does not diffuse into the blood.  
 o Does not enter CNS.  
 o Quaternary derivatives of atropine (polar). |
| **Pharmacokinetics** | o Given by aerosol inhalation.  
 o Have delayed onset of action (Never used as rescue medications)  
 o Ipratropium: has short duration of action (3-5 hrs)  
 o Tiotropium: has longer duration of action (24 hrs) |
| **Clinical uses** | o Main choice in chronic obstructive pulmonary diseases (COPD).  
 o In asthma combined with β2 agonists & corticosteroids. |
| **ADRs**  | o Have minimal systemic side effects. |
## Methylxanthines
**(Xanthine preparations)**

### MOA
- Are phosphodiesterase inhibitors: $\uparrow$ cAMP $\rightarrow$ bronchodilation
- Adenosine receptors antagonists.
- Increase diaphragmatic contraction
- Stabilization of mast cell membrane

### Pharmacokinetics
- $T\ \frac{1}{2}= 8\ \text{hours}$
- Metabolized by Cyt P450 enzymes in liver.
- Theophylline is given orally.
- Aminophylline is given as slow infusion.

### Pharmacological effects
- Bronchial muscle relaxation.
- $\uparrow$ contraction of diaphragm $\rightarrow$ improve ventilation.
- CVS: $\uparrow$ heart rate, $\uparrow$ force of contraction
- GIT: $\uparrow$ gastric acid secretions
- Kidney: $\uparrow$ 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): $\uparrow$ metabolism of theophylline $\rightarrow$ $\downarrow$ $T\ \frac{1}{2}$.
- Cyt P450 Enzyme inhibitors (erythromycin): $\downarrow$ metabolism of theophylline $\rightarrow$ $\uparrow$ $T\ \frac{1}{2}$.  

---

**Asthma treatment + COPD treatment | SECTION 3**
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
Asthma treatment + COPD treatment

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.
SECTION 3 | Asthma treatment + COPD treatment

**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 (thrust).
  - 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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>A monoclonal antibody directed against human IgE. o Prevents IgE binding with its receptors on mast cells &amp; basophiles. o Decrease the release of allergic mediators.</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Given by inhalation (aerosol, nebulizer). o Have poor oral absorption (10%).</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Prophylactic therapy in asthma especially in children. o Allergic rhinitis. o Conjunctivitis.</td>
</tr>
<tr>
<td>ADRs</td>
<td>Bitter taste o Minor upper respiratory tract irritation (burning sensation, nasal congestion)</td>
</tr>
</tbody>
</table>

*Note: Disadvantages
 Expensive - not first line therapy*
### Mast cell stabilizers

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cromoglycate (also called cromolyn), Nedocromil</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MOA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Act by stabilization of mast cell membrane.</em>&lt;br&gt;<em>They are not bronchodilators, so they are not effective in acute attack of asthma.</em>&lt;br&gt;<em>Prophylactic anti-inflammatory drugs.</em>&lt;br&gt;<em>Reduce bronchial hyperreactivity.</em>&lt;br&gt;<em>Effective in exercise, antigen and irritant-induced asthma.</em>&lt;br&gt;<em>Children respond better than adults.</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Given by inhalation (aerosol, nebulizer).</em>&lt;br&gt;<em>Have poor oral absorption (10%).</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical uses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Prophylactic therapy in asthma especially in children.</em>&lt;br&gt;<em>Allergic rhinitis.</em>&lt;br&gt;<em>Conjunctivitis.</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADRs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bitter taste</em>&lt;br&gt;<em>Minor upper respiratory tract irritation (burning sensation, nasal congestion)</em></td>
<td></td>
</tr>
</tbody>
</table>
## Leukotrienes antagonists

<table>
<thead>
<tr>
<th><strong>Drugs</strong></th>
<th>Zafirlukast, Montelukast and Pranlukast</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Examples of Leukotrienes:</td>
</tr>
<tr>
<td></td>
<td>• Leukotriene B4: chemotaxis of neutrophils.</td>
</tr>
<tr>
<td></td>
<td>• Cysteinyl leukotrienes C4, D4 &amp; E4: bronchoconstriction, ↑ bronchial hyperreactivity and ↑ mucosal edema and mucus secretion.</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
<td>Selective, reversible antagonists of cysteinyl leukotriene receptors (CysLT1 receptors).</td>
</tr>
<tr>
<td></td>
<td>Bronchodilators</td>
</tr>
<tr>
<td></td>
<td>Have anti-inflammatory action</td>
</tr>
<tr>
<td></td>
<td>Less effective than inhaled corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Have glucocorticoids sparing effect.</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Taken orally.</td>
</tr>
<tr>
<td><strong>Clinical uses</strong></td>
<td>Prophylaxis of mild to moderate asthma (e.g. aspirin-induced asthma, antigen and exercise-induced asthma)</td>
</tr>
<tr>
<td></td>
<td>Not effective in acute attack of asthma.</td>
</tr>
<tr>
<td></td>
<td>Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
<td>Elevation of liver enzymes, headache, dyspepsia</td>
</tr>
</tbody>
</table>
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.

**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**

- 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).
# A. Muscarinic antagonists

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Ipratropium, Tiotropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Act by blocking muscarinic receptors (non-selective)</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>Inhibit bronchoconstriction and mucus secretion with no anti-inflammatory action.</td>
</tr>
<tr>
<td></td>
<td>Less effective than β2-agonists.</td>
</tr>
<tr>
<td></td>
<td>Does not diffuse into the blood.</td>
</tr>
<tr>
<td></td>
<td>Does not enter CNS.</td>
</tr>
<tr>
<td></td>
<td>Quaternary derivatives of atropine (polar).</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Given by aerosol inhalation.</td>
</tr>
<tr>
<td></td>
<td>Have delayed onset of action (Never used as rescue medications)</td>
</tr>
<tr>
<td></td>
<td>Ipratropium: has short duration of action (3-5 hrs)</td>
</tr>
<tr>
<td></td>
<td>Tiotropium: has longer duration of action (24 hrs)</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Main choice in chronic obstructive pulmonary diseases (COPD).</td>
</tr>
<tr>
<td></td>
<td>In asthma combined with β2 agonists &amp; corticosteroids.</td>
</tr>
<tr>
<td>ADRs</td>
<td>Have minimal systemic side effects.</td>
</tr>
</tbody>
</table>
### B. Short acting β2 agonist

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Salbutamol, terbutaline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Salbutamol (albuterol): mainly given by inhalation, orally, I.V</td>
</tr>
<tr>
<td></td>
<td>Terbutaline: mainly given by inhalation, orally, s.c.</td>
</tr>
<tr>
<td></td>
<td>Have rapid onset of action (15-30 min)</td>
</tr>
<tr>
<td></td>
<td>Short duration of action (4-6 hr).</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Drugs of choice for acute episodic attack of asthma.</td>
</tr>
</tbody>
</table>

### C. Long acting β2 agonist

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Salmeterol &amp; formoterol are given by inhalation.</td>
</tr>
<tr>
<td></td>
<td>Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect).</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Are NOT used to relieve acute episodes of asthma.</td>
</tr>
<tr>
<td></td>
<td>Used for nocturnal asthma.</td>
</tr>
<tr>
<td></td>
<td>Combined with inhaled corticosteroids to control asthma (prophylactic medication)</td>
</tr>
</tbody>
</table>
### Bronchodilators (relievers for bronchospasm)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>– Short acting</th>
<th>– <strong>main choice</strong> in acute attack of asthma</th>
<th>– Inhalation</th>
<th>↑ Adenyl cyclase</th>
<th>↑ cAMP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B2 agonists</strong></td>
<td>Salbutamol, terbutaline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol, formoterol</td>
<td>Long acting, Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nocturnal asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimuscarinics</strong></td>
<td>Ipratropium (Short)</td>
<td><strong>Main drugs For COPD</strong></td>
<td>Inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tiotropium (long)</td>
<td></td>
<td>Inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Xanthine derivatives</strong></td>
<td>Theophylline</td>
<td>(orally)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aminophylline</td>
<td>(parenterally)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inhibits phosphodiesterase</td>
<td>↑ cAMP</td>
</tr>
</tbody>
</table>

### Anti-inflammatory drugs (prophylactic)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>(Inhibits phospholipase A2)</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone, Fluticasone, budesonide</td>
<td>Inhalation</td>
</tr>
<tr>
<td>prednisolone</td>
<td>Orally</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>parenterally</td>
</tr>
<tr>
<td><strong>Mast stabilizers</strong></td>
<td></td>
</tr>
<tr>
<td>Cromoglycate (Cromolyn), Nedocromil</td>
<td>Inhalation, prophylaxis in children</td>
</tr>
<tr>
<td><strong>Cysteinyl antagonists (CyLT1 antagoist)</strong></td>
<td>orally</td>
</tr>
<tr>
<td>Zafirlukast, montelukast</td>
<td></td>
</tr>
<tr>
<td><strong>Omalizumab (Anti IgE antibody)</strong></td>
<td>Injection (SC)</td>
</tr>
</tbody>
</table>
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.

Beta-receptor agonists

- 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
SECTION 3 | (COPD): Chronic Bronchitis, Emphysema and Bronchiectasis.

### 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

<table>
<thead>
<tr>
<th></th>
<th>Obstructive</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity(FVC)</td>
<td>Normal or slightly Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Forced Expiratory volume in 1 SEC (FEV1)</td>
<td>Decreased</td>
<td>Normal or Decreased</td>
</tr>
<tr>
<td>(FEV1/FVC)</td>
<td>Decreased</td>
<td>Normal or Increased</td>
</tr>
</tbody>
</table>
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.
SECTION 3  | (COPD): Chronic Bronchitis, Emphysema and Bronchiectasis.

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.

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”.

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:**

![Pathogenesis Diagram]

1. **Smoking or air pollutant + genetic predisposition**
2. **Oxidative stress, increased apoptosis and senescence**
3. **Inflammatory cells, release of inflammatory mediators**
4. **Protease-anti-protease imbalance**
5. **Alveolar wall destruction**

**EMPHYSEMA**

- **Tobacco**
  - Nicotine
  - Reactive oxygen species ("free radicals")
- **Macrophage elastase and metalloproteinases**
- **Congenital α1-AT deficiency**
- **Tissue damage**
- **Neutrophil elastase**
- **Neutrophil**
- **Capillary**
- **IL-1, LTB4, TNF**
- **Inactivation of antiproteases ("functional α1 AT deficiency")**

**(COPD): Chronic Bronchitis, Emphysema and Bronchiectasis | SECTION 3**
### Types of emphysema

<table>
<thead>
<tr>
<th>Location</th>
<th>Centriacinar (centrilobular) “most common”</th>
<th>Panacinar (panlobular)</th>
<th>Distal acinar (paraseptal)</th>
<th>Irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central or Proximal alveoli of the acini</td>
<td>Central or Proximal alveoli of the acini</td>
<td>Uniform injury, total damage of the alveoli.</td>
<td>The distal alveoli of the acinus.</td>
<td>Can affect any part of the respiratory tract.</td>
</tr>
<tr>
<td>Cause</td>
<td>Smoking</td>
<td>Genetic condition: Alpha-1 antitrypsin deficiency</td>
<td>Unknown</td>
<td>Invariably associated with scarring such as that resulting from healed inflammatory diseases.</td>
</tr>
<tr>
<td>Features</td>
<td>Common in upper Lobes.</td>
<td>Common in lower lobes</td>
<td>Occurs adjacent to areas of fibrosis or atelectasis.</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More severe in the upper half of the lungs</td>
<td></td>
</tr>
</tbody>
</table>

- **Centriacinar (centrilobular)**: Most common, affecting central or proximal alveoli of the acini. Can affect any part of the respiratory tract.
- **Panacinar (panlobular)**: Uniform injury, total damage of the alveoli. Common in lower lobes.
- **Distal acinar (paraseptal)**: The distal alveoli of the acinus. Occurs adjacent to areas of fibrosis or atelectasis. More severe in the upper half of the lungs.
- **Irregular**: Invariably associated with scarring such as that resulting from healed inflammatory diseases. Asymptomatic.
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.

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

Morphology
- Dilated airways up to four times, reaching the pleura.
- Inflammation
- Fibrosis

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.
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 tract, staphylococcus aureus

Diagnosis:
- Genetic Study.
- Electron Microscope.

Complication
- Recurrent respiratory tract infections, e.g. Sinusitis
- Infertility in Males.
- Deafness (Can’t hear).

Cystic Fibrosis
(Mucoviscidosis)

Definition
An inherited Disease causing thickly, 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:
  o Low FEV₁:FVC ratio - Decreased FVC, even more low FEV₁
  o Normal FEV₁:FVC is 80%. Normal TLC = 7 L.
  o Increased TLC due to air trapping

Chronic bronchitis

What is chronic bronchitis? Why
• chronic productive cough lasting at least 3 months over a minimum of 2 years
• hypertrophy of bronchial mucinous glands--patients cough up cups of mucus

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:
  o Epithelium is pseudostratified columnar
  o 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 chronic bronchitis highly associated?
• Smoking
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 CO₂;
• 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 PAO₂ in lungs (low PAO₂ 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.

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

<table>
<thead>
<tr>
<th>PiM</th>
<th>PiZ</th>
<th>PiZZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norman healthy person</td>
<td>Heterozygotes; usually asymptomatic (low circulating A1AT)</td>
<td>Homozygous mutant</td>
</tr>
<tr>
<td></td>
<td>Significant emphysema risk with smoking</td>
<td>Significant risk for panacinar emphysema and cirrhosis</td>
</tr>
</tbody>
</table>

Differentiate two classic causes of emphysema (destruction of alveolar air sacs).

<table>
<thead>
<tr>
<th>Smoking (no. 1 cause of emphysema)</th>
<th>A1AT deficiency (alpha 1 antitrypsin) -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollutants cause inflammation that induce protease mediated damage to alveoli</td>
<td>A1AT is an important antiprotease that inhibits protease damage to alveoli</td>
</tr>
<tr>
<td>Centriacinar emphysema seen mainly in upper lobes (upper lobes have more air)</td>
<td>Panacinar emphysema seen mainly in lower lobes</td>
</tr>
<tr>
<td>Complications: hypoxemia and cor pulmonale (pulm HTN)</td>
<td>Complications: hypoxemia and cor pulmonale (pulm HTN)</td>
</tr>
<tr>
<td>Can cause liver cirrhosis too</td>
<td></td>
</tr>
</tbody>
</table>

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 bronchitis, bronchioles 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

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 asthma 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 compication 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

Fig: large dilated structures are airway, not coeleaced alveoli
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 excessive obstruction (NO U TURN)

a. In comparison to asthma in a transient reversible process, caused by hyperactivity airways
b. Cigarette smoking is the most important risk factor for COPD (SMOKES)

c. Emphysema occurs distally, while chronic bronchitis involves the airways more proximal airways
   a. Respiratory bronchiolitis (PROXIMAL STREET)
   b. Alveolar duct: (DISTAL, CUL-DE-SAC PATH)
   c. Alveolar sac: (END OF CUL-DE-SAC PATH)

d. Emphysema: Pink Puffer

   a. Affects the distal airways in the alveolar walls

   b. Definition: Permanent enlargement of the terminal airspaces of the corresponding lung hyperinflation and chronic air trapping

      i. Contracting: affects respiratory bronchioles and spares the alveolar ducts and sacs (YELLOW GRASS)
      ii. Toxins collect in the respiratory bronchioles and activate an inflammatory response (TOXIC HOCKEY PUCK)
      iii. Neutrophils recruited to distal airways
      iv. Necrosis alveolus (FIRST RESPONDER CUTTING THE ELASTASE)
      v. This leads to raised COMPLIANCE in the distal airway (Raised compliance book = floppiness)

   c. Emphysema: The distal terminal bronchioles cause air trapping (Collapsed Alveolar Terminals)

   d. Pathology: associated with alpha-1 antitrypsin deficiency but can be seen in severe emphysema (N)
      i. AAT is the major serum inhibitor of neutrophil elastase (AA trouncing)
      ii. AAT deficiency = unbridled neutrophil elastase = destruction of distal airways
      iii. Occurs throughout the lung (leaves all over the cul-de-sac)
      iv. Effects the lower lobes (Bottom of the sink = prone)
      v. AAT is produced in the liver so this accumulation in the hepatocytes leads to liver damage and cirrhosis

   e. Non-secreted AAT exists as positive (PASS FRISBEE)

   f. Young patients: Young women: Inherited

   g. Smoking increases emphysema risk in patients with AAT deficiency (Directly inhibits AAT)
      i. A. Increases neutrophils to the area because of inflammation
      ii. Directly oxidizes and activates AAT

   h. Smoking with poorly AAT will develop symptoms way easier

   i. Signs and Symptoms:
      i. Emphysema presents with gradually progressive dyspnea (Huffing and Puffing)
      ii. Bilateral wheezing (Party Blow)
      iii. Tripod position: arched prepugy (KID SITTING DOWN)
      iv. Purse lips: helps maintain pressure to inflate distal airways (purse lips)
      v. May cause weight loss (basically: run out of weight)
      vi. Muscles are used for breathing

   j. Emphysema can cause pulses paradoxes (causes a >10mmHg decrease in systolic pressure during inspiration)

   k. Distant lung and heart sounds (heart and sounds fall away)

d. X-ray:
   i. Hyper inflat.: Lungs expand and push the chest out
   ii. Chest X-ray: flat diaphragm, 10-15 posterolateral 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 Critical mass (left over after a normal expiration)
   iii. FEV1: second is not enough time for them to breath otherwise the lungs will collapse
      i. (FEV1/FVC) 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)
      i. FEV1: FVC (FEV1 is really low and FVC is low)
      ii. Low ratio (Both signs are dropping)
   v. Less than .7 (The hockey stick)

   c. Emphysema causes a low DLCO (Diffusion capacity of the lung for carbon monoxide (Trash on the street and on the ground)
      i. How well oxygen can get from the alveoli into the lung
      ii. Decreased because of damage into the alveoli
      iii. Hyperventilation EARLY in the course maintains normal arterial oxygen levels (Normal PaO2 = Pink face)

   d. Emphysema causes a low DLCO (Diffusion capacity of the lung for carbon monoxide (Trash on the street and on the ground)
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   e. Bronchiolitis (Blue Blower)
      i. Occurs in the terminal bronchioles (ROAD TERMINATES)
      ii. Chronic Bronchiolitis: Defined as a productive cough (hacking up sports drink)
      iii. Lasts for at least 3 months (NUMBREE 73)
      iv. Chronic Bronchiolitis involves mucus gland hypertrophy and hypersecretion in larger airways (mucous bronchi and bronchioles) (MUCUS ON TRACHEAL STICK)
      v. Mucus hypersecretion causes mucous plugs in the bronchioles a distal airway obstruction & distal airway obstruction (In chronic bronchiolitis)
      vi. Chronic bronchiolitis (as part of chronic bronchiolitis) cause goblet cell metaplasia and proliferation (Goblet bottles in terminal street)
      vii. Early on: mucus plugs trap air in distal airways: increased PaCO2 and respiratory ACIDOSIS (in chronic bronchiolitis) (CO2 FUMES)

   f. Cyanosis of the skin
      i. O2 supplementation can decrease RR causing respiratory failure in COPD patients and inhibits the firing of peripheral chemoreceptors (nose and carotid bodies sense decrease in PaO2) (CO: knocking over arch)
      ii. Heart:
         i. Hypoxic goals stretching out: Chronic hypoxemia in COPD a hypoxic vasoconstriction a pulmonary arterial hypertension
         ii. Coronary heart disease: Pulmonary hypertension due to hypoxic vasoconstriction in COPD can lead to right heart failure (CHF, PULMONALY)
Restrictive Lung Disease

Definition
Group of diseases characterized by reduced expansion of lung parenchyma and decreased total lung capacity.

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.

Note: The final stage of all restrictive lung disease is extensive fibrosis with 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)**
SECTION 3 | Pathology of restrictive lung disease.

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
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 result 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
Pathology of restrictive lung disease  |  SECTION 3

### 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

![Pathogenesis Diagram]

### 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-β1 secondary to down regulation of caveolin I
SECTION 3 | Pathology of restrictive lung disease

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

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.
    - Concentration of the dust in the ambient air.
    - Duration of the exposure.
    - 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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coal dust</td>
<td>Simple coal worker's pneumoconiosis macules and nodules</td>
<td>Coal mining</td>
</tr>
<tr>
<td></td>
<td>Coal worker's pneumoconiosis PMF</td>
<td></td>
</tr>
<tr>
<td>Silica</td>
<td>Silicosis</td>
<td>Sandblasting, quarrying, mining, stone cutting, foundry work, ceramics</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Asbestosis; pleural effusions; pleural plaques; or diffuse fibrosis; mesothelioma; carcinoma of the lung and larynx</td>
<td>Mining, milling, and fabrication of ores and materials; installation and removal of insulation</td>
</tr>
</tbody>
</table>

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.
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 for 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 sexes equally
SECTION 3 | Pathology of restrictive lung disease.

**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:

<table>
<thead>
<tr>
<th>Antigens</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer’s lung</td>
<td>• Thermophilic actinomycetes</td>
</tr>
<tr>
<td></td>
<td>• Micropolyspora faeni in hay</td>
</tr>
<tr>
<td>Pigeon breeder’s (psittacosis)</td>
<td>• Birds</td>
</tr>
<tr>
<td></td>
<td>• Pigeons</td>
</tr>
<tr>
<td>Air-cooler lung</td>
<td>• Thermophilic bacteria</td>
</tr>
<tr>
<td>Bagassosis</td>
<td>• Sugarcane bagasse</td>
</tr>
</tbody>
</table>
Pathology of restrictive lung disease | SECTION 3

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 \(\rightarrow\) low \(pO_2\) high \(pCO_2\))
   - Affects lower part of the lung
   - Bilateral peripheral reticulation \(\rightarrow\) fibrosis shrinks the lung (trapped air \(\rightarrow\) 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 \(\rightarrow\) higher tendency to develop fibrosis
     - Shorter telomeres (Reduced genes that encode for telomerase) \(\rightarrow\) shorter cell life (type I pneumocytes) \(\rightarrow\) senescence + apoptosis \(\rightarrow\) when they die they secrete:
       - TGF-b1 \(\rightarrow\) fibrogenic \(\rightarrow\) stimulating fibroblasts and myofibroblasts \(\rightarrow\) collagen
     - Low Caveolin (inhibits TGF-b1 \(\rightarrow\) 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 \(\rightarrow\) atelectasis \(\rightarrow\) collapse
     - The 50% who survive end up with chronic pulmonary fibrosis
     - Morphology: CT scan \(\rightarrow\) White lung syndrome due to fibrin and debris \(\rightarrow\) 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:
     o Pigeons
     o Desert cooler
     o Incense
     o Birds
     o Farmer’s lung → microsporum → extrinsic allergic alveolitis
Restrictive Diseases

What are 4 examples of restrictive lung disease?

- Idiopathic (1°), 2° pulmonary fibrosis
- Pneumoconioses
- Sarcoidosis
- Hypersensitivity pneumonitis (pigeon breeder’s lung)

What are etiologies of 1° and 2° pulmonary fibrosis?

<table>
<thead>
<tr>
<th>Primary</th>
<th>Increased TGF beta → induce fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>Amiodorone, bliomycin, radiation</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Example</th>
<th>Risk group</th>
<th>Complication</th>
<th>Presentation</th>
</tr>
</thead>
</table>
| 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 |
| Asbestos  | 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
Restrictive Diseases

**What is presentation of sarcoidosis?**
- Sarcoidosis is non-caesating granuloma in multiple organs (most commonly localized in lungs and hyaline 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 Fenton reaction so cells store free Fe in ferretin protein or hemosiderin

<table>
<thead>
<tr>
<th>Ferretin</th>
<th>Hemosiderin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular protein that acts as buffer against Fe overload or shortage (protein can be secreted too)</td>
<td>Intracellular complex made of Ferretin and other stuff</td>
</tr>
<tr>
<td>Fe in Ferretin can be given out when needed</td>
<td>Fe here is poor source to supply to body</td>
</tr>
<tr>
<td>Plasma Ferretin correlates well with total Fe in body; so serum ferretin a common test to access anemia.</td>
<td></td>
</tr>
</tbody>
</table>
2.1 - Restrictive Lung Disease (Overview)
1. Total "Load" Capacity overturned; total lung capacity (TLC) decreased in restrictive lung disease. Therefore unable to take a very large breath
2. 5 second rule
3. Elevated FEV1/FVC sign; Forced Expiratory Volume in 1 sec / Forced Expiratory Volume (FEV1/FVC) is elevated (&gt;80%) in restrictive lung disease
4. Falling FVC sign; FVC decreases in restrictive lung disease (FEV1/FVC increases)
5. FEV1 herring decreased elasticity of pulmonary interstitium (interstitial restrictive lung disease) → airway widening and decreased resistance to expiratory flow → maintains FEV1 (though still decreased)
6. Overturned residual capacity: Functional Residual Capacity (FRC) is decreased in restrictive lung disease.
10. Ripping corset velcro straps: interstitial lung disease (INntrinsic restrictive lung disease) can cause dry crackles ("velcro rales") usually heard best at the lung bases.
11. X-jolly roger: interstitial lung disease (INntrinsic restrictive lung disease) can be seen on x-ray (diffuse reticulo-nodular opacities)
12. Reticular shadowing in radiography (INntrinsic 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. Cocked bottle with heart sign: Pulmonary hypertension can cause right heart failure (COR PULMONALE)
15. Pleural sheet: Pleural diseases (e.g. mesothelioma) and pleural effusions can cause EXTRINSIC restrictive lung disease
16. Muscles and cut communication wire: neuroendocrine diseases (e.g. polio or myasthenia gravis) can cause EXTRINSIC restrictive lung disease when diaphragmatic and intercostal muscles affected
17. Locked chest, chest (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 reserve: 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 thorax, chest: obesity can cause chronic hypoxia → chronic pulmonary vascular constriction → pulmonary hypertension
24. Cocked bottle with heart sign: pulmonary hypertension caused by obesity-related restrictive lung disease can lead to right heart failure (COR PULMONALE)
25. Fibrotic pulmonary trees: idiopathic pulmonary fibrosis (INntrinsic restrictive lung disease)
26. Dusty factory; pneumoconiosis (INntrinsic restrictive lung disease)
27. Soccer player, sarcoidosis (INntrinsic restrictive lung disease)
28. Odorless colorless plastic trash littered on ground; DLCO is LOW in INntrinsic 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"
2.2 - Idiopathic Pulmonary Fibrosis (IPF)

1. Restrictive onset: 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. "Idiopathic Pulmonary Fibrosis (IPF)" is the prototypical fibrosing disorder
4. Repeated red grapes: IPF is associated with repeated cycles of alveolitis (of unknown origin)
5. Cracks in epithelial stroma: 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 grapes: IPF is associated with patchy fibrosis (due to multiple fibrotic foci) on histology
8. "Ugly grapes": usual interstitial pneumonia (UIP) is the patchy fibrotic histology seen in IPF

9. Cobblestone patina: 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
23 - Pneumoniosis
1. Particles in air: pneumoniosis are interstitial lung diseases caused by the inhalation of organic and inorganic particulates
2. Restrictive: pneumoniosis 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 proteaceous 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 5-10 microns in diameter are cleared by mucociliary transport in the trachea and bronchi
6. Bacterial infection: particles 1-5 microns in diameter lodge at the bifurcation of respiratory bronchioles, phagocytized by macrophages
7. Small particles in cages: particles 1-5 microns in diameter are engulfed by alveolar macrophages → cytokine release
8. Dropping dose: cytokines (PDGF, IGF) released from macrophages are the cause of inflammation and fibrosis in pneumoniosis
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 pneumonioses
11. Black panther coal: pulmonary interstitial fibrosis consists of asymmetric pulmonary deposition in interstitial tissue and hilar nodes (contained in macrophage “dust-cells”)®
12. Stained black: strands of anthracotic pigment are seen throughout the lungs (lymphatic spread of “dust cells”)®
13. Hilar coal cason: anthracotic pigment as 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 thickened 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: silicotic causes “eggshell” calcification of the hilar lymph nodes (fibrosed lymph nodes
24. Cowboy breaking cage: silica increases risk of TB infection (disrupts phagolysosome and promote apoptosis)
25. Big rust holes: In the setting of a pulmonary TB infection, nodules of silicobacteriosis can form, containing a central zone of caseation
26. Pink insulation: asbestos exposure can cause asbestosis: a pneumoniosis 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 curvy and flexible (serpentine)
29. Straight nail in shirt: amphibole fibers can penetrate the epithelium and enter the interstitium (more pathogenic than “serpentine”)
30. Lower barricades: 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
2.4 - Sarcoiodosis & Berylliosis

1. Soccer ball: sarcoidosis (a multi-system granulomatous disease with major pulmonary findings)
2. Intact macro-CAGES: sarcoidosis is associated with non-casinging granulomas (a collection of macrophages without an area of central necrosis)
3. Black female soccer captain: sarcoidosis is most common in African Americans (particular young females between 20-35)
4. No smoking sign: sarcoidosis is more common in non-smokers
5. Helper T-spheres: CD4+ helper T-cells are activated in sarcoiodosis
6. "BAL" bottle: bronchoalveolar lavage shows an elevated CD4+ to CD8+ ratio (&gt; 2:1) in sarcoidosis
7. No reaction to further: 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 patches: granulomas may contain multinucleated giant cells (formed by the fusion of activated macrophages)
10. Balls with star panels: giant cells may contain asteroid bodies (stellate inclusions)
11. Snowman with purple dress: granulomas may contain Schaumann bodies that show up as a purple spot on histology
12. Calcified feather dress: Schaumann bodies contain laminated calcium and protein
13. Balls in the field: non-casinging granulomas can be found throughout the lung interstitium in sarcoidosis
14. Soccer balls at the midline: non-casinging granulomas can occur in hilar and paratracheal lymph nodes → hilar lymphadenopathy
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 fibrosis
17. Dyspeptic player: pulmonary sarcoidosis presents with a gradual onset of dyspepsia (on exertion)
18. Coughing player: pulmonary sarcoidosis can present with a dry cough
19. Skinny goateed with flame bandana: sarcoidosis presents with other constitutional symptoms (malaise, fever, anorexia, weight loss)
20. Painful spotted skin 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 bilateral pleural effusion → 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 hypercalcitoninemia D)
29. 1-o-Box: activated macrophages in granulomas produce 1α-hydroxylase (converts Vitamin D into its active form, 1,25-dihydroxy vitamin D)
30. Sunny street lights: extra 1α-hydroxylase produced in the granulomas may lead to hypercalcitoninemia 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-casinging granulomas (similar to sarcoidosis)
36. Particles falling on top of fibrotic lung tree: interstitial fibrosis in berylliosis may be more prominent in upper lobes
Lung Function in Health and Disease

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.
**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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**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:
  - 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:
Lung function parameters
- FVC
- FEV1
- FEF 25-75% were impaired in subjects exposed to crude oil spill in sea water.
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 (FEV₁).

There are 2 key pieces of data from a PFT involving the measurement of FVC:

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. FEV₁ (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 FEV₁/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 FEV₁/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 the situation during a maximal forced expiration.

- 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.
Lung Function in Health and Disease

• 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. Regardless, 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 (FEV₁/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, FEV₁, and FEV₁/FVC.

Obstructive pulmonary disease
Obstructive disease is characterized by an increase in airway resistance that is measured 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 during a maximal forced expiration from TLC, a smaller than normal volume is slowly expired.

• Depending upon the severity of the disease, FVC may or may not be reduced. 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)
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 FEV₁ is also reduced, the FEV₁/FVC is often increased.
- However, the critical distinction is low FVC with low FRC and RV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obstructive Pattern (e.g., Emphysema)</th>
<th>Restrictive Pattern (e.g., Fibrosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>FEV₁</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>FVC</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>↓</td>
<td>↑ or normal</td>
</tr>
<tr>
<td>Peak flow</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FRC</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>RV</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

- FVC is always decreased when pulmonary function is significantly compromised. A decrease in FEV₁/FVC ratio is evidence of an obstructive pattern. A normal or increased FEV₁/FVC ratio is evidence of a restrictive pattern, but a low TLC is 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.
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, the loop begins and 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.
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:
  2. Costal 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 Supracleural 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.
**Respiratory Chapter**

**SECTION 3 | Anatomy of Lung and Pleura**

**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 intercostal nerves

- **Visceral**
  - sensitive to stretch only and is supplied by the 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**

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>Lies one inch above the medial 1/3 of the Clavicle.</td>
</tr>
<tr>
<td>Anterior margin</td>
<td><strong>Right pleura:</strong> extends vertically from Sternoclavicular joint to xiphisternal joint (6th costal cartilage). <strong>Left pleura:</strong> 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).</td>
</tr>
<tr>
<td>Inferior margin</td>
<td>Passes around the chest wall, on the 8th rib in midclavicular line, 10th rib in mid-axillary line and finally reaching to 12th rib adjacent to vertebral column posteriorly (T12).</td>
</tr>
<tr>
<td>Posterior margin</td>
<td>Along the vertebral column from the apex (C7) to the inferior margin (T12).</td>
</tr>
</tbody>
</table>
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 mid-clavicular 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 of clavicle).
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 the heart.
  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:**

<table>
<thead>
<tr>
<th>Bronchi</th>
<th>Right lung root</th>
<th>Left lung root</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchi</td>
<td>2 bronchi Lie posterior</td>
<td>One bronchus Lies posterior</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>Superior</td>
<td></td>
</tr>
<tr>
<td>Pulmonary veins</td>
<td>Are inferior and anterior</td>
<td></td>
</tr>
</tbody>
</table>
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.
    - Posterior intercostal vessels
    - Intervertebral discs
    - 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 & parasympathetic fibers.

- 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 autonomic nerves.
- The **segmental vein** lies in the inter-segmental C.T. septa between the segments.
- Diseased segment can be **removed surgically**, because it is a **structural unit**.

**Note:** Segmental vein can’t be removed, since it also gives the neighbor segment.
Lung and Pleura

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 thoracic cavity (Figure II-2-5). The external parietal pleura lines and attaches to the inner surfaces of the chest wall, diaphragm, and mediastinum. The innermost visceral layer reflects from the parietal layer at the 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 (Figure 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 reflex 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 of the lung.
- The visceral pleura tightly invests the surface of the lungs, following all of the fissures and lobes of 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.
Lung and Pleura

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.

- The pleural cavity is the potential space between the parietal and 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 the 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.
Lung and Pleura

**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.

**Pleural Recesses**

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.

<table>
<thead>
<tr>
<th>Line</th>
<th>Visceral Pleura</th>
<th>Parietal Pleura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midclavicular line</td>
<td>6th rib</td>
<td>8th rib</td>
</tr>
<tr>
<td>Midaxillary line</td>
<td>8th rib</td>
<td>10th rib</td>
</tr>
<tr>
<td>Paravertebral line</td>
<td>10th rib</td>
<td>12th rib</td>
</tr>
</tbody>
</table>

**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.
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.

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.
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).

![Lymphatic Drainage](Figure II-2-10. Lymphatic Drainage)
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.

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?**

<table>
<thead>
<tr>
<th>Spontaneous pneumothorax</th>
<th>Tension pneumothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often due to rupture of emphysematous bleb</td>
<td>Often due to penetrating chest wall injury</td>
</tr>
<tr>
<td>Often seen in young adults</td>
<td></td>
</tr>
<tr>
<td>X-ray: trachea deviates to side of collapse</td>
<td>X-ray: trachea pushed to opposite side of injury; medical emergency; put chest tube</td>
</tr>
</tbody>
</table>

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)
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 basic and use of tuberculin skin (Mantoux) test.

List the common clinical presentation of tuberculosis & List the complication and prognosis of tuberculosis.

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.

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 immunocompromised 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.
**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.

**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.

**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.

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 hominis

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.

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 contains 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.

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.
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
- 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

### Host factors
- 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

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**

**Exposed to TB**

- Infection (Primary) 10-30%
- No infection 70-90%

**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-γ:** 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.
SECTION 3 | PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY of TB

**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 lobes (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.

---

**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 focus + Nodal lesions**

**Healed primary pulmonary tuberculosis**

**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.

**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.

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).
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 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.

<table>
<thead>
<tr>
<th>Ziehl-Neelsen Stain</th>
<th>Kinyoun Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Fast Organisms</td>
<td>Non-Acid Fast Organisms</td>
</tr>
<tr>
<td>A small amount of organism suspended in saline solution is fixed on a slide.</td>
<td></td>
</tr>
<tr>
<td>Slide is flooded with Carbol Fuchsin and phenol for 3 minutes, and gently dried with water.</td>
<td></td>
</tr>
<tr>
<td>Slide is decolorized with 3% HNO₃ in 70% alcohol until color appears to be removed (approx. 2 mins), and rinsed with water.</td>
<td></td>
</tr>
<tr>
<td>Slide is flooded with methylene blue counterstain for 30 secs, rinsed with water and air-dried.</td>
<td></td>
</tr>
</tbody>
</table>

**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.

**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-γ 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.
**Respiratory Chapter**

**SECTION 3**

**PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY of TB**

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### 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**

**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 giant cells). Both Langhans (Classic TB) and foreign-body giant cells are common.

**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”, vertebræ”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](image)

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), i.e., 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-α activating other macrophages wailing 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 hydrolyses

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-α release

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 tuberculosis. "Hat being shot off"

20. Treatment - combination of RifPE, Rifampin, Isoniazid, Pyrazinamide, ethambutol

21. Prophylaxis - Rifampin or Isoniazid - 9 months
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
Discuss the etiology of tuberculosis.
Discuss the common route for transmission of the disease.
Discusses the outline for treatment of tuberculosis.
Discuss the drugs used in the first & second line Regarding:
- The mechanism of action.
- Adverse effects.
- Drug interactions.
- Contraindications.
Discuss tuberculosis & pregnancy.
Discuss tuberculosis & breast feeding.

**Objective**

1st line treatment:

<table>
<thead>
<tr>
<th>Isoniazid (INH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overview</strong></td>
</tr>
<tr>
<td>Bacteriostatic works on resting bacilli</td>
</tr>
<tr>
<td>Bactericidal works on rapidly growing bacilli</td>
</tr>
<tr>
<td><strong>Site of action</strong></td>
</tr>
<tr>
<td>Intracellular &amp; extracellular bacilli</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
</tr>
<tr>
<td>Inhibits the synthesis of mycolic acid, an important component of mycobacterial cell wall.</td>
</tr>
<tr>
<td>Penetrates macrophages.</td>
</tr>
<tr>
<td><strong>Clinical uses</strong></td>
</tr>
<tr>
<td>Treatment of TB.</td>
</tr>
<tr>
<td>Prophylaxis against active TB in individuals who are in great risk.</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
</tr>
<tr>
<td>Peripheral neuritis, i.e. loss pin &amp; needles sensation in the feet.</td>
</tr>
<tr>
<td>Optic neuritis &amp; atrophy ***.</td>
</tr>
<tr>
<td>Hepatitis (toxic metabolites) ****.</td>
</tr>
<tr>
<td><strong>Drug interaction</strong></td>
</tr>
<tr>
<td>INH inhibits cytochrome P450 2C19 isoform (enzyme inhibitor).</td>
</tr>
<tr>
<td>It prevents the metabolism of drugs that are metabolized by 2C19 which leads to accumulation of these drugs and then toxicity</td>
</tr>
<tr>
<td>Slow &amp; fast acetylators.</td>
</tr>
</tbody>
</table>

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:

Acetylation 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

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.

Treatment: Anti-TB
Drugs combination is important to prevent development of drug resistance. Periods of treatment is minimum 6 months.

Objective

1st line treatment:
**Rifampin (Rifampicin) (RIF)**

<table>
<thead>
<tr>
<th>Overview</th>
<th>Bactericidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of action</td>
<td>Intracellular &amp; extracellular bacilli</td>
</tr>
<tr>
<td>MOA</td>
<td>Binds to bacterial DNA-dependent RNA polymerase enzyme &amp; thus inhibits RNA synthesis.</td>
</tr>
</tbody>
</table>
| Clinical uses | o Treatment of TB.  
| o Prophylaxis, such as in case of meningococcal & staphylococcal infections. |
| ADRs | o Harmless red-orange discoloration of body secretions: saliva, sweat, urine, tears.  
| o Hepatitis. Less common compared to INH.  
| o Flu-like syndrome  
| o Hemolytic anemia |
| Drug interaction | o **RIF strongly induces** most cytochrome P450 isoforms **2C19, 2C9, 3A4**.  
| o Clinically significant drug interactions: warfarin, methadone will be metabolized faster, therefore their activity is reduced. |

**Ethambutol**

<table>
<thead>
<tr>
<th>Overview</th>
<th>Bacteriostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of action</td>
<td>Intracellular &amp; extracellular bacilli</td>
</tr>
<tr>
<td>MOA</td>
<td>Inhibits mycobacterial <strong>arabinosyl transferase</strong>; essential enzyme for mycobacterial cell wall synthesis, thus disrupts the assembly of mycobacterial cell wall.</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Treatment of TB in combination with other drugs.</td>
</tr>
</tbody>
</table>
| ADRs | o Impaired visual acuity.  
| o Red-green color blindness. |
| Contraindication | It is contraindicated in children under 5 years old. |
### Streptomycin

<table>
<thead>
<tr>
<th>Overview</th>
<th>Bactericidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of action</td>
<td>Extracellular bacilli</td>
</tr>
<tr>
<td>MOA</td>
<td><strong>Inhibitor of protein synthesis</strong> by binding to 30S ribosomal subunit. It is an aminoglycoside; this is their mechanism of action.</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Injectable drug used in severe, life-threatening form of TB as meningitis, disseminated disease.</td>
</tr>
</tbody>
</table>
| ADRs             | o Ototoxicity like vertigo & hearing loss may be permanent.  
o Nephrotoxicity.  
o Neuromuscular block. |

**Note:**
Streptomycin 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.

### Pyrazinamide (PZA)

<table>
<thead>
<tr>
<th>Overview</th>
<th>Bacteriostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of action</td>
<td>Intracellular bacilli</td>
</tr>
<tr>
<td>MOA</td>
<td>Pyrazinamide is converted to <strong>pyrazinoic acid</strong> (the active form) which <strong>disrupts mycobacterial cell membrane metabolism &amp; transport functions.</strong></td>
</tr>
</tbody>
</table>
| Clinical uses    | o Mycobacterial infections mainly in multidrug resistance cases.  
o It is important in short course (6 months) regimen.  
o Prophylaxis of TB. |
| ADRs             | o **Hepatotoxicity.**  
o Hyperuricemia → gouty arthritis.  
o Drug fever & skin rash |
Treatment: Anti-TB

2nd line treatment:

<table>
<thead>
<tr>
<th>Ethionamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
</tr>
<tr>
<td>Clinical uses</td>
</tr>
</tbody>
</table>
| ADRs        | o Teratogenic.  
|             | o Poorly tolerated due to severe gastric irritation & neurological manifestation. |

<table>
<thead>
<tr>
<th>Aminosalicylic acid (PAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview</td>
</tr>
<tr>
<td>MOA</td>
</tr>
</tbody>
</table>
| Clinical uses            | o As a 2nd line agent is used in the treatment of chronic pulmonary & other forms of TB.  
|                          | o Help to slow development of resistance to other drugs, especially INH & streptomycin. |
| ADRs                     | o GIT upset  
|                          | o 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. Regimens 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), fluoroquinolone, 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action and resistance</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>• Inhibit mycolic synthesis&lt;br&gt;• Produce requiring conversion by catalase&lt;br&gt;• High level resistance-deletions in <em>katG</em> gene (encodes catalase needed for INH bioactivation)</td>
<td>• Hepatitis (age-dependent)&lt;br&gt;• Peripheral neuritis (use vitamin B6)&lt;br&gt;• Sideroblastic anemia (use vitamin B6)&lt;br&gt;• SLE in slow acetylatros (rare)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Inhibit DNA-dependent RNA polymerase (nucleic acid synthesis inhibitor)</td>
<td>• Hepatitis&lt;br&gt;• Induction of P450&lt;br&gt;• Red-orange metabolites</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Inhibit synthesis of arabinogalactan (cell-wall component)</td>
<td>Dose-dependent retrobulbar neuritis → ↓visual acuity and red-green discrimination</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td>• Hepatitis&lt;br&gt;• Hyperuricemia</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Protein synthesis inhibiton</td>
<td>• Deafness&lt;br&gt;• Vestibular dysfunction&lt;br&gt;• Nephrotoxicity</td>
</tr>
</tbody>
</table>
SECTION 3 | Pathology of Lobar pneumonia & broncho pneumonia

- Understand that pneumonia is an inflammatory condition of the lung characterized by consolidation (solidification) of the pulmonary tissue.
- Is aware of the pathogenesis of pneumonia and its classification which principally include bronchopneumonia, lobar pneumonia and atypical pneumonia.
- Is able to appreciate the etiology and pathogenesis of lung abscess.

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.

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.

Note: It causes deformities in the fetus, so it's contraindicated in pregnancy.
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.**

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 influenzae, 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 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.

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 with neutrophils, 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).
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.
Also called Primary atypical pneumonia or interstitial pneumonitis.

**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)

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Severe underlying conditions, e.g. Immunosuppression.</td>
<td>Gram-negative organisms like Klebsiella, Pseudomonas aeruginosa and E.coli.</td>
</tr>
<tr>
<td>- Prolonged antibiotic therapy.</td>
<td></td>
</tr>
<tr>
<td>- Intravascular catheter.</td>
<td></td>
</tr>
<tr>
<td>- Patients with mechanical ventilator.</td>
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</tr>
</tbody>
</table>
### Aspiration pneumonia

A necrotizing pneumonia with fulminant clinical course, common complication (abscess) and frequent cause of death.

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Debilitated patients</td>
<td>Chemical injury due gastric acid and bacterial infection (anaerobic bacteria admixed with aerobic bacteria, e.g. Bacteroides, Fusobacterium and Peptococcus).</td>
</tr>
<tr>
<td>- Comatose</td>
<td></td>
</tr>
<tr>
<td>- Alcoholic</td>
<td></td>
</tr>
<tr>
<td>- Those who aspirated gastric contents.</td>
<td></td>
</tr>
</tbody>
</table>

### Chronic pneumonia

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.

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>

### Opportunistic pneumonia

Immunosuppressed patients (AIDS, cancer patients and transplant recipients).

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressed patients</td>
<td>Cytomegalovirus, Pneumocystis jiroveci (carinii), Mycobacterium avium-intracellulare, Invasive aspergillosis, Invasive candidiasis and &quot;Usual&quot; bacterial, viral, and fungal organisms.</td>
</tr>
</tbody>
</table>

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), 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.

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.
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?**

<table>
<thead>
<tr>
<th>Lobar pneumonia</th>
<th>Bronchopneumonia</th>
<th>Interstitial pneumonia (aka atypical pneumonia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affects whole lobe</td>
<td>Affects area around bronchioles (mostly multifocal)</td>
<td>Inflammation of interstitium without consolidation of air sacks (see increased lung markings in X-ray)</td>
</tr>
<tr>
<td>Cause is mostly bacterial</td>
<td>Cause is mostly bacterial</td>
<td>Called atypical because need special media to grow the bacteria. Viruses also cause it</td>
</tr>
</tbody>
</table>
| Most common cause:  
- Strep. Pneumoniae (95%)  
- Klebsiella pneumoniae  
- H influenzae | Bacterial causes:  
- Mycoplasma pneumoniae  
- Chlamydia phillila  
- Legionella (pathoma puts legionella in broncho) | |
| Treat: ceftriaxone | | Treatment: |
## Pulmonary Infections

### Exudate in interstitial pneumonia

![Image: lobar pneumonia (right), bronchopneumonia (middle), interstitial pneumonia (left). Note lack of alveolar](image.png)

<table>
<thead>
<tr>
<th>Lobar pneumonia Bacteria</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep pneumo</td>
<td>Most common cause of community acquired pneumonia</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>• enteric flora that's aspirated.</td>
</tr>
<tr>
<td></td>
<td>• Common seen in alcoholics, nursing home pt.</td>
</tr>
<tr>
<td></td>
<td>• Bacteria has thick mucoid capsule, so see currant jelly sputum.</td>
</tr>
<tr>
<td></td>
<td>• Often complicated by <strong>lung abscess</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Broncho pneumonia bacteria</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph aureus</td>
<td>• <strong>Most common cause of secondary pneumonia</strong> (pneumonia superimposed on viral upper respiratory tract infection)</td>
</tr>
<tr>
<td></td>
<td>• Often complicated by <strong>abscess or emphyema</strong> (free pus in pleural space)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>• <strong>Common cause of secondary pneumonia</strong></td>
</tr>
<tr>
<td></td>
<td>• Associated with <strong>COPD</strong></td>
</tr>
<tr>
<td>Pseduomonas aeruginosa</td>
<td>Associated with <strong>cystic fibrosis patients</strong></td>
</tr>
<tr>
<td>Moxarella catarrhalis</td>
<td>• Associated with <strong>COPD</strong></td>
</tr>
<tr>
<td></td>
<td>• Community acquired</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>• Transmitted from water source</td>
</tr>
<tr>
<td></td>
<td>• Associated with <strong>COPD</strong> and immunocompromised states</td>
</tr>
<tr>
<td></td>
<td>• Intracellular organism visualized by silver stain</td>
</tr>
<tr>
<td></td>
<td>• Pt. Presents with pneumonia, diarrhea, and hyponatremia</td>
</tr>
</tbody>
</table>
### Pulmonary Infections

<table>
<thead>
<tr>
<th>Atypical pneumonia organism</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>• <strong>Most common cause of atypical pneumonia</strong></td>
</tr>
<tr>
<td></td>
<td>• Affects young adult in close quarters (military recruits, dorm students)</td>
</tr>
<tr>
<td></td>
<td>• Complications: <strong>autoimmune hemolytic anemia</strong> (IgM against I antigen on RBC), erythema multiforme</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>2nd <strong>most common</strong> cause of atypical pneumonia in young adults</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>Most common cause of pneumonia in <strong>infants</strong></td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Associated with <strong>posttransplant immunosuppressive therapy</strong></td>
</tr>
<tr>
<td>Influenza virus</td>
<td>• Commonly seen in <strong>elderly</strong>, immunocompromised, or people with preexisting lung disease</td>
</tr>
<tr>
<td></td>
<td>• <strong>Increases risk for S aureus or H influenza secondary pneumonia</strong></td>
</tr>
<tr>
<td>Coxiella burnetti</td>
<td>• Pneumonia with high fever (Q fever; generally, pneumonia has low fever)</td>
</tr>
<tr>
<td></td>
<td>• Associated with farmers and veterinarians</td>
</tr>
<tr>
<td></td>
<td>• Coxiella is different from rickettsia in 3 ways: causes pneumonia, does not require arthropod for transmission (transmitted as spores), does not produce rash</td>
</tr>
</tbody>
</table>

**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
SECTION 3 | Hospital Acquired pneumonia

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.


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%.
Hospital Acquired pneumonia | SECTION 3

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 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, Atelectasis.
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 fluorescein
- 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

**Pathogenesis**
- Endotoxin causes inflammation 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% population); 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 (oft en superinfection, i.e., infection while on antibiotics)
- Chronic granulomatous disease: pneumonias, septicemias (Pseudomonas 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 aureus colonies 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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical symptoms</th>
<th>Pathogenicity factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis (food poisoning)—toxin ingested preformed in food</td>
<td>2-6 hours after ingesting toxin: nausea, abdominal pain, vomiting, followed by diarrhea</td>
<td>Enterotoxin A-E preformed in food</td>
</tr>
<tr>
<td>Infective endocarditis (acute) (most common cause)</td>
<td>Fever, malaise, leukocytosis, heart murmur (may be absent initially)</td>
<td>Fibrin-platelet mesh, cytolytic toxin</td>
</tr>
<tr>
<td>Abscesses and mastitis</td>
<td>Subcutaneous tenderness, redness and swelling; hot</td>
<td>Coagulase, cytolysins</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>Fever, hypotension, scarlatiniform rash that desquamates (particularly on palms and soles), multiorgan failure</td>
<td>TSST-1</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Erythematous papules to bullae</td>
<td>Coagulase, exofoliatins</td>
</tr>
<tr>
<td>Scalded skin syndrome</td>
<td>Diffuse epidermal peeling</td>
<td>Coagulase, exofoliatins</td>
</tr>
</tbody>
</table>
### Some Bacteria causing hospital acquired pneumonia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical symptoms</th>
<th>Pathogenicity factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>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</td>
<td>Coagulate, cytolysins</td>
</tr>
<tr>
<td>Surgical infection</td>
<td>Fever with cellulitis and/or abscesses</td>
<td>Coagulate, exofoliats ± TSSTs</td>
</tr>
<tr>
<td>Osteomyelitis (most common cause)</td>
<td>Bone pain, fever ± tissue swelling, redness, lytic bone lesions on imaging</td>
<td>Cytolysins, coagulate</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>Monoarticular joint pain; inflammation</td>
<td>Cytolysins, coagulate</td>
</tr>
</tbody>
</table>

**Treatment**

- Gastroenteritis is self-limiting.
- Nafcillin/oxacillin are drugs of choice because of widespread penicillinase-producing stains.
- 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 UTI's
15. Pruritic folliculitis ( Hot tub folliculitis)
16. Dalmatian Dog - Can lead to ecchyma gangrenosum (black spots on the Dalmatian)
17. ear trumpet maid listening - Otitis Externa ( swimmers ear)
18. 1st suit in green - Exotoxin A - Ribosilation of elongation factor 2, leads to inhibition of protein synthesis and cell death
19. Piper suit and Suiter with a Sai and flower - Treatment - Piperacillin (penicillin) , aminoglycosides and Fluoroquinolones
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 light bulb – Beta Hemolytic
5. Tall 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 lamp – 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 due 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.
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.

Pneumonia

Definition:
It’s 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)

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

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.
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.
**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

**May cause:**

- Respiratory infections
- Non respiratory infections
- Pneumonia, sinusitis, otitis
- Non respiratory infections
- Bacteremia, meningitis

**Virulence factors:**

- **Capsule:** More than 90 capsular types
- **Pneumolysin**
- **Autolysin** Similar to lysozyme.
- **Neuraminidase:** help them to spread.

**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

Symptoms:
Insidious onset, and Usually mild in all typical organisms except Legionella it is the most severe
- Headache
- Malaise
- Fever
- Dry cough
- Arthralgia / myalgia

Signs:
- Minimal
- Low grade fever
- Few crackles

Diagnosis:
- X-ray
- CBC: Mild elevation WBC
- Urea & Electrolytes: Low serum Na → Legionella
- 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: β 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

**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 β-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

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

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).
**Respiratory Chapter**

**SECTION 3**

**Community Acquired pneumonia**

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.

---

<table>
<thead>
<tr>
<th></th>
<th>Outpatient, healthy patient with no exposure to antibiotics in the last 3 months</th>
<th>Outpatient, patient with co-morbidity or exposure to antibiotics in the last 3 months</th>
<th>Inpatient: Not in ICU</th>
<th>Inpatient: In ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
<td>√</td>
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<tr>
<td>Doxycycline</td>
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<tr>
<td>Levofloxacin</td>
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<tr>
<td>B-Lactam &amp; Macrolide</td>
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<tr>
<td>B-Lactam &amp; Lev</td>
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</table>
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 influenza 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 teichoic acids are highly inflammatory in CNS; CSF reveals high WBCs (neutrophils) 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; ceftriaxone 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
  o Pediatric (PCV, pneumococcal conjugate vaccine): 13 of most common serotypes; conjugated to diphtheria toxoid; prevents invasive disease
  o 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 immunofluorescence 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 and 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 fluorescent-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
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 fluorescent antibody) on biopsy, (+) by Dieterle silver stain
- Fourfold increase in antibody

**Treatment**: fluoroquinolone (levofloxacin) 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. a knight tournament – a 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 Mezzanine, Children on the Ground - 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.
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 can't 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
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
Chlamydia Trachomatis, Pneumonia, philapstitaci: 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 INFECTION 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. Reticulate 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 and sacroiliac joint. "can't see, can't 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, Ghan has a mucopusulent 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 Venereum - 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 cephraxone
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.
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**

<table>
<thead>
<tr>
<th>Overview</th>
<th></th>
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<tbody>
<tr>
<td>- Amoxicillin-Clavulanic acid. Beta Lactams are sometimes combined with beta lactamase inhibitors such as: clavulanic acid.</td>
<td></td>
</tr>
<tr>
<td>- 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.</td>
<td></td>
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<tr>
<td>- Act on both gram +ve and gram –ve microorganisms.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MOA</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>- Inhibit bacterial wall synthesis through inhibition of peptidoglycan layer on the cell wall.</td>
<td></td>
</tr>
<tr>
<td>- Bactericidal</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Given orally or parenterally</td>
<td></td>
</tr>
<tr>
<td>- Not metabolized in human</td>
<td></td>
</tr>
<tr>
<td>- Relatively lipid insoluble</td>
<td></td>
</tr>
<tr>
<td>- Excreted mostly unchanged in urine</td>
<td></td>
</tr>
<tr>
<td>- Probenecid slows their elimination and prolongs their half life by inhibiting the renal excretion of penicillin.</td>
<td></td>
</tr>
<tr>
<td>- Half-life: 30-60 min (increased in renal failure)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical uses</th>
<th>URTIs &amp; LRTIs</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ADRs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypersensitivity reactions nausea and vomiting as a start, followed by urticaria, laryngeal edema, and finally anaphylactic shock and cardiovascular collapse.</td>
<td></td>
</tr>
<tr>
<td>- Diarrhea</td>
<td></td>
</tr>
<tr>
<td>- Superinfections an infection that occurs as a result of killing the normal.</td>
<td></td>
</tr>
<tr>
<td>- Nephritis flora along with the pathogen after using antibiotics (especially broad spectrum antibiotics)</td>
<td></td>
</tr>
<tr>
<td>- Convulsions (after high I.V dose or in renal failure)</td>
<td></td>
</tr>
</tbody>
</table>
## 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**
<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td>Cefuroxime, Cefaclor</td>
<td>Ceftriaxone, Cefotaxime, Cefixime</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Inhibits bacterial protein synthesis by binding to 50S subunit of the bacterial ribosomal RNA.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- They are bacteriostatic, but when used at higher concentration → bactericidal.</td>
<td></td>
</tr>
<tr>
<td>Half life</td>
<td>6-8 hours</td>
<td>3 days</td>
</tr>
<tr>
<td>Dose</td>
<td>Twice a day</td>
<td>One dialy</td>
</tr>
<tr>
<td>Antibacterial Spectrum</td>
<td>More effective on G+ve bacteria</td>
<td>More effective on G-ve bacteria</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Stable at gastric acidity.</td>
<td>- Stable at Gastric Acidity.</td>
</tr>
<tr>
<td></td>
<td>- Inhibition cytochrome P450 system.</td>
<td>- No effect on cytochrome P-430.</td>
</tr>
<tr>
<td></td>
<td>- Metabolized in liver to active metabolites.</td>
<td>- Undergo Some Hepatic Metabolism (inactive metabolite)</td>
</tr>
<tr>
<td></td>
<td>- Biliary route is the major route of elimination.</td>
<td>- Biliary route Is The major route of elimination.</td>
</tr>
<tr>
<td></td>
<td>- Only 10-15% excreted unchanged in the urine.</td>
<td>Only 10-15% excreted unchanged the urine</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Chlamydial &amp; Legionella Pneumonia</td>
<td></td>
</tr>
<tr>
<td>ADRs</td>
<td>GI Disturbances: Nausea, Vomiting, abdominal cramps, diarrhea.</td>
<td>Hypersensitivity Reaction</td>
</tr>
</tbody>
</table>
# Fluoroquinolones

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Ciprofloxacin</th>
<th>Moxifloxacin Gatifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Block bacterial DNA synthesis by inhibiting DNA Gyrase enzyme (an enzyme involved in DNA supercoiling).</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Twice a day</td>
<td>One daily</td>
</tr>
<tr>
<td>Antibacterial Spectrum</td>
<td>G –ve bacteria highly active against Pseudomonas species</td>
<td>G –ve &amp; G +ve. highly active against Pseudomonas species</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Given orally or parenterally.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Di &amp; tri-valent cations interfere with its absorption. (divalent cation is a cation with +2 charge, like calcium, trivalent with +3 like aluminium).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Concentrate in many tissues (kidney, prostate, lung &amp; bones/joints) which means it can treat infections in these organs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Excretion mainly through the kidney.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Long half-life</td>
<td></td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Acute exacerbation of chronic obstructive pulmonary disease.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Community-acquired pneumonia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Legionella pneumonia</td>
<td></td>
</tr>
<tr>
<td>ADRs</td>
<td>GI Disturbances: Nausea, Vomiting, abdominal cramps, diarrhea.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hypersensitivity Reaction</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>Not recommended for patients younger than 18 years.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pregnancy &amp; Breastfeeding Women</td>
<td></td>
</tr>
</tbody>
</table>
**Aminoglycosides**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td></td>
</tr>
<tr>
<td>- Bactericidal antibiotics.</td>
<td></td>
</tr>
<tr>
<td>- Inhibits protein synthesis by binding to 30S ribosomal subunits</td>
<td></td>
</tr>
<tr>
<td><strong>Antibacterial Spectrum</strong></td>
<td>Only active against Gram –Ve Aerobic organisms</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
</tr>
<tr>
<td>- Given parenterally (IM, IV) poorly absorbed orally.</td>
<td></td>
</tr>
<tr>
<td>- Cross placenta contraindicated in pregnancy, may cause hearing loss.</td>
<td></td>
</tr>
<tr>
<td>- Excreted unchanged in urine.</td>
<td></td>
</tr>
<tr>
<td>- Half-life: 2-3 h &amp; increased to 24-48 h in renal impairment</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical uses</strong></td>
<td>Extreme infection caused by gram -ve organisms</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
<td></td>
</tr>
<tr>
<td>- Ototoxicity</td>
<td></td>
</tr>
<tr>
<td>- Nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td>- In very high doses → neuromuscular blockade that results in respiratory paralysis</td>
<td></td>
</tr>
</tbody>
</table>

*Note:* Other types of Aminoglycosides: Neomycin, streptomycin
**Tetracyclines**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Doxycycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>It inhibit protein synthesis by binding reversibly to 30-5 subunit of the bacterial ribosome.</td>
</tr>
<tr>
<td>Antibacterial Spectrum</td>
<td>Broad Spectrum Bacteriostatic. Active against many gram +ve and gram -ve bacteria</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- long acting</td>
</tr>
<tr>
<td></td>
<td>- Usually given orally</td>
</tr>
<tr>
<td></td>
<td>- Absorption is 90-100%. Absorbed in the upper small intestine &amp; best in absence of food.</td>
</tr>
<tr>
<td></td>
<td>- Food &amp; di &amp; tri-valent cations (Ca, Mg, Fe, Al) impair absorption it binds with Ca decreasing the absorption, patients should avoid dairy products.</td>
</tr>
<tr>
<td></td>
<td>- Protein binding 40-80 %</td>
</tr>
<tr>
<td></td>
<td>- Distributed well, including CSF</td>
</tr>
<tr>
<td></td>
<td>- Cross placenta and excreted in milk.</td>
</tr>
<tr>
<td></td>
<td>- Largely metabolized in the live</td>
</tr>
<tr>
<td>Clinical uses</td>
<td>Treatment of URTIs caused by S.pyogenes,  S.pneumonia &amp; H.influenza.</td>
</tr>
<tr>
<td>ADRs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Nausea, vomiting ,diarhea &amp; epigastric pain (given with food that doesn't contain dairy products)</td>
</tr>
<tr>
<td></td>
<td>- Thrombophlebitis if given IV</td>
</tr>
<tr>
<td></td>
<td>- Hepatic toxicity (prolonged therapy with high dose)</td>
</tr>
<tr>
<td></td>
<td>- Brown discolouration of teeth in children</td>
</tr>
<tr>
<td></td>
<td>- Deformity or growth inhibition of bones in children</td>
</tr>
<tr>
<td></td>
<td>- Phototoxicity in sun or light exposure</td>
</tr>
<tr>
<td></td>
<td>- Vertigo</td>
</tr>
<tr>
<td></td>
<td>- Superinfections.</td>
</tr>
<tr>
<td>Contraindications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pregnancy &amp; breastfeeding</td>
</tr>
<tr>
<td></td>
<td>- Children (below 10 years) because it causes bone deformities in newborns.</td>
</tr>
</tbody>
</table>
SECTION 3 | Respiratory fungal infection and aspergillosis

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.

Etiology:

Opportunistic

- Yeast
- Mould fungi

Primary infections

Dimorphic fungi:
- Histoplasma capsulatum
- Blastomyces dermatitidis
- Paracoccidioides brasiliensis
- Coccidioides immitis

- Candida → Candidiasis
- Cryptococcus neoformans and C. gattii → Cryptococcosis
- Aspergillus species → Aspergillosis
- Zygomycetes, Rhizopus and Mucor → Zygomycosis
- Other mould

Note: Cryptococcosis Usually seen in meningitis rather than respiratory
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

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. fumigatus → most virulent
- A. flavus → most common in Riyadh
- A. niger
- A. terreus
- A. nidulans
Respiratory fungal infection and aspergillosis

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**.

Treatment:
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

<table>
<thead>
<tr>
<th>Signs &amp; symptom</th>
<th>Cough</th>
<th>Hemoptysis</th>
<th>Fever</th>
<th>Leukocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Radiology: will show lesions with halo sign.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Chronic Aspergillosis (Colonizing Aspergillosis)

<table>
<thead>
<tr>
<th>Types</th>
<th>Aspergilloma of lung</th>
<th>Maxillary (sinus) aspergilloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>Aspergilloma, which is also known as (Aspergillus fungus ball).</td>
<td></td>
</tr>
<tr>
<td>Signs &amp; symptom</td>
<td>Dry cough</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Radiology: will show mass in the lung. radiolucent crescent air surround the mass.</td>
<td></td>
</tr>
</tbody>
</table>

### Allergic

<table>
<thead>
<tr>
<th>Types</th>
<th>Allergic bronchopulmonary</th>
<th>Aspergillosis (ABPA)</th>
<th>Allergic Aspergillus sinusitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs &amp; symptom</td>
<td>Symptoms of Asthma</td>
<td>Bronchial obstruction</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Skin test reactivity to Aspergillus</td>
<td>Serum antibodies to Aspergillus.</td>
<td>Serum IgE&gt; 1000 ng/m</td>
</tr>
</tbody>
</table>

### Persistence without disease

| Signs & symptom | Colonisation of the airways or nose/sinuses. |
Respiratory fungal infection and aspergillosis

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
Respiratory fungal infection and aspergillosis

Aspergillus niger black-brownish

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, hemoptyisis. 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

---

**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, Absidia (Zygomycophyta)**

- Opportunistic Fungi
- Nonseptate filamentous fungi
- Environmental Source: soil; sporangiospores are inhaled

Disease.

- These fungi penetrate without respect to anatomical barriers, progressing rapidly from sinuses 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 immediately. Fatality rate is high due to rapid growth and invasion
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 fluids or biopsy.
- Treatment is trimethoprim/sulfamethoxazole for mild disease and dapsone for moderate/severe disease.

![Figure II-3-23. Pneumocystis, Silver Stain, Exudate](image-url)
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 - Bronchoalvar 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
Aspergilus 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 - Conidiophores 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
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
## Middle and Lower Respiratory System Infections

<table>
<thead>
<tr>
<th>Type Infection</th>
<th>Case Vignette/Key Clues</th>
<th>Most Common Causal Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory difficulty or obstruction</strong></td>
<td>Inflamed epiglottis; patient often 2–3 and unvaccinated</td>
<td><em>Haemophilus influenzae</em> (epiglottitis)</td>
</tr>
<tr>
<td></td>
<td>Infant with fever, sharp barking cough, inspiratory stridor, hoarse phonation</td>
<td>Parainfluenza virus (Croup)</td>
</tr>
<tr>
<td><strong>Pneumonia Typical: high fever, productive cough, diffuse infiltrates</strong></td>
<td>Poorly nourished, unvaccinated baby/child; giant cell pneumonia with hemorrhagic rash</td>
<td>Measles: malnourishment ↑ risk of pneumonia and blindness</td>
</tr>
<tr>
<td></td>
<td>Adults (including alcoholics) #1 CA Rusty sputum, often follows influenza</td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Neutropenic pts, burn pts, CGD, CF</td>
<td><em>Pseudomonas</em></td>
</tr>
<tr>
<td></td>
<td>Foul smelling sputum, aspiration possible</td>
<td>Anaerobes, mixed infection <em>(Bacteroides, Fusobacterium, Peptococcus)</em></td>
</tr>
<tr>
<td></td>
<td>Alcoholic, abscess formation, aspiration, facultative anaerobic, gram-negative bacterium with huge capsule, currant jelly sputum</td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Nosocomial, ventilator, post-influenza, Abscess formation, Gram +, catalase +, coagulase + Salmon-colored sputum</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><strong>Atypical: low fever, dry cough, diffuse infiltrates</strong></td>
<td>Pneumonia teens/young adults; bad hacking cough; initially non-productive cough</td>
<td><em>Mycoplasma pneumoniae</em> (most common cause of pneumonia in school age children)</td>
</tr>
<tr>
<td></td>
<td>Atypical with air conditioning exposure especially &gt;50 yr, heavy smoker, drinker</td>
<td><em>Legionella spp.</em></td>
</tr>
<tr>
<td></td>
<td>Atypical with bird exposure, hepatitis</td>
<td><em>Chlamydophila psittaci</em></td>
</tr>
<tr>
<td></td>
<td>AIDS patients with staccato cough; “ground glass” x-ray; biopsy: honeycomb exudate with silver staining cysts, progressive hypoxia</td>
<td><em>Pneumocystis jirovecii</em></td>
</tr>
</tbody>
</table>
## Middle and Lower Respiratory System Infections

<table>
<thead>
<tr>
<th>Type Infection</th>
<th>Case Vignette/Key Clues</th>
<th>Most Common Causal Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress</td>
<td>Travel to Far East, winter, early spring, hypoxia</td>
<td>SARS-CoV</td>
</tr>
<tr>
<td></td>
<td>Spring, 4 corners region, exposure to rodents</td>
<td>Hanta virus</td>
</tr>
<tr>
<td>Acute pneumonia or chronic cough with weight loss,</td>
<td>Over 55, HIV+, or immigrant from developing country</td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>night sweats, calcifying lesions</td>
<td>Dusty environment with bird or bat fecal contamination (Missouri chicken farmers), yeasts packed into phagocytic cells</td>
<td><em>Histoplasma capsulatum</em></td>
</tr>
<tr>
<td></td>
<td>Desert sand, SW U.S.</td>
<td><em>Coccidioides immitis</em></td>
</tr>
<tr>
<td></td>
<td>Rotting contaminated wood, North and South Carolina</td>
<td><em>Blastomyces dermatitidis</em></td>
</tr>
</tbody>
</table>
**Objective**

- Know the epidemiology of lung cancer
- Know the classification of bronchogenic carcinoma which include: squamous carcinoma, adenocarcinoma, small cell and large cell (anaplastic) carcinomas.
- Understand the predisposing factors of bronchogenic carcinoma.
- Understands the clinical features and gross pathology of bronchogenic carcinoma.
- Know the precursors of squamous carcinoma (squamous dysplasia) and adenocarcinoma (adenocarcinoma in situ and atypical adenomatous hyperplasia).
- Know about neuroendocrine tumors with special emphasis on small cell carcinoma and bronchial carcinoid.
- 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.

**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.

Malignant Lung Tumor

### Lung Tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Small Cell Lung Carcinoma (70%-75%)</td>
<td></td>
</tr>
<tr>
<td>Small cell lung carcinoma (20%-25%)</td>
<td></td>
</tr>
<tr>
<td>Combine patterns (5%-10%)</td>
<td></td>
</tr>
<tr>
<td>Carcinoid tumours</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma (25%-35%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma, including bronchidoalveolar carcinoma (30%-35%)</td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma (10%-15%)</td>
<td></td>
</tr>
<tr>
<td>Mixed squamous cell carcinoma and adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Mixed squamous cell carcinoma &amp; SCLC</td>
<td></td>
</tr>
<tr>
<td>Benign cancer arising from Neuroendocrine cells</td>
<td></td>
</tr>
</tbody>
</table>

Note:
The majority of lung cancers are NSCLC and SCLC, and the most common lung cancer out of bronchogenic carcinomas is adenocarcinoma.
Respiratory Chapter

SECTION 3 | Tumors of the lung

Bronchogenic carcinoma:
A common cause of cancer death in both men and women. For therapeutic purposes, bronchogenic carcinoma are classified into:

<table>
<thead>
<tr>
<th>NSCLC</th>
<th>SCLC</th>
</tr>
</thead>
</table>
| o **Surgical**: offers the best chance for curing.  
 o **Radiation**: controls local disease. It's used to palliate symptoms.  
 o **Chemotherapy**: not effective  
 o Monoclonal therapy nowadays. | o **Chemotherapy** is very effective because SCLC are highly responsive to chemotherapy  
 o **Surgery** is not effective because it's usually detected late, after metastasis. |

<table>
<thead>
<tr>
<th>Central tumors (related to smoking)</th>
<th>Peripheral tumors (related to scar)</th>
</tr>
</thead>
</table>
| o Squamous cell carcinoma  
 o Small cell carcinoma | o Adenocarcinoma:  
 - Bronchial derived  
 - Bronchioalveolar CA  
 o 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:

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.
   - Composed entirely of dysplastic cells growing along preexisting alveolar septa without rupturing it (Atypical glandular cells line the alveoli along the basement membrane → hyperplasia).
   - Lepidic growth pattern but once invasive (>3 cm) it forms desmoplasia (fibrosis).
   - No feature of necrosis or invasion.

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: Adrenocorticotrophic 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**
SECTION 3  |  Tumors of the lung

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 destruction 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.
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

- Small cell lung carcinoma (SCC) (20%-25%)
  - Simple staging due to its aggressiveness and fast growth and metastasis

- Non Small cell carcinomas
  - TNM staging system
    - T: Size of the Tumor
    - N: Lymph nodes involvement
    - M: Metastasis
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%).

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 $\rightarrow$ leading to Cushing's syndrome. ADH $\rightarrow$ 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:

- 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.

<table>
<thead>
<tr>
<th>Type of infusion</th>
<th>Pathogenesis</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transude → Less than 30g protein/L</td>
<td>Increased hydrostatic P</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Decreased oncotic P</td>
<td>○ Vena caval obstruction ○ Hypoalbuminemia</td>
</tr>
<tr>
<td>Exudate → More than 30g protein/L</td>
<td>Infections</td>
<td>Bacterial (e.g. TB)</td>
</tr>
<tr>
<td></td>
<td>Neoplasm</td>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td></td>
<td>Pulmonary infarction</td>
<td>Thromboembolism disease</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disease</td>
<td>Rheumatoid disease Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Abdominal disease</td>
<td>Pancreatitis Subphrenic abscesses</td>
</tr>
</tbody>
</table>
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?

<table>
<thead>
<tr>
<th>Small cell carcinoma (15% of all lung carcinoma)</th>
<th>Non-small cell carcinoma (85% of all lung carcinoma)</th>
</tr>
</thead>
</table>
| Usually no amenable to surgery (treat with chemotherapy and radiation) | • 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%) |

Treat upfront with surgery (doesn't respond well to chemotherapy)

What are different types of lung cancer?

<table>
<thead>
<tr>
<th>S.N</th>
<th>Cancer type</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Small Cell carcinoma</td>
<td>Treat with chemotherapy</td>
</tr>
<tr>
<td>2</td>
<td>Non-small cell carcinoma</td>
<td><strong>Subtype</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bronchoalveolar carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Adenocarcinoma in situ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Large cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Bronchial) carcinoid tumor</td>
</tr>
<tr>
<td>3</td>
<td>Mesothelioma</td>
<td>related to asbestos</td>
</tr>
<tr>
<td>4</td>
<td>Metastasis</td>
<td>Common origin of metastasis - breast, colon</td>
</tr>
</tbody>
</table>
### Lung Cancer

#### Classify the different types of lung cancer

<table>
<thead>
<tr>
<th>Neuroendocrine (NE) tumor</th>
<th>Adenocarcinoma</th>
<th>Related to smoking: small, large, squamous, adeno</th>
<th>Paraneoplastic syndrome</th>
<th>Undifferentiated and poor prognosis</th>
<th>Excellent prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma</td>
<td>Adenocarcinoma</td>
<td>Squamous cell carcinoma (most common in male smokers)</td>
<td>Squamous cell carcinoma (PTHrp)</td>
<td>Small cell carcinoma</td>
<td>Bronchoalveolar carcinoma</td>
</tr>
<tr>
<td>(Bronchial) carcinoid tumor (well differentiated NE cells)</td>
<td>Bronchioalveolar carcinoma (adenocarcinoma in situ)</td>
<td>Small cell carcinoma (male smokers)</td>
<td>Small cell carcinoma (ADH, ACTH, Ab for Ca channel)</td>
<td>Large cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>• Adenocarcinoma (most common in female smokers and non-smokers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• bronchoalveolar carcinoma not associated with smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Describe the following types of cancer.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Histology</th>
<th>Association</th>
<th>Location</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| 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 ACTH  
                          • Produces ADH  
                          • Produces Ab for Eaton-Lambert syndrome (presynaptic Ca channel Ab) (paraneoplastic syndromes)  
                          • Anti-neuronal antibody syndrome (limbic encephalitis, cerebellar degeneration, opsoclonus, GI dysmotility, poly radiculopathy)  
                          • Amplification of myc oncogene  
                          • LOVES TO GO TO BRAIN - give prophylactic cranial irradiation  
                          • MOST AGGRESSIVE TYPE OF LUNG CANCER |
| Adenocarcinoma       | Glands or mucin            | Most common tumor in nonsmokers and female smokers | Peripheral |                                                                                      |

Fig: glandular structure in adenocarcinoma
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Histology</th>
<th>Association</th>
<th>Location</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>Keratin pearls or intercellular bridges (by definition)</td>
<td>Most common tumor in male smoker</td>
<td>Central</td>
<td>• May produce PTHrp (paraneoplastic syndrome)</td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="keratin pearl" /></td>
<td></td>
<td><img src="image2" alt="intracellular bridge" /></td>
<td>• Hilar mass from bronchus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Associated with double C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o HyperCalcemia- due to PTHrp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o Cavitation</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>Poorly differentiated and highly anaplastic cells (no keratin pearls, intercellular bridges, glands or mucin)</td>
<td>Smoking</td>
<td>Central or peripheral</td>
<td>• Poor prognosis</td>
</tr>
<tr>
<td>(Bronchial) Carcinoid tumor</td>
<td><img src="image3" alt="chromogranin positivity" /></td>
<td>Not related to smoking</td>
<td>Central or peripheral</td>
<td>• Poor response to chemotherapy; remove surgically</td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="chromogranin positivity" /></td>
<td></td>
<td></td>
<td>• Paraneoplastic – may secrete B-HCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• MOST COMMON PRIMARY LUNG CANCER IN CHILDREN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 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</td>
</tr>
</tbody>
</table>
### Lung Cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Histology</th>
<th>Association</th>
<th>Location</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Bronchiol oalveolar carcinoma (adenocarcinoma in situ) | Columnar cells that grow along preexisting bronchioles and alveoli; arise from clara cells | 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 |                                                                         |
| Mesothelioma                            | 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. Metastasis from other cancers is common in lung
2. Prevalence: breast, renal, and colon cancers
3. Risk factors: smoking, radon, asbestos, and silica exposure
4. Symptoms: cough, chest pain, shortness of breath, weight loss, and fatigue
5. Staging:
   - T: tumor size
   - N: lymph node involvement
   - M: metastasis

3.2 + Small Cell Carcinoma
1. Small, round, undifferentiated cells
2. High mitotic rate and rapid growth
3. Often arises in the bronchial tree
4. Common in smokers

3.3 + Non-Small Cell Carcinoma
1. Divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma
2. Adenocarcinoma: most common type
3. Squamous cell carcinoma: arises from the bronchial epithelium
4. Large cell carcinoma: least common type

3.4 + Pancoast Tumor (Pancoast Syndrome)
1. Arises in the upper lobe of the lung
2. Involves the brachial plexus and cervical spinal nerves
3. Symptoms: arm pain, numbness, and weakness

3.5 + Metastatic Tumors to the Lung
1. Common metastases: breast, prostate, and lungs
2. Symptoms: cough, hemoptysis, and weight loss
3. Treatment: chemotherapy, surgery, and palliative care

3.6 + Pulmonary Embolism
1. Occurs when a clot from the legs travels to the lungs
2. Symptoms: sudden shortness of breath, chest pain, and cough
3. Treatment: anticoagulation and thrombolytics

3.7 + Pulmonary Hypertension
1. Increased pressure in the pulmonary arteries
2. Symptoms: shortness of breath, chest pain, and fatigue
3. Treatment: medication, surgery, and oxygen therapy

3.8 + Bronchiectasis
1. Dilated bronchi due to chronic inflammation
2. Symptoms: chronic cough, sputum production, and wheezing
3. Treatment: antibiotics, airway clearance, and surgery

3.9 + Pulmonary Fibrosis
1. Scarring and inflammation of the lungs
2. Symptoms: shortness of breath, cough, and fatigue
3. Treatment: oxygen therapy, medication, and lung transplantation

3.10 + Primary Lung Tumors
1. Benign tumors: cysts, lipomas, and hamartomas
2. Malignant tumors: adenocarcinoma, squamous cell carcinoma, and small cell carcinoma
3. Treatment: surgery, chemotherapy, and radiation therapy

3.11 + Pulmonary Vein Stenosis
1. Narrowing of the pulmonary veins
2. Symptoms: shortness of breath, cough, and fatigue
3. Treatment: medical management and possibly surgical intervention

3.12 + Pulmonary Arterial Hypertension
1. Increased pressure in the pulmonary arteries
2. Symptoms: shortness of breath, chest pain, and fatigue
3. Treatment: medication, surgery, and oxygen therapy

3.13 + Pulmonary Edema
1. Fluid accumulation in the lungs
2. Symptoms: shortness of breath, cough, and fever
3. Treatment: diuretics, oxygen therapy, and vasodilators

3.14 + Pulmonary HTN
1. Increased pressure in the pulmonary arteries
2. Symptoms: shortness of breath, chest pain, and fatigue
3. Treatment: medication, surgery, and oxygen therapy

3.15 + Pulmonary Edema
1. Fluid accumulation in the lungs
2. Symptoms: shortness of breath, cough, and fever
3. Treatment: diuretics, oxygen therapy, and vasodilators

3.16 + Pulmonary Fibrosis
1. Scarring and inflammation of the lungs
2. Symptoms: shortness of breath, cough, and fatigue
3. Treatment: oxygen therapy, medication, and lung transplantation

3.17 + Pulmonary Hypertension
1. Increased pressure in the pulmonary arteries
2. Symptoms: shortness of breath, chest pain, and fatigue
3. Treatment: medication, surgery, and oxygen therapy

3.18 + Pulmonary Edema
1. Fluid accumulation in the lungs
2. Symptoms: shortness of breath, cough, and fever
3. Treatment: diuretics, oxygen therapy, and vasodilators

3.19 + Pulmonary Hypertension
1. Increased pressure in the pulmonary arteries
2. Symptoms: shortness of breath, chest pain, and fatigue
3. Treatment: medication, surgery, and oxygen therapy

3.20 + Pulmonary Edema
1. Fluid accumulation in the lungs
2. Symptoms: shortness of breath, cough, and fever
3. Treatment: diuretics, oxygen therapy, and vasodilators
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

**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 & pleura

Content:
- Thymus gland
- Lymph nodes
Anatomy of Mediastinum

### 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
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
Respiratory Chapter

SECTION 3
Anatomy of Mediastinum

**Lymphatic vessels in thorax**

- Lymph from the right side of the head, neck, 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, neck, 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.

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 structures 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
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](image-url)
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.
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.
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).
- Sometimes it's 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.
- 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 a 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.
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-2-50. Chest: CT, T4

Figure II-2-51. Chest: CT, T5
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
SECTION 4: MISCELLANEOUS

BIOCHEMISTRY:
Phospholipids of physiological significance

RESPIRATORY CHAIN

PHYSIOLOGY:
Effects of low and high gas pressure on the body

PHYSIOLOGY:
Effect of Exercise on respiratory

PHARMACOLOGY:
Anti-cholinergic drugs

PHARMACOLOGY:
Adrenergic drugs

PHARMACOLOGY:
Anaphylactic shock

FAMILY MEDICINE:
Tobacco smoking
Phospholipids of clinical significance

What are phospholipids?
Major lipids of cell membranes, they are polar, ionic compounds that contain an alcohol group attached either to:
- Diacylglycerol \( \rightarrow \) Glycerophospholipids
- Sphingosine \( \rightarrow \) Sphingophospholipids.

Properties:
They are Amphipathic which have two components
- Phospho=Hydrophilic = polar which means interacting with the aqueous environment
- Lipid = Hydrophobic = non-polar which is 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)

<table>
<thead>
<tr>
<th>Consist of</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphatidylserine (PS)</td>
<td>Serine + PA</td>
</tr>
<tr>
<td>Phosphatidylethanolamine (PE) (cephalin)</td>
<td>Ethanolamine + PA</td>
</tr>
<tr>
<td>Phosphatidylcholine (PC) (lecithin)</td>
<td>Choline + PA</td>
</tr>
<tr>
<td>Phosphatidylinositol (PI)</td>
<td>Inositol + PA</td>
</tr>
<tr>
<td>Phosphatidylglycerol (PG)</td>
<td>Glycerol + PA * by phosphodiester bond</td>
</tr>
</tbody>
</table>

[Diagram of membrane structure and lipid composition]

[Image of phospholipid structures with chemical formulas and functions]
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

- **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
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.
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**
- **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**
- **Structure:** 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**
Phospholipids of clinical significance

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)

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.

Extra Explanation:
Phospholipases D: involved in signal transduction, generating phosphatidic acid and choline from phosphatidylcholine and diacylglycerol.
**In Summary:**

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.
SECTION 4  |  Respiratory chain

Objective

1. Understand how energy-rich molecules including glucose are metabolized by series of oxidation-reduction reactions ultimately yielding CO₂ 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 bc₁

**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:
  - F₁: Extra-membranous domain (In the mitochondrial matrix)
  - F₀: Membrane spanning domain (In the intermembrane space), it is called Fo because it can be inhibited by oligomycin

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 = 7.3 kcal/mol, and it is the energy 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.

**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)

**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**

- 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.
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.
- 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).

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.

These problems confront SCUBA (Self Contained Underwater Breathing Apparatus.)
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.

Nitrogen effect at high pressure:
Nitrogen is the most element among respiratory elements that’s affected by Henry’s law.
- Henry’s 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.

![Image of graph showing oxygen-hemoglobin dissociation curve]

*Figure 45-2.* Quantity of O2 dissolved in the fluid of the blood and in combination with hemoglobin at very high Po2 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.

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 $\frac{1}{4}\text{ - }\frac{1}{5}$ the narcotic effect of nitrogen on CNS.
- It is $\frac{1}{7}$ the molecular weight of nitrogen.
- Low density leading to decreased airway resistance of diver.
- Helium is about $\frac{1}{2}$ 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.
Alveolar PO\textsubscript{2} at different altitudes:
- As the barometric pressure decreases, the oxygen partial pressure (PO\textsubscript{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 it is 40 mmHg and it is only 18 mmHg at 50,000 feet.
- Even at high altitude CO\textsubscript{2} 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\textsubscript{2}:
A person remaining at high altitudes for days, weeks or years becomes more and more acclimatized to low PO\textsubscript{2}. 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\textsubscript{2} through increased number of mitochondria and oxidative enzymes activity.
  - Increased red blood cells.

(If there is a decrease in O\textsubscript{2} the kidney will respond by producing Erythropoietin which will go to the bone marrow and synthesize RBCs + Hb, so more O\textsubscript{2} will be carried on Hb and more O\textsubscript{2} 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 alveolar PO2, those 2 values are also reduced; they are permanently depressed unless enriched oxygen is inspired. Therefore, PAO2 < 100 mm Hg, PaO2 < 100 mm Hg, and the low arterial PO2 stimulates the peripheral chemoreceptors and increases alveolar ventilation. At high altitude, then, the main drive for ventilation changes from CO₂ on the central chemoreceptors at sea level to a low PO2 drive of the peripheral chemoreceptors, and hyperventilation ensues.

<table>
<thead>
<tr>
<th></th>
<th>Acute Changes</th>
<th>Acclimatization</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAO2 and PaO2</td>
<td>decreased</td>
<td>remains decreased</td>
</tr>
<tr>
<td>PACO2 and PaCO2</td>
<td>decreased</td>
<td>remains decreased</td>
</tr>
<tr>
<td>Systemic arterial pH</td>
<td>increased</td>
<td>decreases to normal via renal compensation</td>
</tr>
<tr>
<td>Hb concentration</td>
<td>no change</td>
<td>increases (polycythemia)</td>
</tr>
<tr>
<td>Hb % sat</td>
<td>decreased</td>
<td>remains decreased</td>
</tr>
<tr>
<td>Systemic arterial O2 content</td>
<td>decreased</td>
<td>increases to normal</td>
</tr>
</tbody>
</table>

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% O₂ and 79% N₂), the partial pressure of O₂ and N₂ 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 N₂ 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 PAO₂, similar to hypoventilation. All the observations described here apply, except for PCO₂. At high altitude, a subject hyperventilates, and thus PACO₂ and PAO₂ are reduced.
**SECTION 4 | Effects of exercise on Respiration**

- Identify the development of the laryngotracheal (respiratory) diverticulum.
- Describe the effects of moderate and severe exercise on oxygen consumption, and ventilation volumes.
- Interpret the effects of exercise on arterial PO$_2$ and PCO$_2$.
- Define the diffusing capacity of the respiratory membrane, and its typical values at rest, and explain its changes in exercise.
- 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 increases.
- The depth of breathing increases 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:
- O$_2$ consumption and CO$_2$ formation may increase 20 folds.
- The arterial PO$_2$, PCO$_2$, 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 ventilation rate. (From Gray JS. Pulmonary Ventilation and Its Physiological Regulation. Springfield, IL: Charles C Thomas, 1950.)](image)
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

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

- Peripheral & Central Chemoreceptors
- Stretch Receptors in the Lung
- Proprioceptors in the Joint & Muscles
- Core Temperature
- Hypothalamus
- Respiratory control center (medulla & pons)
- Chemical state in blood (PO2 & PCO2 & H+)
- Plasma epinephrine & K+ concentration
- Motor cortex & Subcortical region
- Ventilatory muscles
Effects of exercise on Respiration

SECTION 4  |  Effects of exercise on Respiration

**Relation Between Chemical and Nervous Factors in the Control of Respiration During Exercise.**

 Boulder: 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 PCO₂-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 PCO₂ at the normal level of 40 mm Hg both in the resting state and during heavy exercise.]

304 | Respiratory Chapter
**Diffusion capacity of the respiratory membrane**

### O₂ diffusing capacity

- **During Rest:**
  Even if the oxygen pressure difference across the respiratory membrane is 11 mmHg — \(11 \times 21 = 230\) ml oxygen diffusing through the membrane each minute. So, 11 mmHg is the minimal pressure difference we need to maintain normal O₂ consumption. During rest tissues consume 250 ml O₂/min = \(12 \times 21\). 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.

### CO₂ 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, \(20 \times 21 = 400\) ml CO₂/min /mmHg.

- **During Exercise:**
  The diffusing capacity increase 3 times during exercise \(65 \times 20 = 1300\) ml/min/mmHg.
Effects of exercise on Respiration

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.

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
Classification of antibiotics.

- Misuses of antibiotics.
- Choice of antibiotics
- Bacterial resistance and ways to prevent it.
- General principles of antibiotic therapy.
- Indications for antibiotics prophylaxis

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:

- Narrow spectrum
  - penicillin G, aminoglycosides

- Broad spectrum
  - ampicillin, amoxicillin

- 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: They will not cure infections caused by viruses.

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

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
Choice of Antibiotic

Clinical diagnosis:
- e.g. Syphilis

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.

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)

2-Drug & Allergy.
- Pregnancy and Lactation:
  - Genetic factors: e.g. Patients with G-6-PD deficiency treated with *sulfonamides* (Hemolysis).
  - Extreme Age: Neonates and elderly
- Renal function: e.g. Aminoglycosides (renal failure)

Note:
- Microbiological information: a culture for the bacteria is done to test the sensitivity
- 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)

**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.

*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.
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:**
   - Higher cost
   - Possibility of antagonism
   - Increased risk of sensitivity or toxicity
   - Increased risk of colonization and infection with a resistant bacteria

2. **Exceptions where combining antibiotics is a good option:**
   - Desperately ill patient of unknown etiology
   - To prevent emergence of resistance (e.g. TB)
   - To achieve synergism e.g. piperacillin + gentamicin (pseudomonas aeruginosa)

**Usage of multiple antimicrobial**

**Indications for Antibiotics Prophylaxis:**

<table>
<thead>
<tr>
<th>Surgical prophylaxis</th>
<th>Immunosuppressed Patients</th>
<th>Dental extractions controversial</th>
</tr>
</thead>
</table>
| bowel surgery, joint replacement, etc. to prevent postoperative infections. | o Very old  
o Very young  
o Diabetics  
o Anaemics  
o AIDS  
o Cancer pts | o Pts with total joint replacements  
o Pts with cardiac abnormalities |
Objectives

- Describe the structures and functions of the conductive and respiratory zones of airways.
- Identify the classification of anticholinergic drugs.
- Describe pharmacokinetics and dynamics of muscarinic antagonists.
- Identify the effects of atropine on the major organ systems. List the clinical uses of muscarinic antagonists.
- Know adverse effects & contraindications of anticholinergic drugs.
- Identify at least one antimuscarinic agent for each of the following special uses: mydriasis, cyclopedia, peptic ulcer & parkinsonism.

Classification Anticholinergic drugs

According to Source:

<table>
<thead>
<tr>
<th>Natural</th>
<th>Synthetic / Semisynthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine (Hyoscyamine)</td>
<td>Homatropine (Semisynthetic)</td>
</tr>
<tr>
<td>Hyoscine (Scopolamine)</td>
<td>Tropicamide</td>
</tr>
</tbody>
</table>

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.

According to Structure:

<table>
<thead>
<tr>
<th>Tertiary amines “Lipid soluble”</th>
<th>Quaternary ammonium “Water soluble”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine (Hyoscyamine)</td>
<td>Glycopyrrolate</td>
</tr>
<tr>
<td>Hyoscine (Scopolamine)</td>
<td>Ipratropium</td>
</tr>
</tbody>
</table>

According to selectivity:

<table>
<thead>
<tr>
<th>Non-selective</th>
<th>Selective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine (Hyoscyamine)</td>
<td>Pirenzepine (M1)</td>
</tr>
<tr>
<td>Hyoscine (Scopolamine)</td>
<td>Darifenacin (M3)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td></td>
</tr>
</tbody>
</table>
Anticholinergic drugs | SECTION 4

**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 heart are intermediate.
- Atropine & hyoscine can block all muscarinic receptors because they are (not selective).

**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).

**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

**SECRETIONS:**
- ↓ 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)
## Anticholinergic drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Organ</th>
<th>Clinical uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benztropine &amp; Benhexol</td>
<td>CNS</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Hyoscine</td>
<td></td>
<td>Vomiting (Motion sickness) Preanesthetic</td>
</tr>
<tr>
<td>Tropicamide &amp; homatropine</td>
<td>Ophthalmic disorders</td>
<td>Ophthalmoscopical examination (Fundus examination) of retina</td>
</tr>
<tr>
<td>Atropine substitute with short duration of action</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Glycopyrrolate & Hyoscine butyl bromide | GIT | o Intestinal spasm.  
 o Biliary and renal colics.  
 o 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 and CNS    | Preanesthetic Sinus bradycardia                   |
| Cholinergic poisoning        |                | Mushroom poisoning.  
 Atropine reverses muscarinic effects of cholinergic poisoning.  
 Cholinesterase inhibitors (insecticides) |
| Sweating gland               |                | Hyperhydrosis “excessive sweating”                |

**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.
- Atropine IV/IM Used to increase heart rate through vagolytic effects, causing increase in cardiac output.
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.

**SECRETIONS**
- 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

<table>
<thead>
<tr>
<th>Target</th>
<th>receptor</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Sphincter Ciliary muscle</td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Heart</td>
<td>SA node AV node</td>
<td>( M_2 )&lt;br&gt;( M_1 )</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchioles&lt;br&gt;Glands</td>
<td>( M_3 )&lt;br&gt;( M_1 )</td>
</tr>
<tr>
<td>GI tract</td>
<td>Stomach&lt;br&gt;Gland&lt;br&gt;Intestine</td>
<td>( M_3 )&lt;br&gt;( M_1 )&lt;br&gt;( M_3 )</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Sphincter</td>
<td></td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Glands</td>
<td></td>
<td>( M_3 )</td>
</tr>
<tr>
<td>Blood vessels (endothelium)</td>
<td>( M_3 )</td>
<td>Dilation (via NO/endothelium-derived relaxing factor)-no innervation, no effects of indirect agonists</td>
</tr>
</tbody>
</table>

| \( M_1 \) and \( M_3 \) | \( G_q \) coupled | ↑ phospholipase C → ↑ IP<sub>3</sub>, DAG, Ca<sup>2+</sup> |
| \( M_2 \) | \( G_i \) coupled | ↓ adenyl cyclase → ↓ cAMP |
| \( N_N \) and \( N_M \) | No 2<sup>nd</sup> 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical and/or characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Antispasmodic, antisecretory, management of AChE inhibitor OD, antidiarrheal, ophthalmology (but long action)</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>Ophthalmology (topical)</td>
</tr>
<tr>
<td>Ipratropium, tiotropium</td>
<td>Asthma and COPD (inhalational)-no CNS entry, no change in mucus viscosity</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Used in motion sickness, causes sedation and short-term memory block</td>
</tr>
<tr>
<td>Benztropine, trihexyphenidyl</td>
<td>Lipid-soluble (CNS entry) used in parkinsonism and in acute extrapyramidal symptoms included by antipsychotics</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Used in overactive bladder (urge incontinence)</td>
</tr>
</tbody>
</table>
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. Iris
  2. Accommodation (eyepiece)
- **Norepinephrine**
  1. Hypertonic
  2. Accommodation to far vision, leads to cycloplegia (paralysis of accommodation)

- **α1 agonists**
  1. HTN
  2. Less constriction

**Figure II-1-2. Autonomic Feedback Loop**

\[
BP = TPR \times CO \\
CO = HR \times SV
\]

<table>
<thead>
<tr>
<th>Needed for explanations of tracings</th>
<th>(\uparrow TPR (\uparrow \alpha_1))</th>
<th>reflex bradycardia ((\uparrow M_2))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\downarrow TPR (\uparrow \beta_2))</td>
<td>reflex tachycardia ((\uparrow \beta_1))</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>α2</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-synaptic</td>
<td>Pre-synaptic</td>
</tr>
<tr>
<td>o Inhibition of norepinephrine release</td>
<td>o Increase release of norepinephrine</td>
</tr>
<tr>
<td>(negative feedback mechanism)</td>
<td>(Positive feedback mechanism)</td>
</tr>
<tr>
<td>o How? this mainly happen by an Auto-</td>
<td></td>
</tr>
<tr>
<td>receptor 'presynaptic receptor' which is</td>
<td></td>
</tr>
<tr>
<td>present on the neuron releasing the</td>
<td></td>
</tr>
<tr>
<td>neurotransmitter itself, the neurotransmitter bind to the receptor of the same neuron it</td>
<td></td>
</tr>
<tr>
<td>was released by and inhibiting further release of the neurotransmitter, producing a</td>
<td></td>
</tr>
<tr>
<td>negative feedback mechanism)</td>
<td>o Increase release of norepinephrine</td>
</tr>
</tbody>
</table>
Adrenergic drugs | SECTION 4

### Post-synaptic:

<table>
<thead>
<tr>
<th>α1</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-synaptic located in tissue</strong> <em>(meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)</em></td>
<td></td>
</tr>
<tr>
<td>excitatory in function (cause contraction) except in GIT</td>
<td>inhibitory in function (cause relaxation)</td>
</tr>
<tr>
<td>Present mainly in smooth muscles</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraction of pregnant uterus</th>
<th>Relaxation of the uterus (Delay premature labor) also called tocolytic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction of skin &amp; peripheral blood vessels → increased peripheral resistance (resistance to blood flow due to constriction of blood vessels)→ hypertension. Agonists used as nasal decongestants.</td>
<td>Relaxation of skeletal &amp; coronary blood vessels (vasodilatation)</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>β1</th>
<th>β3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-synaptic located in tissue</strong> <em>(meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)</em></td>
<td>In adipose tissue</td>
</tr>
<tr>
<td>excitatory in function, present mainly in heart, juxtaglomerular cells of the kidney</td>
<td></td>
</tr>
<tr>
<td>↑ heart rate: chronotropic effect (Tachycardia)</td>
<td>↑ lipolysis</td>
</tr>
<tr>
<td>↑ force of contraction: + inotropic effect Increase cardiac output</td>
<td>↑ free fatty acids</td>
</tr>
<tr>
<td>↑ conduction velocity: + dromotropic effect (via A.V. node)(dromotropic effect means an effect in the speed of conduction of electrical impulses)</td>
<td></td>
</tr>
<tr>
<td>↑ blood pressure</td>
<td></td>
</tr>
<tr>
<td>↑ 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)</td>
<td></td>
</tr>
</tbody>
</table>
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:**

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Non-Catecholamines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly acting</td>
<td>Delayed action</td>
</tr>
<tr>
<td>Have short half-life, due to rapid degradation by MAO (Monoamine Oxidase) &amp; COMT (Catechol-O-MethylTransferase) in GIT</td>
<td>Have Long half-life, because they resist degradation by MOA &amp; COMT in GIT</td>
</tr>
<tr>
<td>Have catechol ring water soluble (polar), thus not effective orally and have Poor penetration to CNS</td>
<td>Lack catechol ring Lipid soluble, thus Effective orally and Cross BBB well, have Prominent CNS effects</td>
</tr>
<tr>
<td>Parenterally administered</td>
<td>Orally administered</td>
</tr>
<tr>
<td>Natural: Adrenaline, Noradrenaline, Dopamine Synthetic: Isoprenaline.</td>
<td>e.g. Ephedrine, amphetamine, phenylephrine.</td>
</tr>
</tbody>
</table>

- **According to MODE OF ACTION:**

<table>
<thead>
<tr>
<th>Direct-Acting</th>
<th>Indirect-Acting</th>
<th>Dual-Acting (Mixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate adrenergic receptors directly e.g. adrenaline, noradrenaline, dopamine, isoprenaline, phenylephrine, clonidine, dobutamine, salbutamol, methoxamine</td>
<td>Stimulate adrenergic receptors by: ↑noradrenaline release from presynaptic adrenergic nerve endings. e.g. amphetamine, Tyramine Or Inhibit uptake of noradrenaline e.g. Cocaine &amp; antidepressants</td>
<td>Direct and indirect stimulation of adrenergic receptors (mixed) e.g. ephedrine, pseudoephedrine</td>
</tr>
</tbody>
</table>

- **According to SPECTRUM OF ACTION:**

<table>
<thead>
<tr>
<th>Non-selective adrenergic agonist:</th>
<th>selective adrenergic agonist:</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Adrenaline (α1, α2, β1, β2, β3)</td>
<td>* Phenylephrine (α1)</td>
</tr>
<tr>
<td>* Noradrenaline (α1, α2, β1)</td>
<td>* α-Methyl Dop - clonidine (α2)</td>
</tr>
<tr>
<td>* Isoprenaline (β1, β2, β3)</td>
<td>* Dobutamine (β1)</td>
</tr>
<tr>
<td>* Dopamine (D1, β1, α1)</td>
<td>* Salbutamol, terbutaline, ritodrine (β2)</td>
</tr>
<tr>
<td>* Ephedrine</td>
<td></td>
</tr>
</tbody>
</table>
Adrenaline

Receptor:
Non-selective $\alpha_1; \alpha_2; \beta_1; \beta_2; \beta_3$

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 ($\beta_1$).
- **Blood pressure**:  
  - $\uparrow$ systolic ($\beta_1$) ($\alpha_1$)  
  - $\downarrow$ diastolic ($\beta_2$) and vasorelaxation.
- **Vascular**:  
  - Vasoconstriction of blood vessels in skin + peripheral ($\alpha_1$).  
  - Vasodilatation of blood vessels of skeletal muscles and coronaries ($\beta_2$).
- **Eye**: mydriasis ($\alpha_1$) $\rightarrow$ no effect on accommodation
- **Lung**: bronchodilatation ($\beta_2$)
- **GIT**: $\downarrow$ motility ($\beta_2$) / contract sphincter ($\alpha_1$)
- **Bladder**:  
  - relaxation of detrusor muscle ($\beta_2$)  
  - contraction of sphincter ($\alpha_1$)
- **CNS**: little (rare), headache, tremors & restlessness due to vasoconstrictor effects, less oxygen to brain cells
- **Pregnant uterus**: relaxation tocolytic effect ($\beta_2$), and cause relaxation of uterus “suppresses contractions” to prevent premature labor
- **Metabolism**:  
  - $\downarrow$ insulin ($\alpha_2$), $\uparrow$ glucagon ($\beta_2$)  
  - $\uparrow$ liver glycogenolysis +skeletal muscle glycolysis ($\beta_2$)  
  - $\uparrow$ adipose lipolysis ($\beta_3$)

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 (B2) + ↓ 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.)**

**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.

**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.
# Adrenergic drugs

## Direct acting Adrenergic Agonists

<table>
<thead>
<tr>
<th>Noradrenaline (Norepinephrine)</th>
<th>Isoprenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>overview</strong></td>
<td>o Synthetic direct acting catecholamine, and has very similar effects of Adrenaline</td>
</tr>
<tr>
<td></td>
<td>o shows no reuptake nor breakdown by MAO which leads to longer action.</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>o Parenteral in cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>o inhalation rarely in acute attack of asthma</td>
</tr>
<tr>
<td><strong>Receptor</strong></td>
<td>non-selective β agonist It Acts on β1, β2, β3</td>
</tr>
<tr>
<td></td>
<td>▶ β1:</td>
</tr>
<tr>
<td></td>
<td>o + inotropic effect</td>
</tr>
<tr>
<td></td>
<td>o + chronotropic effect</td>
</tr>
<tr>
<td></td>
<td>o increase cardiac output</td>
</tr>
<tr>
<td></td>
<td>▶ β2:</td>
</tr>
<tr>
<td></td>
<td>o Vasodilatation of blood vessels of</td>
</tr>
<tr>
<td></td>
<td>o skeletal muscles and coronaries</td>
</tr>
<tr>
<td></td>
<td>o Bronchodilatation</td>
</tr>
<tr>
<td></td>
<td>o Relaxation of uterus</td>
</tr>
<tr>
<td></td>
<td>o Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>▶ β3:</td>
</tr>
<tr>
<td></td>
<td>o lipolysis</td>
</tr>
<tr>
<td><strong>Pharmacological Action</strong></td>
<td>▶ Locally:</td>
</tr>
<tr>
<td></td>
<td>o Severe vasoconstriction (α1)</td>
</tr>
<tr>
<td></td>
<td>o Increase force of contraction but decrease H.R.</td>
</tr>
<tr>
<td></td>
<td>o Reflex bradycardia due to severe vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>▶ Systemically:</td>
</tr>
<tr>
<td></td>
<td>o hypotensive states:</td>
</tr>
<tr>
<td></td>
<td>o in spinal anesthesia, especially in birth via C-section.</td>
</tr>
<tr>
<td></td>
<td>o in septic shock (hypotension) if fluid replacement and inotropic fail.</td>
</tr>
<tr>
<td></td>
<td>▶ Uses:</td>
</tr>
<tr>
<td></td>
<td>o Used mainly in cardiac arrest (Parenteral).</td>
</tr>
<tr>
<td></td>
<td>o Rarely in acute attack of asthma (inhalation).</td>
</tr>
<tr>
<td></td>
<td>▶ Contraindications:</td>
</tr>
<tr>
<td></td>
<td>o In hyperthyroidism &amp; Congestive heart disease CHD</td>
</tr>
</tbody>
</table>

**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.
### Direct acting Adrenergic Agonists

<table>
<thead>
<tr>
<th>Overview</th>
<th>Dopamine</th>
<th>Dobutamine</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural catecholamine &amp; CNS neurotransmitter.</td>
<td>• Direct acting.</td>
<td>• Synthetic non catecholamine</td>
<td>• Synthetic non catecholamine</td>
</tr>
<tr>
<td>Released from postganglionic adrenergic fibres.</td>
<td>• Decrease BP</td>
<td>• Direct acting.</td>
<td>• Direct acting.</td>
</tr>
<tr>
<td></td>
<td>• Increase BP</td>
<td>• Metabolized by COMT, thus has a short duration</td>
<td>• Has prolonged duration of action, since it's not inactivated by COMT</td>
</tr>
<tr>
<td>Administration</td>
<td>Given parenterally by infusion</td>
<td>IV</td>
<td>Orally</td>
</tr>
<tr>
<td>Receptor</td>
<td>D1 &gt; β1 &gt; α1 (in order)</td>
<td>Selective β1–agonist</td>
<td>Selective α1</td>
</tr>
<tr>
<td>Pharmacological Action</td>
<td>D1: Low dose:</td>
<td>On heart:</td>
<td>• increased both systolic &amp; diastolic blood pressure (hypertension) due to vasoconstriction (α1)</td>
</tr>
<tr>
<td></td>
<td>• Vasodilatation of mesenteric, coronary, renal blood vessels.</td>
<td>• +ve inotropic with little chronotropic effect. as it increases cardiac output and heart contractility.</td>
<td>• Reflex Bradycardia due to ↑ BP</td>
</tr>
<tr>
<td></td>
<td>• Diuresis (increase excretion of urine)</td>
<td>• On BP: Hardly any effect; β1 &amp; β2 counterbalance + no α1. since β1 agonists</td>
<td>• Adverse effects:</td>
</tr>
<tr>
<td></td>
<td>• Decrease BP</td>
<td>• increase BP, and β2 decrease it by vasodilatory effect)</td>
<td>± Hypertension.</td>
</tr>
<tr>
<td></td>
<td>β1: Intermediate dose:</td>
<td></td>
<td>• Midothrine. It peaks in 20 min, duration 30 min only.</td>
</tr>
<tr>
<td></td>
<td>• +ve inotropic</td>
<td></td>
<td>Systemically: Vasopressor (anti-hypotensive) agent in hypotension &amp; terminates atrial tachycardia by its reflex bradycardia action.</td>
</tr>
<tr>
<td></td>
<td>• +ve chronotropic effects</td>
<td></td>
<td>Topically:</td>
</tr>
<tr>
<td></td>
<td>• Increase BP</td>
<td></td>
<td>• Haemostatic with Local anesthesia.</td>
</tr>
<tr>
<td></td>
<td>α1: High dose:</td>
<td></td>
<td>• Mydriatic (in ophthalmic solutions to facilitate eye examination).</td>
</tr>
<tr>
<td></td>
<td>• Vasoconstriction</td>
<td></td>
<td>• Nasal decongestant “vasoconstriction” topically, nasal drops in allergic rhinitis, cold.</td>
</tr>
</tbody>
</table>

### 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.

### Note:
- Phenylephrine
  - Hypertension is one of its Adverse effects. Thus, another drug is more preferable to produce hypertension that doesn’t last for long.
- Pharyngitis:记得虹膜括约肌“aka: constrictor pupillae, circular muscle of iris” decreases IOP when contracted.
# Direct acting Adrenergic Agonists

<table>
<thead>
<tr>
<th>Overview</th>
<th>Clonidine</th>
<th>Brimonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Imidazoline</td>
<td>Imidazoline</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration</th>
<th>Direct Acting Adrenergic Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orally or patch</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Direct Acting Adrenergic Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presynaptic $\alpha_2$ agonist</td>
<td>$\alpha_2$ agonist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacological Action</th>
<th>Direct Acting Adrenergic Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acts centrally ($\alpha_2$) at nucleus tractus solitarius to decrease sympathetic outflow to heart &amp; vessels.</td>
<td>Used in glaucoma as it reduces formation of aqueous humor and therefore decrease intraocular pressure (IOP).</td>
</tr>
<tr>
<td>Inhibit sympathetic vasomotor centers.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uses</th>
<th>Direct Acting Adrenergic Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive drug: used in essential hypertension to lower BP.</td>
<td></td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Overview</th>
<th>Salbutamol</th>
<th>Terbutaline</th>
<th>Ritodrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic non catecholamines</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration</th>
<th>Salbutamol</th>
<th>Terbutaline</th>
<th>Ritodrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orally, inhalation or injection</td>
<td></td>
<td>Orally or injection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Salbutamol</th>
<th>Terbutaline</th>
<th>Ritodrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective $\beta_2$ agonists</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacological Action</th>
<th>Salbutamol</th>
<th>Terbutaline</th>
<th>Ritodrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator for acute attacks of asthma &amp; COPD. N.B. Salmeterol &amp; Formoterol act longer</td>
<td>Bronchodilator &amp; Tocolytic</td>
<td>Tocolytic relaxation of uterus to treat premature labor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uses</th>
<th>Salbutamol</th>
<th>Terbutaline</th>
<th>Ritodrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 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. $\alpha_2$ agonists and antagonists
5. Agonists and blockers of $\alpha_1$ and $\beta_1$ 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 L- aromatic 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\textsuperscript{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

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α₁</strong></td>
<td></td>
</tr>
<tr>
<td>Eye: radial (dilator) muscle</td>
<td>Contraction: mydriasis</td>
</tr>
<tr>
<td>Arterioles (skin, viscera)</td>
<td>Contraction: ↑ TPR, ↑ diastolic pressure, ↑ afterload</td>
</tr>
<tr>
<td>Veins</td>
<td>Contraction: ↑ venous return, ↑ preload</td>
</tr>
<tr>
<td>Bladder trigone and sphincter and prostatic urethra</td>
<td>Contraction: urinary retention</td>
</tr>
<tr>
<td>Male sex organ</td>
<td>Vas deferens: ejaculation</td>
</tr>
<tr>
<td>Liver</td>
<td>↑ glycoegenolysis</td>
</tr>
<tr>
<td>Kidney</td>
<td>↓ renin release</td>
</tr>
</tbody>
</table>

| **α₂** | |
| Prejunctional nerve terminals | ↓ transmitter release and NE synthesis |
| Platelets | Aggregation |
| Pancreas | ↓ insulin secretion |

| **β₁** | |
| Heart SA node | ↑ HR (positive chronotropy) |
| AV node | ↑ conduction velocity (positive dromotropy) |
| Arterial and ventricular muscle | ↑ force of contraction (positive inotropy), conduction velocity, CO and oxygen consumption |
| His-Purkinje | ↑ automaticity and conduction velocity |
| Kidney | ↑ renin release |

| **β₂** | |
| Blood vessels (all) | Vasodilation: ↓ TPR: ↓ diastolic pressure, ↓ afterload |
| Ureter | Relaxation |
| Bronchioles | Dilatation |
| Skeletal muscle | ↑ glycoegenolysis: contractility (tremor) |

| **D₁ (peripheral)** | |
| Renal, mesenteric, coronary, vasculature | Vasodilation: in kidney ↑ RBF, ↑ GFR, ↑ Na⁺ secretion |
**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**

Fenoldopam is a D₁ agonist used for severe hypertension.

**Direct-acting adrenoceptor agonists**

**α₁ 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

**α₂ 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)
Adrenergic Neuroeffector Junctions

β agonist
Systemically, beta-agonists decrease mean BP via vasodilation (β₂)and and increase HR (β₁)

Drugs and uses:
- Isoproterenol (β₁ = β₂)
- Dobutamine (β₁ > β₂): congestive heart failure
- Selective β₂ agonists: salmeterol, albuterol, terbutaline (asthma); terbutaline (premature labor)

Mixed-acting agonists:
Norepinephrine Vs. Epinephrine
- Norepinephrine (α₁, α₂, β₁)
  
  Dose-dependent effects:
  Low-dose: β₂ stimulation (see Figure II-3-5a)
  High-dose: α₂, β₁(β₂) (see Figure II-3-5c)
Adrenergic Neuroeffector Junctions

**β2-specific effects**
Smooth muscle relaxation: bronchioles, uterus, blood vessels

**Metabolic effects:**
- \( \uparrow \) glycogenolysis (muscle and liver)
- \( \uparrow \) gluconeogenesis
- \( \uparrow \) mobilization and use of fat

**Differentiation of high-dose epinephrine versus norepinephrine:**
Epinephrine reversal: Use of \( \alpha_1 \) blocker to reverse hypertension to hypotension in a patient receiving too much epinephrine
Hypertension was due to predominant \( \alpha_1 \) tone on the vasculature
Hypotension results from unmasking \( \beta_2 \) receptors

**Uses of norepinephrine and epinephrine**
- Cardiac arrest
- Adjunct to local anesthetic
- Hypotension
- Anaphylaxis (epinephrine only)
- Asthma (epinephrine only)

**Indirect-acting adrenergic receptor agonists**

**RELEASES**
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 \( \uparrow \) 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 Anywhere (metabolizes NE, 5HT, and tyramine)
MAO type B: mainly in Brain (metabolizes DA)
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 α₁ blocker)

Drugs:
- Nonselective blocker: phentolamine (competitive inhibitor)
- phenoxybenzamine (noncompetitive inhibitor)
- Selective α₁ blocker: prazosin, doxazosin, terazosin, tamsulosin
- Selective α₂ blocker: mirtazapine (used as antidepressant)

β-receptor antagonists
- β₁ blockade
  - ↓ HR, ↓ SV, ↓ CO
  - ↓ renin release
- β₂ 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 β₁ receptors, but through glucagon receptors that are G-protein linked to adenyl cyclase → basis for its use in beta-blocker overdose.
Adrenergic Antagonists

Cardioselectivity ($\beta_1$):
- 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 ($\beta_1$)
- Slight vasodilation or bronchodilation ($\beta_2$)
- Minimal change in plasma lipids ($\beta_3$)
- 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, essential tremor (propranolol)

Combined alpha-1 and beta blocking activity:
- Labetalol and carvedilol
- Use in CHF (carvedilol) and in hypertensive emergencies (labetalol)
- $K^+$-channel blockade and $\beta$-blocking activity: sotalol

<table>
<thead>
<tr>
<th>Drugs</th>
<th>$\beta_1$-selective</th>
<th>ISA</th>
<th>Sedation</th>
<th>Blood lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Atenolol</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>↑↑</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>↑↑</td>
</tr>
<tr>
<td>Pindolol</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Propranolol</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>↑↑</td>
</tr>
<tr>
<td>Timolol</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Recall Question
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
Anaphylactic shock

- Perceive the differences between anaphylactic shock and other types of shock.
- Recognize its nature, causes & characteristics.
- Specify its diagnostic features.
- Identify its standard emergency management protocol.
- 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
  - **Mucous swelling**
    - Rhinitis 16%
    - Airway 56%
    - Angioedema 88%
    - GIT 30%
  - **Blood vessels**
    - Vasodilation
    - Leakiness
    - Hypo-perfusion
  - **Heart**
    - ↓Output
    - ↓Coronary flow
    - Circulatory Collapse
  - **Skins**
    - Pruritus
    - Urticaria
    - Edema

**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:

<table>
<thead>
<tr>
<th>Life Threatening Problems</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airway</strong>: swelling, hoarseness, stridor.</td>
<td><strong>Respiratory support</strong></td>
</tr>
<tr>
<td><strong>Breathing</strong>: rapid breathing, wheezing, cyanosis, fatigue, confusion, oxygenated Hb (SpO2) &lt; 92%</td>
<td></td>
</tr>
<tr>
<td><strong>Circulation</strong>: pale, clammy, low BP, faintness, drowsy/coma.</td>
<td><strong>Circulatory support</strong></td>
</tr>
<tr>
<td>• Adrenaline (give IM by Auto injector or by syringe, unless there is a specialist to give IV)</td>
<td></td>
</tr>
<tr>
<td>• IV fluid challenge, Crystalloid is given for children to increase the blood plasma level.</td>
<td></td>
</tr>
<tr>
<td><strong>1st Line Therapy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td></td>
</tr>
<tr>
<td>• Chlorpheniramine (first generation H1 blocker) (IM or slow IV).</td>
<td></td>
</tr>
<tr>
<td>• Hydrocortisone (Glucocorticoid) (IM or slow IV).</td>
<td></td>
</tr>
</tbody>
</table>

**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.
### Adrenaline  
**(A Sympathomimetic)**

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nonselective</strong> Adrenergic agonist ((\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3)).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Actions</th>
</tr>
</thead>
</table>
| **\(\alpha\) 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. |  
| **\(\beta\) agonist:**  
- \(\beta_2\): Dilates bronchial airways + ↓ histamine & leukotriene release from mast cells.  
- \(\beta_1\): ↑ 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.  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare in a setting of anaphylaxis</td>
</tr>
<tr>
<td>Not given for cardiac patient who are older than 40 years</td>
</tr>
</tbody>
</table>
| Patients taking \(\beta\)-blockers either are: why? because of the \(\beta\) blocking action  
  - **Refractory:** as it may antagonize \(\beta\) effects of adrenaline.  
    - \((\beta_2\) receptors won’t be stimulated since they’re blocked, no ↑ cAMP, no effect)  
  - **Rebound hypertension** (unopposed \(\alpha\) effect), specially when adrenaline is repeated (glucagon is used in this case). |  

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
</table>
| **ARDs** | Causes dysrhythmias if given IV.  
| 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 → nodysrhythmias 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 \((\alpha_1, \alpha_2, \beta_1)\). It has no effect on \(\beta_2\) stimulation of \(\alpha_1\) (vasoconstriction) causes hypertension, but this vasoconstriction is not opposed by the stimulation of \(\beta_2\) (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.
### 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 allergenic 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).

### 2nd line therapy

<table>
<thead>
<tr>
<th>Examples</th>
<th>H1 Blockers</th>
<th>H2 Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pheniramine</td>
<td>Ranitidine, Cimetidine, Pantorole</td>
</tr>
</tbody>
</table>

**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.

**Administration**
- Given slowly I.V or I.M
- It can not be used alone (not life saving).

**Contra-indication**

### Adjuvant 2nd line therapy

<table>
<thead>
<tr>
<th>Examples</th>
<th>H2 Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cimetidine shouldn’t be given to elderly, renal/hepatic failure, or if on b-blockers.</td>
</tr>
</tbody>
</table>

**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.
Adjuvant 2nd line

### Bronchodilators
(used for asthma as well)

<table>
<thead>
<tr>
<th><strong>Salbutamol</strong></th>
<th><strong>Ipratropium</strong></th>
<th><strong>Aminophylline</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>Anticholinergic</td>
<td>Parenteral IV</td>
</tr>
<tr>
<td>β2 agonist</td>
<td>Antimuscarinic</td>
<td></td>
</tr>
</tbody>
</table>

- 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

**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.

---

**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 that of the heart → no evident bronchodilation

**Clinical uses**

- Drug of choice for severe anaphylaxis in patients taking β-blockers, because adrenaline won’t be effective
H₂ 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
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 400,000 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.
  - Accidents 54,000
  - 2nd Hand Smoke 38,000
  - Alcohol 45,000
  - HIV/AIDS 32,000
  - Suicide 31,000
  - Homicide 21,000
  - Drugs 14,200

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.
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.”

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.

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
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).

- **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.

---

**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.”
**SECTION 4 | Tobacco consumption**

**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 tongue, 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 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.
Respiratory Chapter | SECTION 4

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.

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

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”
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

有期徒 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.
  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.

🍼 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

<table>
<thead>
<tr>
<th></th>
<th>Bupropion</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M.O.A.</strong></td>
<td>Inhibits the uptake of norepinephrine, serotonin, and dopamine reducing the urge of smoking.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Features</strong></td>
<td>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.</td>
<td>It increases the chances of a successful quit attempt 2-3-fold compared with non pharmacologic assistance.</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
<td>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</td>
<td>Increased risk of coronary events.</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>A history of seizure disorder.</td>
<td>The presence of eating disorders.</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled hypertension</td>
<td></td>
</tr>
</tbody>
</table>
What is pneumonia?
Pneumonia is inflammation of the lung parenchyma caused by a lower respiratory tract infection. It occurs often 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.

Treatment
Remember this as BAPP:
- Breathing: maintain oxygen saturation levels.
- Antibiotics: treat the underlying cause (check hospital guidelines).
- Pain: give analgesics.
- Pneumococcal vaccines for these at risk, e.g., diabetics, the immunosuppressed and those over 65 years old.

Causative organisms

<table>
<thead>
<tr>
<th>Children</th>
<th>Community acquired pneumonia</th>
<th>Hospital acquired pneumonia</th>
<th>HIV patients or immunocompromised patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>Streptococcus pneumoniae</td>
<td>Gram-negative bacteria</td>
<td>Pneumocystis jiroveci</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Haemophilus influenzae</td>
<td>Staphylococcus aureus</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>Moraxella catarrhalis</td>
<td>Streptococcus pneumoniae</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>Chlamydia pneumoniae (A)</td>
<td>Anaerobes</td>
<td>Herpes simplex virus</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae (A)</td>
<td>Fungi</td>
<td>Mycobacterium tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Legionella pneumophila (A)</td>
<td>Legionella pneumophila</td>
<td>Bacterial infection, e.g., Staphylococcus aureus</td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

A = Atypical

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
- CUR: 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
- Confusion.
- Urea >7 mmol/L.
- Respiratory rate >30/min.
- BP <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.
**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.

[Diagram showing allergen leading to Th2 cells, then to interleukin (IL)-4 stimulating eosinophils and stimulating B lymphocytes. B lymphocytes produce IgE, which causes mast cells to degranulate. When mast cells degranulate, they release histamine and the histamine causes bronchoconstriction. IL-5 stimulates eosinophils. IL-13 stimulates mucus secretion.]

**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 + beclomethasone (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.
  - Thickening of the skin.
  - Striae formation.
  - Cataracts.
  - Cushing's syndrome.
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:
- Genetics: alpha-1 antitrypsin deficiency results in the loss of protection against proteases.
- Air pollution.
- Smoking.
- Exposure through occupation, e.g., coal mining.
- Secondhand 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 breathers’ 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.

MAP 2.4 Chronic Obstructive Pulmonary Disease (COPD)

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:
- Cor pulmonale: right-sided heart failure due to chronic pulmonary hypertension.
- Lung cancer.
- Infections: usually treat with macrolide antibiotics.
- Pneumothorax.
- Polythemia.
- Respiratory failure.

Treatment
Remember this as ABCS, oxygen therapy and pulmonary rehabilitation:
- Anticholinergics, e.g., ipratropium.
- Bronchodilators, e.g., salmeterol.
- Corticosteroids.
- Smoking cessation is imperative.
- Oxygen therapy: long-term oxygen therapy (LTOT) or noninvasive ventilation (NIV).
MAP 2.5 Pneumoconiosis

**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.

**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.
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 known as oat cell carcinoma.
- Very aggressive, therefore treat solely with chemotherapy regime.
- Adrenocorticotropic 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.

MAP 2.6 Lung Cancer

Apex

Central location

Peripheral location

Pleura

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.
**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.

**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).

**Differential diagnosis**
Remember as ABC:
- A musculoskeletal injury.
- Baker's cyst rupture.
- Cellulitis.

**MAP 2.7 Deep Vein Thrombosis (DVT)**

**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.

**Complications**
- Pulmonary embolism.
- Post-thrombotic syndrome.

**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.
**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 A₂ 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.
- Dyspnœa.
- Tachypnoea.
- Hypoxia.
- Cyanosis.
- Auscultation: decreased on affected side.
- Percussion: hyper-resonant or normal.

**Causes**
- Ruptured pleural bleb.
- Chronic obstructive pulmonary disease (COPD).
- Tuberculosis.
- Sarcoïdosis.
- 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, sarcoïdosis 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**

**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.

**Investigations**
- CXR: pleural line; may show tracheal deviation away from lesion.
- CT scan.
- ABG: hypoxia.

**Complications**
- Risk of future pneumothorax.
- Respiratory failure.
- Cardiac arrest.
<table>
<thead>
<tr>
<th></th>
<th>Type 1: hypoventilation with V/Q mismatch</th>
<th>Type 2: hypoventilation with or without V/Q mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Pneumonia</td>
<td>Chronic obstructive pulmonary disease (COPD) and asthma</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td>Opiate overdose</td>
</tr>
<tr>
<td></td>
<td>Pulmonary oedema</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>Fibrosing alveolitis</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Remember this as <strong>ABCD:</strong></td>
<td>Remember this as <strong>ABCD:</strong></td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Breathlessness</td>
<td>Breathlessness</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Drowsiness and fatigue</td>
<td>Drowsiness and fatigue</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>Central cyanosis</td>
<td>Remember this as <strong>ABC:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A flapping tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bounding pulse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyanosis</td>
</tr>
<tr>
<td><strong>PaO_2</strong></td>
<td>↓ (&lt;8.0 kPa)</td>
<td>↓ (&lt;8.0 kPa)</td>
</tr>
<tr>
<td><strong>PaCO_2</strong></td>
<td>Normal (~6.7 kPa)</td>
<td>↑ (~6.7 kPa)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Oxygen replacement therapy</td>
<td>Noninvasive ventilation</td>
</tr>
<tr>
<td></td>
<td>Treatment of underlying cause</td>
<td>Treatment of underlying cause</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Nosocomial infections, e.g. pneumonia</td>
<td>Nosocomial infections, e.g. pneumonia</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
<td>Pericarditis</td>
</tr>
</tbody>
</table>
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

Look what I can do!
RESPIRATORY ACIDOSIS

- Hypoventilation → Hypoxia
- Rapid, Shallow Respirations
- ↓ BP with Vasodilation
- Dyspnea
- Headache
- Hyperkalemia
- Dysrhythmias (↑ K)
- I can’t catch my breath.

- Drowsiness, Dizziness, Disorientation
- Muscle Weakness, Hyperreflexia
- Causes: ↓ Respiratory Stimuli (Anesthesia, Drug Overdose), COPD, Pneumonia, Atelectasis

Retention of CO₂ by Lungs

pH (↓ 7.35), pCO₂ (↑ 45mm Hg)
Tuberculosis

*Mycobacterium tuberculosis* is carried through the air in infectious droplets produced when infected individuals cough.

- Fever, fatigue, weight loss, productive cough, and blood-streaked sputum
- Night sweats

The PPD test consists of a subcutaneous injection of tuberculin antigen with a subsequent reading in 48 to 72 hours.

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".

- Headache
- Chills
- Swollen Lymph Glands
- Pain in RUQ with Liver Involvement
- Fatigue
- Decreased Energy

Cause:
Epstein Barr Virus (EBV)

- Fever “101°-104°”
- Sore Throat
- Pain Mid-Epigastic and LUQ with Spleen Enlargement
- Loss of Appetite
- Body Aches

Diagnostic:
- Mono Spot
- Liver Enzymes
- CMV - As Cytomegalovirus Can Mimic Mono Symptoms

Treatment:
- Rest
- Throat Soothing Measures
- Acetaminophen / Ibuprofen
- Low Energy / Impact Activity
- Gradual ↑ Activity
**RUBEOLA** (Ordinary Measles)
- Conjunctivitis
- Cough
- Cortza
- 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
- Cortza
- 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
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

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TENSION PNEUMOTHORAX

Air enters the pleural space, compresses the lung, and shifts the mediastinum.

- Tracheal Deviation
- Whisper...
- Decreased Breath Sounds
- Hyperresonance

Is the chest tube in yet?!

Treated with needle decompression in the 2nd intercostal space at the midclavicular line, followed by tube thoracostomy.

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6-PS OF DYSPNEA

- Pulmonary Bronchial Constriction
- Possible Foreign Body
- Pulmonary Embolus
- Pneumothorax
- Pump Failure
- Pneumonia
<table>
<thead>
<tr>
<th>Breath Sounds</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 anteriorily and between scapulae posteriorly  
Intermediate intensity |
| Fine Crackles         | Abnormal - discontinous  
High pitched  
Popping quality        |
| Coarse Crackles       | Abnormal - discontinuous  
Low pitched  
Louder & Longer        |
| Wheeze                | Abnormal - continuos  
High pitched  
Musical quality        |
| Rhonchi               | Abnormal - continuos  
Low pitched  
Gurgling quality        |
ADVENTITIOUS BREATH SOUNDS

CRACKLES (RALES)
- CRACKLE!
- SNAP!
- POP!
- BRONCHIECTASIS
- BRONCHITIS
- PNEUMONIA
- FIBROSIS
- CHF

WHEEZES
- WHEEEEEEZEEE!

RHONCHI
- Zzz...

ASTHMA, COPD, AND OTHER CAUSES OF AIRWAY OBSTRUCTION

SNOOOORE...

SUGGEST SECRETIONS IN THE LARGE AIRWAYS

DISCONTINUOUS

CONTINUOUS

© 2016 JORGE MUNIZ
SMOKING CESSATION

DECREASED RISK OF STROKE

DECREASED RISK OF OSTEOPOROSIS AND FRACTURE

THREE YEARS AFTER SMOKING CESSATION, THE RISK OF RECURRENT MYOCARDIAL INFARCTION DECREASES TO THAT OF A NONSMOKER

DECREASED RISK OF PULMONARY INFECTIONS SUCH AS BACTERIAL PNEUMONIA AND TUBERCULOSIS

DECREASED RISK OF LUNG, KIDNEY, BLADDER, STOMACH, AND CERVICAL CANCERS, AMONG OTHERS

YUCK!
Appendix: 
First Aid
For USMLE STEP 1 2019
Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Know obstructive vs restrictive lung disorders, V/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.
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.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>STRUCTURAL DEVELOPMENT</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic (weeks 4–7)</td>
<td>Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi</td>
<td>Errors at this stage can lead to tracheoesophageal fistula.</td>
</tr>
<tr>
<td>Canalicular (weeks 16–25)</td>
<td>Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.</td>
<td>Airways increase in diameter. Respiration capable at 25 weeks. Pneumocytes develop starting at 20 weeks.</td>
</tr>
<tr>
<td>Alveolar (week 36–8 years)</td>
<td>Terminal sacs → adult alveoli (due to 2° septation). In utero, “breathing” occurs via aspiration and expulsion of amniotic fluid → vascular resistance through gestation.</td>
<td>At birth, fluid gets replaced with air → 1 in pulmonary vascular resistance.</td>
</tr>
</tbody>
</table>

**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.

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 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.
Right lung has 3 lobes; Left has Less Lobes (2) and Lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart.

Relation of the pulmonary artery to the bronchus at each lung hilum is described by RALS—Right Anterior; Left Superior. Carina is posterior to ascending aorta and anteromedial to descending aorta.

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 (e.g., 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: “esophagus”
  - T12: aortic hiatus

1 (IVC) ate (8) ten (10) eggs (esophagus) at (aorta) twelve (12).

C3, 4, 5 keep the diaphragm alive.

Other bifurcations:
- The common carotid bifurcates at C4.
- The trachea bifurcates at T4.
- The abdominal aorta bifurcates at L4.
### RESPIRATORY—PHYSIOLOGY

#### Lung volumes

<table>
<thead>
<tr>
<th>Volume Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory reserve volume</td>
<td>Air that can still be breathed in after normal inspiration</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>Air that moves into lung with each quiet inspiration, typically 500 mL</td>
</tr>
<tr>
<td>Expiratory reserve volume</td>
<td>Air that can still be breathed out after normal expiration</td>
</tr>
<tr>
<td>Residual volume</td>
<td>Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry</td>
</tr>
<tr>
<td>Inspiratory capacity</td>
<td>IRV + TV</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>RV + ERV</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>TV + IRV + ERV</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>IRV + TV + ERV + RV</td>
</tr>
</tbody>
</table>

Note: a capacity is a sum of ≥2 physiologic volumes.

#### Determination of physiologic dead space

\[
V_D = V_T \times \frac{P_{aco_2} - P_{eco_2}}{P_{aco_2}}
\]

\(V_D\) = 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.

\(P_{aco_2}\) = arterial \(P_{co_2}\).

\(P_{eco_2}\) = expired air \(P_{eco_2}\).

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 V/Q defects.

### Ventilation

<table>
<thead>
<tr>
<th>Ventilation Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation</td>
<td>Total volume of gas entering lungs per minute</td>
</tr>
<tr>
<td></td>
<td>(V_T = V_T \times RR)</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
<td>Volume of gas that reaches alveoli each minute</td>
</tr>
<tr>
<td></td>
<td>(V_A = (V_T - V_D) \times RR)</td>
</tr>
</tbody>
</table>

Normal values:

- Respiratory rate (RR) = 12–20 breaths/min
- \(V_T\) = 500 mL/breath
- \(V_D\) = 150 mL/breath
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 ΔV/ΔP 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.

**Respiratory system changes in the elderly**

- Aging is associated with progressive ↓ in lung function. TLC remains the same.
- Compliance (loss of elastic recoil) → Chest wall compliance (↑ chest wall stiffness)
- RV → FVC and FEV<sub>1</sub>
- V/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<sub>2</sub>, thus promoting release/unloading of O<sub>2</sub>.
- Oxygenated form has high affinity for O<sub>2</sub> (300×). Hb exhibits positive cooperativity and negative allostery.
- ↑ Cl<sup>-</sup>, H<sup>+</sup>, CO<sub>2</sub>, 2,3-BPG, and temperature favor deoxygenated form over oxygenated form (shifts dissociation curve right → ↑ O<sub>2</sub> unloading).

Fetal Hb (2α and 2γ subunits) has a higher affinity for O<sub>2</sub> than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus. ↑ O<sub>2</sub> affinity results from ↓ affinity of HbF for 2,3-BPG.

Hemoglobin acts as buffer for H<sup>+</sup> 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 \( \dagger \) anaerobic metabolism. Both can lead to pink or cherry red skin (usually postmortem finding), seizures, and coma.

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>Cyanide</th>
<th>Carbon monoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byproduct of synthetic product combustion, ingestion of amygdalin (cyanogenic glucoside found in apricot seeds) or cyanide.</td>
<td>Odorless gas from fires, car exhaust, or gas heaters.</td>
<td></td>
</tr>
</tbody>
</table>

| 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, although rarely seen with cyanide toxicity as well. |

| EFFECT ON OXYGEN-HEMOGLOBIN DISSOCIATION CURVE | Curve normal; oxygen saturation may appear normal initially. | \( \downarrow \) oxygen-binding capacity with left shift in curve, \( \downarrow \) \( O_2 \) unloading in tissues. Binds competitively to Hb with 200x greater affinity than \( O_2 \) to form carboxyhemoglobin. |
Methemoglobin

Oxidized form of Hb (ferrous, Fe³⁺), does not bind O₂ as readily as Fe²⁺, but has 1 affinity for cyanide. Fe²⁺ binds O₂. Iron in Hb is normally in a reduced state (ferrous, Fe²⁺; “just the 2 of us”). Leads to tissue hypoxia from ↓ O₂ saturation and ↓ O₂ 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 Fe²⁺ to Fe³⁺. 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 O₂ molecules and has higher affinity for each subsequent O₂ 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 O₂ (facilitates unloading of O₂ to tissue) → ↑ P₅₀ (higher P₅₀ required to maintain 50% saturation).

Shifting the curve to the left → ↓ O₂ unloading → renal hypoxia → ↑ EPO synthesis → compensatory erythrocytosis. Fetal Hb has higher affinity for O₂ than adult Hb (due to low affinity for 2,3-BPG), so its dissociation curve is shifted left.

Oxygen content of blood

O₂ content = (1.34 × Hb × SaO₂) + (0.003 × PaO₂)

Hb = hemoglobin concentration; SaO₂ = arterial O₂ saturation

PaO₂ = partial pressure of O₂ in arterial blood

Normally 1 g Hb can bind 1.34 mL O₂; normal Hb amount in blood is 15 g/dL. O₂ binding capacity = 20 mL O₂/dL of blood.

With ↓ Hb there is ↓ O₂ content of arterial blood, but no change in O₂ saturation and PaO₂. O₂ delivery to tissues = cardiac output × O₂ content of blood.

<table>
<thead>
<tr>
<th>CO poisoning</th>
<th>Anemia</th>
<th>Polycythemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb CONCENTRATION</td>
<td>↓ (CO competes with O₂)</td>
<td>Normal</td>
</tr>
<tr>
<td>% O₂ SAT OF Hb</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>DISSOLVED O₂ (PaO₂)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>TOTAL O₂ CONTENT</td>
<td>↑</td>
<td>Normal</td>
</tr>
</tbody>
</table>
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 $P_{O_2}$ 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: $V_{gas} = A \times D_k \times \frac{P_1 - P_2}{\Delta \rho}$ where

$A$ = area, $\Delta \rho$ = 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.

Pulmonary vascular resistance

$$PVR = \frac{P_{pulmonary} - P_{atrium}}{cardiac output}$$

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$

$$R = \frac{8 \eta l}{\pi r^4}$$

Alveolar gas equation

$$P_{AO_2} = P_{Io_2} - \frac{P_{CO_2}}{R}$$

$\approx 150$ mm Hg - $\frac{P_{CO_2}}{0.8}$

$^a$At sea level breathing room air

$P_{AO_2}$ = alveolar $P_{O_2}$ (mm Hg)

$P_{Io_2}$ = $P_{O_2}$ in inspired air (mm Hg)

$P_{CO_2}$ = arterial $P_{CO_2}$ (mm Hg)

$R$ = respiratory quotient = $CO_2$ produced/$O_2$ consumed

A-a gradient = $P_{AO_2} - P_{AaO_2}$. Normal A-a gradient estimated as $(age/4) + 4$, eg, for a person < 40 years old, gradient should be <$14$. 

$P_{pulmonary}$ = pressure in pulmonary artery

$P_{atrium}$ = pulmonary capillary wedge pressure

$Q$ = cardiac output (flow)

$R$ = resistance

$\eta$ = viscosity of blood

$l$ = vessel length

$r$ = vessel radius

$P_{AO_2}$ = partial pressure of gas in pulmonary capillary blood

$P_{Io_2}$ = partial pressure of gas in alveolar air
Oxygen deprivation

<table>
<thead>
<tr>
<th>Hypoxia (↓ O2 delivery to tissue)</th>
<th>Hypoxemia (↓ Pao2)</th>
<th>Ischemia (loss of blood flow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ cardiac output</td>
<td>Normal A-a gradient</td>
<td>Impeded arterial flow</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td></td>
<td>↓ venous drainage</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO poisoning</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A-a gradient

- High altitude
- Hypoventilation (eg, opioid use, obesity hypoventilation syndrome)
- ↓ A-a gradient
- V/Q mismatch
- Diffusion limitation (eg, fibrosis)
- Right-to-left shunt

Ventilation/perfusion mismatch

Ideally, ventilation is matched to perfusion (ie, V/Q = 1) for adequate gas exchange.

Lung zones:
- V/Q at apex of lung = 3 (wasted ventilation)
- V/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 → V/Q ratio approaches 1.

Certain organisms that thrive in high O2 (eg, TB) flourish in the apex.

V/Q = 0 = “airway” obstruction (shunt). In shunt, 100% O2 does not improve Pao2 (eg, foreign body aspiration).

V/Q = ∞ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O2 improves Pao2 (eg, pulmonary embolus).
Carbon dioxide transport

CO₂ is transported from tissues to lungs in 3 forms:

1. **HCO₃⁻** (70%).
2. Carbaminohemoglobin or HbCO₂ (21–25%). CO₂ bound to Hb at N-terminus of globin (not heme). CO₂ favors deoxygenated form (O₂ unloaded).
3. Dissolved CO₂ (5–9%).

In lungs, oxygenation of Hb promotes dissociation of H⁺ from Hb. This shifts equilibrium toward CO₂ formation; therefore, CO₂ is released from RBCs (Haldane effect).

In peripheral tissue, ↑ H⁺ from tissue metabolism shifts curve to right, unloading O₂ (Bohr effect).

Majority of blood CO₂ is carried as HCO₃⁻ in the plasma.

---

Response to high altitude

↑ atmospheric oxygen (PIO₂) → ↓ Pao₂ → ↑ ventilation → ↓ PaCO₂ → 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 O₂).
Cellular changes (↑ mitochondria).
↑ renal excretion of HCO₃⁻ to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

---

Response to exercise

↑ CO₂ production.
↑ O₂ consumption.
↑ ventilation rate to meet O₂ demand.
V/Q ratio from apex to base becomes more uniform.
↑ pulmonary blood flow due to ↑ cardiac output.
↑ pH during strenuous exercise (↑ to lactic acidosis).
No change in Pao₂ and Paco₂, but ↑ in venous CO₂ content and ↓ in venous O₂ content.
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 (opharyngeal), 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, 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**

V/Q mismatch, hypoxemia, respiratory alkalosis. Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia. Large emboli or saddle embolus 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). May have SIQ3T3 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.

Types: Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor. 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 O₂ 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**

<table>
<thead>
<tr>
<th>FLOW-VOLUME PARAMETER</th>
<th>Obstructive lung disease</th>
<th>Restrictive lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>FRC</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>TLC</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁ / FVC</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁ / FVC</td>
<td>FEV₁ decreased more than FVC</td>
<td>Normal or ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEV₁ decreased proportionately to FVC</td>
</tr>
</tbody>
</table>

**OBSTRUCTIVE**

Loop shifts to the left

**NORMAL**

**RESTRICTIVE**

Loop shifts to the right

Volume (L)
**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). 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: ↓ FEV₁, ↓ FVC → ↓ FEV₁/FVC ratio (hallmark), V/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!”

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PRESENTATION</th>
<th>PATHOLOGY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic bronchitis</strong> (“blue bloater”)</td>
<td>Findings: wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO₂ retention, 2° polycythemia.</td>
<td>Hypertrophy and hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) &gt; 50%, DLCO usually normal.</td>
<td>Diagnostic criteria: productive cough for &gt; 3 months in a year for &gt; 2 consecutive years.</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, pulsum paradoxus, mucus plugging E. Triggers: viral URIs, allergens, stress. Diagnosis supported by spirometry and methacholine challenge.</td>
<td>Hyperresponsive bronchi → reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Curschmann spirals F (sherd epithelium forms whorled mucous plugs), and Charcot-Leyden crystals G (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). DLCO normal or ↓.</td>
<td>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.</td>
</tr>
</tbody>
</table>
Obstructive lung diseases (continued)

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PRESENTATION</th>
<th>PATHOLOGY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>Findings: purulent sputum, recurrent infections, hemoptysis, digital clubbing</td>
<td>Chronic necrotizing infection of bronchi or obstruction → permanently dilated airways.</td>
<td>Associated with bronchial obstruction, poor ciliary motility (e.g., smoking, Kartagener syndrome), cystic fibrosis, allergic bronchopulmonary aspergillosis.</td>
</tr>
</tbody>
</table>

Restricted lung diseases

Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: ↑ FEV₁/FVC ratio. Patient presents with short, shallow breaths.

Types:
- Poor breathing mechanics (extrapulmonary, normal DLCO, normal A-a gradient):
  - Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome
  - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary, ↓ DLCO, ↑ A-a gradient):
  - Pneumoconioses (e.g., coal workers’ pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncasing granuloma; ↑ ACE and Ca²⁺
  - 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, 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. CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy.

Associated with Bell palsy, Uveitis, Granulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), Lupus pernio (skin lesions on face resembling lupus), Interstitial fibrosis (restrictive lung disease), Erythema nodosum, Rheumatoid 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, NH₃) → 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).
**Respiratory Pathology**

### 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).

### Berylliosis

Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncascading) **D** on histology and therefore occasionally responsive to steroids. ↑ risk of cancer and cor pulmonale.

### Coal workers’ pneumoconiosis

Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis.

Also known as black lung disease. ↑ risk of Caplan syndrome.

### 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.
Mesothelioma

Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening. 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):

- Abnormal chest X-ray (bilateral lung opacities)
- Respiratory failure within 1 week of alveolar insult
- Decreased PaO₂/FiO₂ (ratio < 300, hypoxemia due to intrapulmonary shunting and diffusion abnormalities)
- Symptoms 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 PaO₂ during the day. Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death. Hypoxia → ↑ EPO release → ↑ erythropoiesis.

<table>
<thead>
<tr>
<th>Obstructive sleep apnea</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central sleep apnea</td>
<td>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.</td>
</tr>
<tr>
<td>Obesity hypoventilation syndrome</td>
<td>Obesity (BMI ≥ 30 kg/m²) → hypoventilation → ↑ PaCO₂ during waking hours (retention); ↓ PaO₂ and ↑ PaCO₂ during sleep. Also known as Pickwickian syndrome.</td>
</tr>
</tbody>
</table>

| 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**

<table>
<thead>
<tr>
<th>Pulmonary arterial hypertension</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left heart disease</td>
<td>Causes include systolic/diastolic dysfunction and valvular disease.</td>
</tr>
<tr>
<td>Lung diseases or hypoxia</td>
<td>Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).</td>
</tr>
<tr>
<td>Chronic thromboembolic</td>
<td>Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>Causes include hematologic, systemic, and metabolic disorders, along with compression of the pulmonary vasculature by a tumor.</td>
</tr>
</tbody>
</table>
### Lung—physical findings in select lung diseases

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>PERCUSSION</th>
<th>FREMITUS</th>
<th>TRACHEAL DEVIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>Dull</td>
<td>↑</td>
<td>None if small</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Away from side of lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>if large</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Dull</td>
<td>↓</td>
<td>Toward side of lesion</td>
</tr>
<tr>
<td>Simple pneumothorax</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>None</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>Away from side of lesion</td>
</tr>
<tr>
<td>Consolidation (lobar pneumonia, pulmonary edema)</td>
<td>Bronchial breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy</td>
<td>Dull</td>
<td>↑</td>
</tr>
</tbody>
</table>

**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 between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid.

**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. Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.

<table>
<thead>
<tr>
<th><strong>Primary spontaneous pneumothorax</strong></th>
<th>Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males and smokers.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary spontaneous pneumothorax</strong></td>
<td>Due to diseased lung (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.</td>
</tr>
<tr>
<td><strong>Traumatic pneumothorax</strong></td>
<td>Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.</td>
</tr>
<tr>
<td><strong>Tension pneumothorax</strong></td>
<td>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. May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return → ↓ cardiac output. Needs immediate needle decompression and chest tube placement.</td>
</tr>
</tbody>
</table>
## Pneumonia

<table>
<thead>
<tr>
<th>TYPE</th>
<th>TYPICAL ORGANISMS</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lobar pneumonia</strong></td>
<td><em>S. pneumoniae</em> most frequently, also <em>Legionella</em>,</td>
<td>Intra-alveolar exudate → consolidation: may involve entire lobe or the whole lung.</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em></td>
<td></td>
</tr>
<tr>
<td><strong>Bronchopneumonia</strong></td>
<td><em>S. pneumoniae</em>, <em>S. aureus</em>, <em>H. influenzae</em>,</td>
<td>Acute inflammatory infiltrates from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe.</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em></td>
<td></td>
</tr>
<tr>
<td><strong>Interstitial (atypical) pneumonia</strong></td>
<td><em>Mycoplasma, Chlamydophila pneumoniae, Chlamydophila psittaci, Legionella, viruses (RSV, CMV, influenza, adenovirus)</em></td>
<td>Diffuse patchy inflammation localized to interstitial areas at alveolar walls; CXR shows bilateral multifocal opacities. Generally follows a more indolent course (“walking” pneumonia).</td>
</tr>
<tr>
<td><strong>Cryptogenic organizing pneumonia</strong></td>
<td>Etiology unknown. Secondary organizing pneumonia caused by chronic inflammatory diseases (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone).</td>
<td>Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.</td>
</tr>
</tbody>
</table>

### Natural history of lobar pneumonia

<table>
<thead>
<tr>
<th>DAYS</th>
<th>FINDINGS</th>
<th>RED HEATIZATION</th>
<th>GRAY HEATIZATION</th>
<th>RESOLUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>Congestion</td>
<td>Red-purple, partial consolidation of parenchyma</td>
<td>Red-brown, consolidated</td>
<td>Uniformly gray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exudate with mostly bacteria</td>
<td>Exudate with fibrin, bacteria, RBCs, and WBCs</td>
<td>Exudate full of WBCs, lysed RBCs, and fibrin</td>
</tr>
<tr>
<td>3–4</td>
<td></td>
<td>Red-brown, consolidated</td>
<td>Uniformly gray</td>
<td>Enzymes digest components of exudate</td>
</tr>
<tr>
<td>5–7</td>
<td></td>
<td>Exudate with fibrin, bacteria, RBCs, and WBCs</td>
<td>Uniformly gray</td>
<td>Enzymes digest components of exudate</td>
</tr>
<tr>
<td>8+</td>
<td></td>
<td>Uniformly gray</td>
<td>Uniformly gray</td>
<td>Enzymes digest components of exudate</td>
</tr>
</tbody>
</table>
### 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: Liver (jaundice, hepatomegaly), Adrenals, Bone (pathologic fracture), Brain; “Lung ‘mets’ Love Affection Boneheads and Brainiacs.”

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:
- Superior vena cava/thoracic outlet syndromes
- Pancoast tumor
- Horner syndrome
- Endocrine (paraneoplastic)
- Recurrent laryngeal nerve compression (hoarseness)
- Effusions (pleural or pericardial)

Risk factors include smoking, secondhand smoke, radon, asbestos, family history.

Squamous and Small cell carcinomas are Sentinel (central) and often caused by Smoking.

#### Location

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Characteristics</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell</td>
<td></td>
<td></td>
<td>Neoplasm of neuroendocrine</td>
</tr>
<tr>
<td>Small cell (oat cell)</td>
<td></td>
<td></td>
<td>Kulchitsky cells → small dark blue cells A.</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
<td></td>
<td>Chromogranin A®, neuron-specific enolase, synaptophysin.</td>
</tr>
<tr>
<td><strong>Non-small cell</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Peripheral</td>
<td>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.</td>
<td>Clandular pattern on histology, often stains mucin. Bronchioloalveolar subtype: grows along alveolar septa → apparent “thickening” of alveolar walls. Tall, columnar cells containing mucus.</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Central</td>
<td>Hilar mass arising from bronchus; Cavitation; Cigarettes; hyperCalcaemia (produces PTHrP).</td>
<td>Keratin pearls and intercellular bridges.</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Peripheral</td>
<td>Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically. Strong association with smoking.</td>
<td>Pleomorphic giant cells.</td>
</tr>
<tr>
<td>Large cell</td>
<td>Peripheral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Central or peripheral</td>
<td>Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).</td>
<td>Nests of neuroendocrine cells, chromogranin A.</td>
</tr>
</tbody>
</table>

---

![Image A](imageA.png)  ![Image B](imageB.png)  ![Image C](imageC.png)  ![Image D](imageD.png)  ![Image E](imageE.png)
**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.
### Histamine-1 blockers

**Reversible inhibitors of H_1_ histamine receptors.**

**First generation**
- Diphenhydramine, dimenhydrinate, chlorpheniramine, doxylamine.
- **Clinical Use**: Allergy, motion sickness, sleep aid.
- **Adverse Effects**: Sedation, antimuscarinic, anti-α-adrenergic.

**Second generation**
- Loratadine, fexofenadine, desloratadine, cetirizine.
- **Clinical Use**: Allergy.
- **Adverse Effects**: Far less sedating than 1st generation because of low 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** (agonizes 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelin receptor antagonists</strong></td>
<td>Competitively antagonizes endothelin-1 receptors → ↓ pulmonary vascular resistance.</td>
<td>Hepatotoxic (monitor LFTs). Example: bosentan.</td>
</tr>
<tr>
<td><strong>PDE-5 inhibitors</strong></td>
<td>Inhibits PDE-5 → ↓ cGMP → prolonged vasodilatory effect of NO.</td>
<td>Also used to treat erectile dysfunction. Contraindicated when taking nitroglycerin or other nitrates (due to risk of severe hypotension). Example: sildenafil.</td>
</tr>
<tr>
<td><strong>Prostacyclin analogs</strong></td>
<td>PGI_2_ (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.</td>
<td>Side effects: flushing, jaw pain. Examples: epoprostenol, iloprost.</td>
</tr>
</tbody>
</table>
Asthma drugs

Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

**β₂-agonists**
- **Albuterol**—relaxes bronchial smooth muscle (short acting β₂-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 FceRI. Used in allergic asthma with ↑ IgE levels resistant to inhaled steroids and long-acting β₂-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 (M₃) agonist. Used in bronchial challenge test to help diagnose asthma.
CHAPTER 10

Respiratory

EMBRYOLOGY
  Respiratory Development
  Congenital Malformations

ANATOMY
  Airways
  Lungs
  Diaphragm
  External Anatomy
  Muscles of Respiration
  Flail Chest

HISTOLOGY
  Respiratory Epithelium
  Alveoli
  Olfactory Cells

PHYSIOLOGY
  Lung Volumes and Capacities
  Ventilation
  Blood Gases

PATHOLOGY
  Pathology on Physical Examination
    Nasopharynx
  Obstructive Lung Diseases
  Restrictive Lung Diseases
  Pulmonary Vascular Diseases
  Respiratory Tract Cancers
  Pulmonary Infections
  Pleural Effusion
  Pneumothorax
  Allergy
  Hypersensitivity Pneumonitis

PHARMACOLOGY
  Histamine Blockers
  Mucoactive Agents
  Dextromethorphan
  α-Adrenergic Agonists
  Pulmonary Hypertension Drugs
  Asthma Drugs
Embryology

RESPIRATORY DEVELOPMENT

The respiratory system allows for blood oxygenation and clearance of carbon dioxide (CO₂), 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

---

**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.

---

**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.
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.
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).

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).

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 pleuropertoneal membranes, which then fuse with the septum transversum.
- The body wall also extends from the dorsal and lateral sides (after the pleuropertoneal 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.
**Esophageal Atresia and Tracheoesophageal Fistula**

The ventral laryngotraceal 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-
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**.

**Chapter 10: Respiratory**

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.

**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.

**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**.

**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.

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**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 \( P = \frac{2T}{r} \). 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.
Airways

The passages that transmit air from the environment to the lungs can be divided into conducting and respiratory airways (Table 10-1).

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, O₂-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.

MNEMONIC

RALS:
Right pulmonary artery is A(n)terior, L(left) pulmonary artery is S(sup)erior to the 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 10-9. 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.

Figure 10-10. Gross anatomy of the respiratory system. Overview (left) and conducting airways (right).
Small bronchial veins unite to form a single vessel in each lung that empties into the azygos vein on the right and the hemiazgos 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>
<thead>
<tr>
<th>Function</th>
<th>CONDUCTING AIRWAYS</th>
<th>RESPIRATORY AIRWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm, humidify, and filter air; no gas exchange (anatomic dead space)</td>
<td>Gas exchange</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structures</th>
<th>Nose/mouth, pharynx</th>
<th>Respiratory bronchioles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td></td>
<td>Alveolar ducts</td>
</tr>
<tr>
<td>Bronchi</td>
<td></td>
<td>Alveoli</td>
</tr>
<tr>
<td>Bronchioles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal bronchioles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 10-2. Anatomy of the Right and Left Lungs

<table>
<thead>
<tr>
<th>Lobes</th>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Three (upper, middle, and lower)</td>
<td>Two (upper with lingula, and lower)</td>
</tr>
<tr>
<td>Main bronchus entry</td>
<td>Smaller angle (more continuous with trachea)</td>
<td>Sharper angle (greater deviation from trachea)</td>
</tr>
<tr>
<td>Main bronchus shape</td>
<td>Shorter and wider</td>
<td>Longer and narrower</td>
</tr>
<tr>
<td>Pulmonary artery entry</td>
<td>Anterior to right mainstem bronchus</td>
<td>Superior to left mainstem bronchus</td>
</tr>
</tbody>
</table>

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.

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.
CHAPTER 10 RESPIRATORY 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.

**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 10-11. 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.

**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.

---

**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).

**MNEMONIC**

I 8 10 EGGS AAT 12 (“I ate ten eggs at twelve”):

- Inferior vena cava: T8
- Esophagus, vagus nerve: T10
- Aorta, azygos vein, thoracic duct: T12

**MNEMONIC**

The intercostal vein, artery, and nerve 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.
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...
gas exchange. Specialized epithelial cell layers along these different airways contribute to their distinct functional capacities. The conducting airways are lined by thick pseudostatified 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 bronchiules. 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**

<table>
<thead>
<tr>
<th>TYPE I CELLS</th>
<th>TYPE II CELLS</th>
<th>ENDOTHELIAL CELLS</th>
<th>MACROPHAGES</th>
<th>CLARA CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Cover 95% of alveolar surface area. Comprise 10% of cell population</td>
<td>Cover 5% of alveolar surface area. Comprise 12% of the cell population</td>
<td>40% of the cell population</td>
<td>Variable</td>
</tr>
<tr>
<td>Structure</td>
<td>Flat and extremely thin (&lt; 500 nm)</td>
<td>Cuboidal</td>
<td>Thin, wrapped into cylinders to form capillaries</td>
<td>Amorphous</td>
</tr>
<tr>
<td>Function(s)</td>
<td>Allow for gas exchange with the adjacent capillaries Nonproliferative</td>
<td>Secrete surfactant Proliferate after lung damage Are source of precursors for new alveolar cells (types I and II)</td>
<td>Allow for gas exchange with the alveolus</td>
<td>Engulf debris (&quot;dust cells&quot;)</td>
</tr>
</tbody>
</table>
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 ambiguous (heterotaxy).

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 10-16. Alveolar structure.**

**FIGURE 10-17. Type II pneumocytes.** A Electron micrograph of type II pneumocytes. B Higher magnification electron micrograph showing lamellar bodies.
CHAPTER 10

Respiratory

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.

 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 O₂ and CO₂ transport (the blood gases).

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 (FEV₁) is normally 70–80% of the forced vital capacity (FVC), or \( \text{FEV₁/FVC} = 0.7–0.8 \).
- In obstructive lung diseases, like asthma or emphysema, FEV₁ is decreased more than FVC, so \( \text{FEV₁/FVC} < 0.7 \) (Figure 10-19 and Table 10-6).

<table>
<thead>
<tr>
<th>TABLE 10-5. Lung Volumes and Capacities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAME</strong></td>
</tr>
<tr>
<td>Volumes</td>
</tr>
<tr>
<td>Tidal volume (TV or VT)</td>
</tr>
<tr>
<td>Inspiratory reserve volume (IRV)</td>
</tr>
<tr>
<td>Expiratory reserve volume (ERV)</td>
</tr>
<tr>
<td>Residual volume (RV)</td>
</tr>
<tr>
<td>Capacities (Sums of 2 or more volumes)</td>
</tr>
<tr>
<td>Inspiratory capacity (IC)</td>
</tr>
<tr>
<td>Functional residual capacity (FRC)</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
</tr>
<tr>
<td>Forced vital capacity (FVC)</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 second (FEV₁)</td>
</tr>
<tr>
<td>Total lung capacity (TLC)</td>
</tr>
</tbody>
</table>

*For 70-kg male.*
In restrictive lung diseases, like pulmonary fibrosis, FEV\textsubscript{1} is decreased to the same extent as, or less than, FVC, so FEV\textsubscript{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:

- **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

$$X = V_o \cdot \left( C_o - C \right) \frac{C}{C_L}$$

---

**CLINICAL CORRELATION**

Pulmonary vascular resistance is lowest at FRC and increases at both higher and lower volumes.

**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.

**Figure 10-19.** Obstructive versus restrictive lung diseases. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV\textsubscript{1}) in normal subjects and patients with lung disease. RV, residual volume; TLC, total lung capacity; VC, vital 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 (i.e., 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 ($V/Q$ mismatch, where $V$ is ventilation rate and $Q$ 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:

$$V_d = V_t \cdot \frac{P_{aco} - P_{eco}}{P_{aco}}$$

where $V_d$ is the physiologic dead space (mL); $V_t$ is the tidal volume (mL); $P_{aco}$ is the arterial partial pressure of carbon dioxide (mm Hg); and $P_{eco}$ is the partial pressure of carbon dioxide in expired air (mm Hg).

### Table 10-6. Lung Volumes in Restrictive Versus Obstructive Disease

<table>
<thead>
<tr>
<th></th>
<th>RV</th>
<th>FRC</th>
<th>TLC</th>
<th>FVC</th>
<th>FEV$_1$</th>
<th>FEV$_1$/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Restrictive</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓↓↓</td>
<td>↑ or normal</td>
</tr>
</tbody>
</table>

FEV$_1$, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

### 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 O₂ 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:

\[ P = \frac{2T}{r} \]

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 \( V/Q \) mismatch and shunting.

### 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.

### 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.

\[
\text{Alveolar ventilation} = (V_T - V_D) \times \text{Breaths/min}
\]

\[
V_A = \frac{V_{CO_2}}{P_{CO_2}} = 0.863 \frac{V_{CO_2}}{P_{CO_2}}
\]
where $V_a$ is alveolar ventilation (L/min), $V_{CO_2}$ is the rate of CO$_2$ production in the body (mL/min), $F_{ACO_2}$ is the fraction of alveolar CO$_2$, $P_{aco_2}$ is the partial pressure of CO$_2$ in the arterial blood, and 0.863 is the temperature and pressure-adjusted conversion between $F_{aco_2}$ and $P_{aco_2}$.

Increasing alveolar ventilation through increased depth (tidal volume) or rate of breathing results in a proportionate decrease in $P_{aco_2}$.

**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.

\[ \text{Compliance (C)} = \frac{\Delta \text{Volume (V)}}{\Delta \text{Pressure (P)}} \]

where C is in mL/cm H₂O, V is in mL, and P is in cm H₂O (1 cm H₂O = 0.74 mm Hg).

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.

---

**KEY FACT**

In **emphysema**, there is destruction of elastic tissue, so C ↑.

In **fibrotic lung disease**, the lungs become stiffer, so C ↓.
**CHAPTER 10: RESPIRATORY**

**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 10-22. 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.

**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.

\[
\text{Intrapleural pressure} = -5 \text{ cm H}_2\text{O} \\
\text{Intra-alveolar pressure} = 0 \text{ cm H}_2\text{O}
\]

In **emphysema**, the lungs have a decreased tendency to collapse due to a loss of elasticity (compliance \( \uparrow \)). 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 \( \downarrow \)), 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:

\[
\text{Intrapleural pressure: Decreases from } -5 \text{ to } -8 \text{ cm H}_2\text{O} \\
\text{Intra-alveolar pressure } < 0 \text{ cm H}_2\text{O}, \text{ so air flows into the lungs}
\]

**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.

\[
\text{Intrapleural pressure} = -8 \text{ cm H}_2\text{O} \\
\text{Intra-alveolar pressure} = 0 \text{ cm H}_2\text{O}, \text{ so no air flows}
\]

**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.

\[
\text{Intrapleural pressure: Increases from } -8 \text{ to } -5 \text{ cm H}_2\text{O (may increase into positive range, depending on the patient)} \\
\text{Intra-alveolar pressure } > 0 \text{ cm H}_2\text{O}, \text{ so air flows out of the lungs}
\]

**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 H2O
Intra-alveolar pressure = 0 cm H2O, 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 H2O). 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.

**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.

\[
\dot{V} = \frac{\Delta P}{R}
\]

where \(\dot{V}\) is the ventilation rate (airflow); \(\Delta P\) is the pressure gradient; and \(R\) is resistance.

Note that the dot over the \(V\) 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:

\[
R = \frac{(8\eta l)/\pi r^4}{
\]

where \(R\) is resistance, \(\eta\) 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).

**Factors That Influence Pulmonary Resistance**

- **Contraction of bronchial smooth muscle:**
  - **Sympathetic stimulation:** Airways dilate via \(\beta_2\)-adrenergic receptors, thus decreasing resistance. **Albuterol** is a common \(\beta_2\) agonist and is used in an inhaled form by patients with asthma or chronic obstructive pulmonary disease (COPD).
  - **Parasympathetic stimulation:** Airways constrict via \(M_2\)-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 (P_{O_2}), and the 50% hemoglobin capacity (P_{50}). Calculated by the equation:
  \[ O_2 \text{ content} = O_2 \text{ bound to hemoglobin} + O_2 \text{ dissolved in blood} \]
  \[ O_2 \text{ content (mL/dL blood)} = (1.34 \text{ mL O}_2/\text{dL blood} \times [\text{Hemoglobin}] \times \text{Spo}_2) + (0.0031 \text{ mL/mm Hg O}_2 \times \text{P}_{\text{aO}_2}) \]
  Using typical values of hemoglobin = 14 g/dL, Sp_{O_2} = 1.00 (100%), and partial arterial pressure of oxygen (P_{aO_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 P_{O_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 P_{CO_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 P_{CO_2}, altitude, 2,3-diphosphoglycerate, or temperature, or an increase in pH, will cause a leftward shift of the curve.
- During exercise, P_{O_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 (α_2γ_2) does not bind 2,3-DPG as strongly as adult hemoglobin (α_2β_2), shifting the curve to the left. This helps the fetus obtain O_2 from the mother’s RBCs.
There are several important regions of the oxygen-hemoglobin dissociation curve worth remembering:

- At a $P_{O_2}$ of > 70 mm Hg, hemoglobin is essentially 100% saturated. Arterial blood has a $P_{O_2}$ of around 100 mm Hg.
- At a $P_{O_2}$ of 40 mm Hg, hemoglobin is 70% saturated. Venous blood is at this level of oxygenation.
- At a $P_{O_2}$ of 25 mm Hg, hemoglobin is 50% saturated. This is the $P_{50}$ (50% saturation point) of hemoglobin.

Carbon Dioxide Transport

CO₂ is produced in the body’s tissues and carried to the lungs via the venous blood. It is transported in three forms:

- HCO₃⁻ (bicarbonate), formed by the combination of CO₂ and H₂O by the enzyme carbonic anhydrase, is the major mode of carbon dioxide transportation, making up 70% of CO₂ in the blood. This reaction reverses in the lungs, where HCO₃⁻ enters RBCs in exchange for Cl⁻, and CO₂ is reformed by carbonic anhydrase and expired (Figure 10-25).
- Dissolved CO₂, 5–9% which is free in the bloodstream.
- Carbaminohemoglobin, 21–25% which is CO₂ bound to hemoglobin. In the lungs, the oxygenation of hemoglobin promotes the dissociation of CO₂ 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 (HCO₃⁻) and acid (H⁺ and fixed [nonvolatile] acids) in the urine, whereas the lungs remove volatile acid from the circulation in the form of exhaled CO₂. 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 CO₂ ($P_{CO_2} > 40$ mm Hg), leading to an increase in blood [H⁺] and [HCO₃⁻].
- Renal compensation: Increased excretion of $H^+$ and $NH_4^+$ and increased reabsorption of HCO₃⁻.
CHAPTER 10
RESPIRATORY

Acute respiratory acidosis: Renal compensation has not yet occurred (intracellular fluid buffering only). Each 10 mm Hg increase in \( P_{aCO_2} \) 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 \( P_{aCO_2} \) 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 \( CO_2 \) \( (P_{aCO_2} < 40 \text{ mm Hg}) \), leading to a decrease in blood [H+] and [\( HCO_3^- \)].

Renal compensation: Decreased excretion of H+ and \( NH_4^+ \), decreased reabsorption of \( HCO_3^- \).

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.

Figure 10-25. Carbon dioxide transport. \( CO_2 \) handling in the RBC. Hb\(^+\), ionized hemoglobin; HHb, deionized hemoglobin.

Figure 10-26. Haldane effect. As RBCs pass through the alveolar capillaries and the partial pressure of oxygen (\( P_{O_2} \)) increases from 70% to almost 100%, the \( CO_2 \) dissociation curve shifts downward. This promotes the dissociation of \( CO_2 \) from the RBCs.
Acute respiratory alkalosis: Renal compensation has not yet occurred (intracellular fluid buffering only). Each 10 mm Hg decrease in PaCO₂ leads to a 2 mEq/L decrease in HCO₃⁻ and a 0.08 rise in pH.

Chronic respiratory alkalosis: Renal compensation has occurred. Each 10 mm Hg decrease in PaCO₂ leads to a 5 mEq/L decrease in HCO₃⁻ 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).

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 CO₂ and thus carbonic acid, although this cannot completely compensate for the acidosis.
- Conversely, in metabolic alkalosis, hypoventilation occurs to retain CO₂ and thus carbonic acid, although this cannot completely compensate for the alkalosis.

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).](image)

<table>
<thead>
<tr>
<th></th>
<th>Acidity</th>
<th>Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>↑ 1 mEq/L</td>
<td>↓ 0.08</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>↑ 3.5 mEq/L</td>
<td>↓ 0.03</td>
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<table>
<thead>
<tr>
<th><strong>Acid-Base Disturbances</strong></th>
<th><strong>Acidosis</strong></th>
<th><strong>Alkalosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCO₃⁻</strong></td>
<td><strong>Δ</strong></td>
<td><strong>Δ</strong></td>
</tr>
<tr>
<td><strong>PH</strong></td>
<td><strong>Δ</strong></td>
<td><strong>Δ</strong></td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td>↑ 1 mEq/L</td>
<td>↓ 0.08</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>↑ 3.5 mEq/L</td>
<td>↓ 0.03</td>
</tr>
</tbody>
</table>

CLINICAL CORRELATION

Treat altitude sickness with acetazolamide, a carbonic anhydrase inhibitor that increases the renal excretion of HCO₃⁻.

KEY FACT

Normal pH in the presence of abnormal HCO₃⁻ or CO₂ suggests a mixed disorder.
Normal pulmonary vascular resistance (PVR) = 20–120 dynes \cdot s \cdot cm^{-5}. This is \sim 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 (V\dot) and perfusion (Q\dot). This is known as V\dot/Q\dot 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.
  - Q\dot is reduced relative to V\dot; therefore, V/Q is increased. In extreme cases, zone 1 can approximate dead space (Q\dot = 0, so V/Q \to \infty).
  - Po2 is the highest and Pco2 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.
  - Q\dot is increased relative to V\dot, so V/Q is decreased. In extreme cases, zone 3 can approximate shunt (Q\dot >> V\dot, so V/Q \to 0).
  - Po2 is the lowest and Pco2 is the highest in zone 3 due to decreased gas exchange and airway closure.

**TABLE 10-8. Calculating Cardiac Output, Pulmonary Vascular Resistance, and Systemic Vascular Resistance**

<table>
<thead>
<tr>
<th>CALCULATION</th>
<th>NORMAL VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>SV \times HR</td>
</tr>
<tr>
<td>PVR</td>
<td>\frac{[\text{MPAP} - \text{MLAP}]/(\text{CO})]}{80}</td>
</tr>
<tr>
<td>Note: Units for pressure and CO should be mm Hg and L/min, respectively. The factor of 80 converts the units to dynes \cdot s \cdot cm^{-5}.</td>
<td></td>
</tr>
<tr>
<td>SVR</td>
<td>\frac{[\text{MAP} - \text{MRAP}]/(\text{CO})]}{80}</td>
</tr>
</tbody>
</table>

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.
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 Pa\(_{O_2}\). In a normal individual, the blood leaving the lungs should have an O\(_2\) tension (Pa\(_{O_2}\)) approximately equal to the O\(_2\) tension within the alveoli (P\(_{A_2}\)).

\[
\text{Pa}_{O_2} = F_iO_2(P_b - P_{H_2O}) - (\text{PaCO}_2/R)
\]

where \(F_iO_2\) is the fraction of inspired air that is O\(_2\) (0.21 on room air, 1.00 for pure oxygen); \(P_b\) is the barometric pressure (760 torr at sea level, where 1 torr = 1 mm Hg = 133 Pa); \(P_{H_2O}\) is the vapor pressure of H\(_2\)O in the alveoli (47 torr at 37°C); \(\text{PaCO}_2\) 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.

**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. \(P_{A_2}\), alveolar pressure; \(P_a\), arterial pressure, \(P_v\), venous pressure.

<table>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW (O_2)</td>
<td>LOW PH</td>
<td>HISTAMINE</td>
<td>PROSTAGLANDINS</td>
<td>NITRIC OXIDE</td>
<td>ENDOThELIN</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
For a patient breathing room air, this can be simplified to:

$$\text{Pao}_2 = 150 - 1.25(\text{Paco}_2)$$

Once $\text{Pao}_2$ is calculated, the actual $\text{Pao}_2$ can be measured via arterial blood gas testing. The difference between the $\text{Pao}_2$ and $\text{Pao}_2$ is the alveolar-arterial $\text{O}_2$ gradient (A-a gradient, or AaD $\text{O}_2$), 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, V/Q mismatch, and diffusion impairment, but it is unchanged in the case of pure hypoventilation or low $\text{FiO}_2$.

**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 $\text{Pao}_2$ and an increased $\text{Paco}_2$. Since alveolar ventilation is also reduced, there is no increase in A-a gradient.

2. **Decreased inspired $\text{O}_2$**: This occurs most commonly at high altitudes, where the $\text{Pb}$ is decreased. This causes a reduction in $\text{Pao}_2$ due to the decrease in $\text{Pao}_2$. 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 $\text{Po}_2$ 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.
   - $\text{O}_2$ is normally a perfusion-limited gas. This means that $\text{O}_2$ 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 $\text{O}_2$ diffusion is a very rare cause of hypoxemia.
   - $\text{O}_2$ 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 $\text{DLco}$ (diffusion capacity of the lung for carbon monoxide) value. CO is used in place
CHAPTER 10

RESPIRATORY

of oxygen because of the very high affinity of hemoglobin for CO. Dlco is a surrogate for the surface area available for gas exchange.

- Dlco is decreased when useful surface area for gas exchange is lost, such as in emphysema, interstitial lung disease, and pulmonary vascular disease.
- Dlco may be increased in the presence of intraparenchymal hemorrhage, increased blood volume due to CHF, or polycythemia (increased hematocrit).

4. V\textsubscript{Q}/Q\textsubscript{Q} mismatch: The V\textsubscript{Q}/Q\textsubscript{Q} ratio is the ratio of ventilation to pulmonary blood flow. Under normal circumstances, V\textsubscript{Q}/Q\textsubscript{Q} ≈ 0.8, although it varies with position in the lungs (see previous discussion of lung zones). When the V\textsubscript{Q}/Q\textsubscript{Q} ratio is altered, hypoxemia can result. There is also an increased A-a gradient. Deviation of the V\textsubscript{Q}/Q\textsubscript{Q} ratio from normal indicates the presence of a shunt (Figure 10-30).

- V\textsubscript{Q}/Q\textsubscript{Q} mismatch in airway obstruction: If the airway is completely blocked and blood flow remains, then V = 0, so V\textsubscript{Q}/Q\textsubscript{Q} = 0, and there is a shunt. Since there is no gas exchange, the values of PO\textsubscript{2} and PCO\textsubscript{2} for pulmonary capillary blood approach the values of mixed venous blood (PaO\textsubscript{2} = 40 mm Hg, PaCO\textsubscript{2} = 46 mm Hg).

- V\textsubscript{Q}/Q\textsubscript{Q} mismatch in pulmonary embolism: If blood flow is completely blocked, then Q = 0, so V\textsubscript{Q}/Q\textsubscript{Q} = \infty and there is complete dead space. This results in increased CO\textsubscript{2} retention, although this is rarely seen since patients with PE often hyperventilate and may even become hypocapnic as a result. Local bron-

2,3-DPG, 2,3-diphosphoglycerate; PaO\textsubscript{2}, partial alveolar pressure of oxygen; PaO\textsubscript{2}, partial arterial pressure of oxygen; PVR, pulmonary vascular resistance.

### KEY FACT

- V\textsubscript{Q}/Q\textsubscript{Q} of 0 suggests airway obstruction (shunt); 100% O\textsubscript{2} does not improve PO\textsubscript{2}.
- V\textsubscript{Q}/Q\textsubscript{Q} of \infty suggests a blood flow obstruction (physiologic dead space); 100% O\textsubscript{2} improves PO\textsubscript{2}.

### QUESTION

A man at sea level suffers from dyspnea. His ABG shows PaO\textsubscript{2} of 70 mm Hg and PaCO\textsubscript{2} of 35 mm Hg. What is the equation for A-a gradient and PaO\textsubscript{2}?

### TABLE 10-10. Response to High Altitude

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO\textsubscript{2}</td>
<td>Decreased (hypoxemia)</td>
</tr>
<tr>
<td>PaO\textsubscript{2}</td>
<td>Decreased (due to ↓ barometric pressure)</td>
</tr>
<tr>
<td>Ventilation rate</td>
<td>Increased (hyperventilation due to hypoxemia)</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>Increased (respiratory alkalosis)</td>
</tr>
<tr>
<td>Hemoglobin concentration</td>
<td>Increased (polycythemia)</td>
</tr>
<tr>
<td>2,3-DPG concentration</td>
<td>Increased</td>
</tr>
<tr>
<td>Hemoglobin-O\textsubscript{2} curve</td>
<td>Right shift</td>
</tr>
<tr>
<td>PVR</td>
<td>Increased (hypoxic vasoconstriction)</td>
</tr>
</tbody>
</table>

2,3-DPG, 2,3-diphosphoglycerate; PaO\textsubscript{2}, partial alveolar pressure of oxygen; PaO\textsubscript{2}, partial arterial pressure of oxygen; PVR, pulmonary vascular resistance.

### 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.
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 (\( P_{O_2} = 150 \text{ mm Hg}, P_{CO_2} = 0 \text{ mm Hg} \)).

- In most cases of \( V/Q \) mismatch, there is neither true shunt nor complete dead space, but simply an abnormal \( V/Q \) 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 \( P_{O_2} \).

5. **Shunt:** As mentioned previously, shunt is an extreme case of \( V/Q \) mismatch that occurs when some blood reaches the systemic circulation without being oxygenated, reducing \( P_{O_2} \). Since the \( P_{O_2} \) 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 \( P_{O_2} \).

- **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 \( P_{O_2} \) since oxygenated blood is returning to the right side of the heart, raising the \( P_{O_2} \).

- True shunt can be differentiated from \( V/Q \) mismatch by giving the hypoxemic patient 100% \( O_2 \). This increases \( P_{O_2} \) in the case of \( V/Q \) 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 \( P_{O_2} \) of at least 400 torr on 100% oxygen.

**Hypercapnia**

Alveolar ventilation is the main determinant of \( P_{CO_2} \). 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.
- \( V/Q \) 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.

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 \( [\text{inspiration-to-expiration}] \) 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
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. CO₂ from arterial blood diffuses into the CSF and combines with H₂O to form H⁺ and HCO₃⁻.
- **Peripheral chemoreceptors in the carotid and aortic bodies:** Increased PaCO₂ or decreased pH or PaO₂ stimulate these chemoreceptors to increase respiratory rate. PaO₂ 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.

**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).

**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**

<table>
<thead>
<tr>
<th>SOUND</th>
<th>DESCRIPTION</th>
<th>COMMON ETIOLOGIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crackles (rales)</td>
<td>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).</td>
<td>Wet crackles: pneumonia, pulmonary edema (eg, congestive heart failure) Dry crackles: pulmonary fibrosis</td>
</tr>
<tr>
<td>Wheezes</td>
<td>Whistling sound. Can be heard during inspiration or expiration. Caused by air passing through narrowed airways.</td>
<td>Obstructive diseases: asthma, chronic obstructive pulmonary disease (COPD), bronchitis, foreign body aspiration (FBA)</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>Low-pitched “snoring” sound. Suggests secretions in large airways.</td>
<td>Asthma, COPD, bronchitis</td>
</tr>
<tr>
<td>Stridor</td>
<td>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 tracheal; often a medical emergency.</td>
<td>Laryngotracheitis (croup), FBA</td>
</tr>
<tr>
<td>Pleural rub</td>
<td>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.</td>
<td>Connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis) Infections (viral, bacterial, fungal)</td>
</tr>
</tbody>
</table>
CHAPTER 10

RESPIRATORY

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>
<thead>
<tr>
<th>TABLE 10-12. Lung Percussion Findings</th>
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<tbody>
<tr>
<td><strong>SOUND</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Dullness, flatness</td>
</tr>
<tr>
<td>Resonance</td>
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<tr>
<td>Hyperresonance, tympany</td>
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<table>
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<tr>
<th>TABLE 10-13. Lung Palpation Findings</th>
</tr>
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<tbody>
<tr>
<td><strong>FEATURE</strong></td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>Chest wall expansion</td>
</tr>
<tr>
<td>Tenderness</td>
</tr>
<tr>
<td>Crepitus</td>
</tr>
<tr>
<td>Tactile fremitus</td>
</tr>
<tr>
<td>Tracheal positioning</td>
</tr>
</tbody>
</table>
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.
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 V/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.
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). $\alpha_1$-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 $\alpha_1$-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 $\alpha_1$-antitrypsin.
- **Hereditary $\alpha_1$-antitrypsin deficiency:** Autosomal dominant. Accounts for 1% of emphysema cases. Emphysema develops secondary to unopposed elastase activity. Patients with $\alpha_1$-antitrypsin deficiency often develop emphysema at a much younger age than smokers, often younger than 45 years.

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).

---

**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.

**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).
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”: $P_{aO_2}$ 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 $V/Q$ mismatch is not severe. Patients require a high minute ventilation to maintain normal levels of $P_{aO_2}$ and $P_{aCO_2}$, 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 $\alpha_1$-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, $P_{aO_2}$ 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 $P_{aCO_2}$, elevated $HCO_3^-$, and slightly decreased pH). During an acute exacerbation, $P_{aO_2}$ drops and $P_{aCO_2}$ 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 $\alpha_1$-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:
  - $\beta_2$-agonists (albuterol, salmeterol, formoterol)
  - Anticholinergics (ipratropium, tiotropium)
- Corticosteroids are used in acute exacerbations (PO/IV) and for long-term control (inhaled).
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; V/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 FEV₁ and FEV₁:FVC ratio. FVC is often preserved.
  - Lung volumes: In patients with dynamic hyperinflation, TLC, FRC, and RV may be increased.
  - Diffusing capacity (DLCO): Typically normal. Despite the airway obstruction due to mucus plugging, the alveolar walls function normally.
- Arterial blood gas testing: PaO₂ is often decreased, and PaCO₂ 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 O₂ can treat hypoxemia, reduce hypoxic vasoconstriction and polycythemia, thereby reducing the incidence of pulmonary hypertension. Supplemental O₂ 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 (e.g., 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>
<thead>
<tr>
<th>MEDIATOR</th>
<th>PHYSIOLOGIC EFFECT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin-1</td>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>NO</td>
<td>PGE₂</td>
</tr>
<tr>
<td>15-HETE</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Cytokines:</td>
<td>Inflammation</td>
</tr>
<tr>
<td>- GM-CSF</td>
<td></td>
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<tr>
<td>- IL-8</td>
<td></td>
</tr>
<tr>
<td>- RANTES</td>
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<tr>
<td>- Eotaxin</td>
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<tr>
<td>Growth factors:</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>- EGF</td>
<td>Smooth muscle hyperplasia</td>
</tr>
<tr>
<td>- IGF-1</td>
<td></td>
</tr>
<tr>
<td>- PDGF</td>
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</tbody>
</table>

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; PGE₂, prostaglandin E₂.
**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 FEV₁ and FEV₁: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).
- **Arterial blood gas testing:** During an attack, Pao₂ is often reduced due to hypoxemia resulting from V/Q mismatch. Paco₂ is also reduced due to hyperventilation. Paco₂ 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.
- β₂-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 fibrosis.

**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 10-38. Mucus plug.](image)

**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.

![Figure 10-39. Bronchiectasis.](image)
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 hemoptyis.

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.

**RESTRICTIVE LUNG DISEASES**

Restrictive lung diseases are characterized by reduced lung expansion (decreased lung volume). TLC and RV are reduced. In turn, FEV<sub>1</sub> and FVC are decreased. FEV<sub>1</sub> and FVC decrease proportionately, resulting in a normal FEV<sub>1</sub>:FVC, or FVC is decreased to a greater degree than FEV<sub>1</sub>, resulting in an increased FEV<sub>1</sub>: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.

---

**KEY FACT**

FEV<sub>1</sub>: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).
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 Vd:Vt ratio, reducing alveolar ventilation and increasing PaCO₂. 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 auto-antibodies 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, FEV₁, FVC, TLC, and RV are usually decreased, but these are neither sensitive nor specific.

**Treatment**

Supplemental O₂ 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 $\text{PaO}_2/\text{FiO}_2$:
   - 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.

Etiologies include pneumonia, inhalation of irritants, $\text{O}_2$ 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 V/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 cardiomediasstinal 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 O₂ may not increase Pao₂ 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).

**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, V/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.
- Fet al 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.
■ **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 O₂ 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 V/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, FEV₁, and FVC, with a normal or increased FEV₁:FVC ratio. Dlco 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

<table>
<thead>
<tr>
<th>NAME</th>
<th>EXPOSURE</th>
<th>PATHOLOGY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestosis</td>
<td>Asbestos fibers (associated with shipbuilding, roofing, plumbing, insulation, construction work)</td>
<td>“Ivory white” calcified pleural plaques are pathognomonic for asbestos exposure but are not precancerous. Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells.</td>
<td>Interstitial fibrosis primarily affects the lower lobes. Associated with an increased incidence of bronchogenic carcinoma and mesothelioma (bronchogenic &gt;&gt; mesothelioma). Concomitant cigarette smoking multiplies the risk of developing lung cancer.</td>
</tr>
<tr>
<td>Coal workers’ pneumonia</td>
<td>Prolonged coal dust exposure (coal miners)</td>
<td>Black lungs; coal dust contains silica and carbon. Progresses from anthracosis (mild, asymptomatic form seen in city dwellers and smokers).</td>
<td>Interstitial fibrosis primarily affects the upper lobes and develops secondary to activation of carbon-laden macrophages. Not associated with lung cancer.</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Silica (associated with sandblasting; also seen in foundries and mines; quartz and other minerals)</td>
<td>“Eggshell” calcification of hilar lymph nodes. Silicotic nodules.</td>
<td>Interstitial fibrosis primarily affects upper lobes. Silica disrupts phagolysosome in macrophages, increasing susceptibility to tuberculosis. Associated with increased risk of bronchogenic carcinoma.</td>
</tr>
</tbody>
</table>

- **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.

**Sarcoïdosis**

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...
in asymptomatic patients on chest film (Figure 10-44A). Less often, presents with extra-
pulmonary 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.
CHAPTER 10

RESPIRATORY

**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.

**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.

**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.
CHAPTER 10

RESPIRATORY

Presentation

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.

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.

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, V/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.
CHAPTER 10 RESPIRATORY

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 S4 and loud P2 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.
  - V/Q scan: Shows an area of V/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 $P_{aO_2}$ due to increased dead space. Decreased $P_{aCO_2}$ due to tachypnea. A-a gradient increased due to V/Q mismatch.

### TABLE 10-16. Types of Emboli

<table>
<thead>
<tr>
<th>TYPE</th>
<th>COMMENTS</th>
<th>EXAMPLE PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Associated with long-bone fractures and liposuction.</td>
<td>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.</td>
</tr>
<tr>
<td>Air</td>
<td>Develops in divers when nitrogen bubbles precipitate in their blood as they ascend too rapidly.</td>
<td>A 26-year-old patient develops rapid-onset dyspnea and pleuritic chest pain. On further questioning, patient reports symptoms developed while scuba diving.</td>
</tr>
<tr>
<td>Thrombus (DVT)</td>
<td>Develops after prolonged immobilization (usually ≥ 3 days).</td>
<td>Five days after abdominal surgery, a 68-year-old woman develops dyspnea and pleuritic chest pain.</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Develops in infective endocarditis, when the bacterial vegetations dislodge from the heart valves. Can travel to brain or lungs, resulting in an abscess.</td>
<td>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.</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>Develops when amniotic fluid leaks into the maternal bloodstream, usually postpartum. Can lead to disseminated intravascular coagulation (DIC).</td>
<td>A 27-year-old woman develops sudden-onset dyspnea shortly after giving birth.</td>
</tr>
<tr>
<td>Tumor cells</td>
<td>Be suspicious of malignancy when an adult presents with signs of new-onset hypercoagulability.</td>
<td>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.</td>
</tr>
</tbody>
</table>

### MNEMONIC

**Types of emboli:**

An embolus moves like a **FAT BAT** (Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor).
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.
RESPIRATORY

DIAGNOSIS

- Physical exam:
  - Lung examination often normal unless pulmonary hypertension is due to concomitant lung disease.
  - Loud P₂, right-sided S₃ and S₄.
  - 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 O₂ 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.

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.

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 PaO₂) and hypercapnia (increased PaCO₂) during sleep secondary to hypoventilation. If associated with obesity hypoventilation syndrome (see Key Fact), these patients will also have increased PaCO₂ 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.
CHAPTER 10

RESPIRATORY

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.

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.

**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.
  - 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.

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.


**CHAPTER 10 RESPIRATORY**

**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.

**Figure 10-51. Superior vena cava and Pancoast tumor.**

- **A** Blushing 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.

**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**

Asbestos 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?
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.

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.

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.

![Pneumonia Classifications](image)

**Figure 10-52.** Pneumonia classifications based on etiology, presentation, and pattern on chest x-ray (CXR).
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 (e.g., 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*.

**Table 10-17. Most Common Causes of Pneumonia by Age**

<table>
<thead>
<tr>
<th>NEONATES (&lt;4 WK)</th>
<th>CHILDREN (4 WK–18 YR)</th>
<th>ADULTS (18–40 YR)</th>
<th>ADULTS (40–65 YR)</th>
<th>ELDERLY (&gt;65 YR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococci</td>
<td>Viruses (RSV)</td>
<td>Mycoplasma</td>
<td><em>S pneumoniae</em></td>
<td><em>S pneumoniae</em></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Mycoplasma</td>
<td><em>C pneumoniae</em></td>
<td><em>Haemophilus influenzae</em></td>
<td>Influenza virus</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em> (infants–3 yr)</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Anaerobes</td>
<td>Anaerobes</td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em> (school-aged children)</td>
<td>Viruses</td>
<td><em>H influenzae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S pneumoniae</em></td>
<td></td>
<td>Mycoplasma</td>
<td>Gram-negative rods</td>
<td></td>
</tr>
</tbody>
</table>
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 $P_{aO_2}$ with normal or reduced $P_{aco_2}$ 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.

| 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* |

**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**

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>CHARACTERISTICS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Gram-positive cocci (chains). Most common cause of community-acquired pneumonia.</td>
<td>Penicillins&lt;br&gt;First- and second-generation cephalosporins&lt;br&gt;Macrolides (if penicillin allergic)&lt;br&gt;Quinolones</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Gram-positive cocci (clusters). Usually causes bronchopneumonia.</td>
<td>MSSA:&lt;br&gt;First or second-generation cephalosporins&lt;br&gt;Penicillinase-resistant penicillins&lt;br&gt;MRSA:&lt;br&gt;Vancomycin, ceftaroline, linezolid, tigecycline</td>
</tr>
<tr>
<td><strong>Gram-Negative Bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Gram-negative coccobacilli. Requires chocolate agar with hematin (factor X) and NAD+ (factor V) for culture.</td>
<td>Amoxicillin +/- clavulanate&lt;br&gt;Second- or third-generation cephalosporins</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>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.</td>
<td>Aminoglycosides&lt;br&gt;First-, second-, or third-generation cephalosporins</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Gram-negative rod. Non-lactose fermenting, oxidase (+). Produces pyocyanin (blue-green pigment) and has grape-like odor.</td>
<td>Extended-spectrum β-lactams&lt;br&gt;Ampicillin&lt;br&gt;Aztreonam&lt;br&gt;Ciprofloxacin&lt;br&gt;Aminoglycosides&lt;br&gt;Colistin, polymyxin B (multidrug-resistant strains)</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>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 (e.g., air conditioning systems, hot water tanks, cruise ships). Labs show hyponatremia.</td>
<td>Macrolides&lt;br&gt;Quinolones</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>Gram-negative diplococcus. Typically associated with otitis media (children) and COPD exacerbations (elderly), but can cause pneumonia in the latter population.</td>
<td>Second- or third-generation cephalosporins&lt;br&gt;Macrolides&lt;br&gt;Quinolones</td>
</tr>
<tr>
<td><strong>Other Bacteria (eg, Anaerobes, Intracellular)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Part of normal oral flora. Associated with aspiration pneumonia.</td>
<td>Clindamycin</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>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.</td>
<td>Macrolides&lt;br&gt;Doxycycline&lt;br&gt;Fluoroquinolone</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Obligate intracellular organisms. Cell wall lacks muramic acid. Does not show up on Gram stain. Giemsa or fluorescent antibody-stained smear shows cytoplasmic inclusions. <em>C pneumoniae</em> and <em>C psittaci</em> cause atypical pneumonia.</td>
<td>Macrolides&lt;br&gt;Doxycycline</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>Ricketsial organism. Obligate intracellular. Causes Q fever, which presents as pneumonia. Transmitted by spore inhalation from cattle/sheep amniotic fluid.</td>
<td>Doxycycline</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-sensitive *S aureus*; NAD+, oxidized nicotinamide adenine dinucleotide.
CHAPTER 10
RESPIRATORY

■ All HIV patients with a CD4+ count lower than 200 cells/mm³ should receive prophylaxis against *Pneumocystis jirovecii* (PCP). Therapy can include trimethoprim-sulfamethoxazole (TMP-SMX; most common, except with sulfal 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, zanamivir) 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.

**Treatment**

Six months of treatment with isoniazid (INH), pyridoxine (vitamin B₆), 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-
CHAPTER 10 RESPIRATORY

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.

**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 B₆). 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).
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.

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.
CHAPTER 10
RESPIRATORY

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**

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>BREATH SOUNDS</th>
<th>PERCUSSION</th>
<th>FREMITUS</th>
<th>TRACHEAL DEVIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atelectasis (bronchial obstruction)</td>
<td>↓</td>
<td>Dull</td>
<td>↓</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>↓</td>
<td>Dull</td>
<td>↓</td>
<td>Midline or contralateral (if large)</td>
</tr>
<tr>
<td>Simple pneumothorax&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↓</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>Midline</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>↓</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Consolidation (lobar pneumonia, pulmonary edema)</td>
<td>Bronchial breath sounds; late inspiratory crackles</td>
<td>Dull</td>
<td>↑</td>
<td>Midline</td>
</tr>
</tbody>
</table>

<sup>a</sup>Simple pneumothorax = nonexpanding (in contrast to tension pneumothorax).

**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).
CHAPTER 10

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.

- H1 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.
CHAPTER 10 RESPIRATORY

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

DRUG NAMES
Diphenhydramine, dimenhydrinate, chlorpheniramine.

MECHANISM
Reversibly inhibit H₁ histamine receptors, which are involved in the inflammatory process. Major effects of H₁ 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: H₁ blockers also competitively inhibit muscarinic receptors, which contribute to the signs and symptoms associated with motion sickness.
- Sleep aid: H₁ 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 H₁ receptors.
- Unlike first-generation H₁ blockers, second-generation H₁ 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.

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.

**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.
CHAPTER 10 RESPIRATORY 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
- **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 (PGI₂). 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.

**β₂-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.

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**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 (M3), 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 β2-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 Fe region (FcεRI).
**Uses**
Considered when asthma is refractory to long-acting $\beta_2$-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.
Respiratory
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.

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.

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**CASE 1**

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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.
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.

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.
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.](image)

(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 β₂-agonist, helps relax bronchial smooth muscle and decrease airway obstruction. However, for long-term control of persistent symptoms, inhaled corticosteroids are the best treatment.
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).

**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.
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).

**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, α1-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.
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.


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 (FEV₁) is decreased, forced vital capacity (FVC) is normal or decreased, and the FEV₁/FVC ratio is < 70% of predicted.
- In restrictive lung disease, decreased vital capacity and total lung capacity result in a FEV₁/FVC ratio of > 80%.

How would this condition affect the patient’s arterial blood gas levels (pH, PaO₂, PaCO₂, and SaO₂)?
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 (PaO₂) decreases, arterial carbon dioxide tension (PaCO₂) increases, and oxygen saturation (SaO₂) 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.
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).

**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).
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): Medial, Anterior, Lateral, Posterior, and Superior (mnemonic: MALPS).

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.
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.
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 \( \beta_2 \)-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.

**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 \( \alpha_1 \)-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.
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                     | Otitis media                   | Conjunctivitis                 |
|                                | Epiglottitis                   | Sinusitis                      | Purpuric fever (Brazilian)     |
|                                | Bacteremia                     | Tracheobronchitis              |                                 |
|                                | Cellulitis                     | Pneumonia                      |                                 |
|                                | Septic arthritis              |                                 |                                 |
| Treatment                      | Cefazidime                     | Cefalosporin                   | Rifampin                       |
|                                | Cefotaxime                     | Fluoroquinolone                |                                 |
|                                | Ceftriaxone                    | Azithromycin                   |                                 |
|                                | Gentamicin                     |                                 |                                 |
|                                |                                 |                                 |                                 |

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.
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).

**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 (FEV₁) and forced vital capacity (FVC) are decreased, but the FEV₁/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.
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).

**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.
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.

**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 pneumoniae* 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.
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 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 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.

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.
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.

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.
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.
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).

**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.
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 blocks, 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 the lungs most likely appear abnormal?

A. Left lower lobe.
B. Left upper.
C. Lingulalobe
D. Lower portion of right lower lobe
E. Right upper lobe.

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

An infant is born to a mother with poorly controlled type 2 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

The correct answer is C. 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 lobe and inferior lobe bronchi. Because of this, aspiration pneumonitis contracted 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. It’s chosen 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 correct. It’s chosen 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 correct. It’s chosen 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. Lingula lung.

E is not correct. 5/10 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 Spine position–Aspirated consonant

Bottom Line: The left 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 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. Abnormal development of the midgut loop would not account for the thoracic findings in this infant. Although the lungs are not properly developed in this scenario, it is the result of the diaphragmatic hernia and 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.

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-Pleuroperitoneal Folds
D-Respiratory diverticulum
E-Tracheoesophageal septum

The correct answer is D. 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 was illustrated for the abnormal location of this infant’s heart sounds). This occurs most commonly as a result of the pleuropertioneal 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 pleuroperitoneal folds, the body wall, and the dorsal mesentery of the esophagus. This can be remembered by the mnemonic: "Seven Parts Diaphragm." The mesonephros gives rise to the mesonephric, which is not at all implicated in this scenario.

Stab wounds to the chest can result in either a hemothorax or pneumothorax. This vignette describes a pneumothorax. A lobular pneumonia is commonly associated with rusty, purulent sputum filled with neutrophils.

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 likely type found on the right-side during x-ray of this patient’s chest?

A-Hemothorax
B-Ninth rib fracture
C-Pleural effusion
D-Pneumothorax

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. With inspiration, the diaphragm descends, lowering the intrapleural pressure. If there 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 the pleural space. This finding is a medical emergency. With pneumothoraces, the patient should be assessed for signs and symptoms of hemodynamic compromise. This patient, for example, is hypotensive, tachypneic, and tachycardic, and therefore requires urgent management.

The correct answer is C. 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. With inspiration, the diaphragm descends, lowering the intrapleural pressure. If there 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 the pleural space. This finding is a medical emergency. With pneumothoraces, the patient should be assessed for signs and symptoms of hemodynamic compromise. This patient, for example, is hypotensive, tachypneic, and tachycardic, and therefore requires urgent management.

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The correct answer is E. 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. With inspiration, the diaphragm descends, lowering the intrapleural pressure. If there 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 the pleural space. This finding is a medical emergency. With pneumothoraces, the patient should be assessed for signs and symptoms of hemodynamic compromise. This patient, for example, is hypotensive, tachypneic, and tachycardic, and therefore requires urgent management.
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 underlying anatomic malformation that led to the development of symptoms seen in this patient?

A-Failure of the pleuropertoneal 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

Transposition of the great vessels of the heart

The correct answer is E. Congenital diaphragmatic hernia (shown in the image) usually represents failure of the pleuropertoneal canal to close completely, leading to protrusion of the abdominal viscera into the chest. It is usually 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. 75% of the patients with a patent ductus arteriosus presents a left-to-right shunt. In other words, it allows blood to flow from the systemic circulation to the pulmonary circulation. Therefore, pulmonary blood flow is excessive. The ductus arteriosus will close within the first few days of life. Moreover, the ductus arteriosus is not connected to the pulmonary circulation during fetal life. This patency is promoted by continuous production of prostaglandin E 2 by the ductus. Prostaglandin antagonists, such as maternal use of nonsteroidal anti-inflammatory medications, can cause fetal closure of the ductus arteriosus. This can be associated with severe fetal cardiac arrhythmias. Normally, functional closure of the ductus arteriosus occurs by about 15 hours of life in healthy infants born at term. However, premature closure can occur in utero or at birth. Premature closure increases the oxygen consumption of oxygenated blood and decreases the oxygen saturation of deoxygenated blood. It increases the Qp/Qs ratio, which in turn causes hypoxemia.

C is not correct. E is not correct. 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 hyperventilation or perinatal 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 abnormality localized at the level of the mitral valve (especially the left atrioventricular valve) that also produces atrial septal defects. Symptoms of PPHN may include tachypnea, cyanosis, and high oxygen saturation.

D is not correct. 25%-50% of the patients with pulmonary hypoplasia result secondary to a diaformic heart, 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 either anatomic anomalies. The hypoxic lung consists of a cavita, a malformed bronchial stump, and absent or poorly differentiated distal lung tissue. In more than 50% of these cases, consisting cardiac, gastrointestinal, genitourinary, and skeletal malformations are present, as well as variations in the bronchopulmonary vascularization. Typically, in the physical examination the external chest may appear normal or be small and leathery, with or without scoliosis. A mediastinal shift is observed toward the involved side, and dullness on percussion is heard over the displaced heart. In a right-sided hypoplasia the heart is displaced to the right, which may lead to a misdiagnosis of bicornurcar. Breath sounds may be decreased or absent on the side of the hypoplasia, especially over the lung bases and apex.

Bottom line: Congenital diaphragmatic hernia usually represents failure of the pleuropertoneal 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. 

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

Tracheoesophageal septum

This is an abnormal development of the esophagus, and 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 heart is pushed to the right side of the thorax. The diaphragm serves as the partition of four fetal structures: the Septum transversum, the Pleuropertoneal folds, the Body wall, and the Occlusal meosery of the esophagus. This can be remembered by the mnemonic “Several Parts Build Diaphragm.”

A is not correct. E is not correct. Mesencephalon gives rise to the midbrain, which is not at all implicated in this scenario.

A is not correct. E is not correct. The mesonephros gives rise to the kidney, which is not at all implicated in this scenario.

A is not correct. E is not correct. 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.

A is not correct. E is not correct. 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 endocardial 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 lung.

A is not correct. E is not correct. Abnormal development of the tracheoesophageal septum might give rise to a tracheoesophageal fistula. I infants with tracheoesophageal fistula 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, desmoids, and pulmonary hypoplasia.

A is not correct. E is not correct. Bottom line: The human diaphragm is derived from four parts: the septum transversum, pleuropertoneal folds, body wall, and dorsal meiosserity of the esophagus. Congenital diaphragmatic hernias result most commonly from failure of the pleuropertoneal 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 burning, and the skin immediately around the injury is moving in and out of respiration. Bilateral percussion of the chest revealed the right side to be more resonant. Which of the following will most likely tybe found on the right-side during x-ray of this patient’s chest?

A-Hemothorax  
B-Bithfracture  
C-Pleural effusion  
D-Pneumothorax  
E-Uppper aerodigestion

B is not correct. 25%-50% of the patients with pulmonary hypoplasia present secondary to a diastrophic heart, 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 either anatomic anomalies. The hypoxic lung consists of a cavita, a malformed bronchial stump, and absent or poorly differentiated distal lung tissue. In more than 50% of these cases, consisting cardiac, gastrointestinal, genitourinary, and skeletal malformations are present, as well as variations in the bronchopulmonary vascularization. Typically, in the physical examination the external chest may appear normal or be small and leathery, with or without scoliosis. A mediastinal shift is observed toward the involved side, and dullness on percussion is heard over the displaced heart. In right-sided hypoplasia the heart is displaced to the right, which may lead to a misdiagnosis of bicornurcar. Breath sounds may be decreased or absent on the side of the hypoplasia, especially over the lung bases and apex.

E is not correct. E is not correct. The mesonephros gives rise to the kidney, which is not at all implicated in this scenario.

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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-Congenital diaphragmatic hernia

B-Congenital thyrocardia

D-Dextrocardia

E-Acquired papillary thyroid cancer

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

A 50-year-old C.C. This image shows noncaseating granulomas (indicated by the circle) involving the lung parenchyma. Noncaseating granulomas are characteristic of sarcoidosis. Sarcoidosis is a multisystem inflammatory disorder of unknown origin. It is thought to be immune mediated. The lungs 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-Globulemia, 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 as alternate-otic agents, such as methotrexate, may be used.

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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 ventilation 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 C.

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. A portable 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 the alveoli?

A-Club (Clara) cells
B-Dust cells
C-Goblet cells
D-Pseudostratified columnar ciliated

E-Type I pneumocytes

- The correct answer is E.

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 granulomas 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

- The correct answer is A.
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 United States 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-Mississippi

- The correct answer is C. *Coccidioides immitis* is a dimorphic fungus with barrel-shaped arthroconidia, shown in the signet ring 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 50 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. 17% choose 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. terreus.* 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, aspergillosis, and invasive aspergillosis.

- B is not correct. 35% choose this Blastomyces dermatitidis is a dimorphic fungus that grows within humans as budding, round yeast-like cells. In 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. 25% choose *Histoplasma capsulatum* 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: *Histoplasma capsulatum* 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 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 positively for which of the following

A-CD20
B-CD30
C-CD5
D-5-S10

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 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, cyclic lung and lytic bone lesions, and cutaneous eruptions. The histiocytes are (dendritic cells) with an oval or irregular pale nucleus, pale cytoplasm, and characteristically cytoplasmic granules Birbeck granules.

- B is not correct. 1% choose this. CD20 is a B lymphocyte marker. It is helpful in diagnosing B lymphocyte-derived malignancies such as follicular lymphoma, diffuse large B-cell lymphoma, or chronic lymphocytic leukemia.

- C is not correct. 15% choose this. CD30 is present on Reed-Sternberg cells (the characteristic cells of Hodgkin lymphoma).

- A is not correct. 14% choose this CD5 is a T cell marker. However, it is also a tumor marker for chronic lymphocytic leukemia (CLL). CLL cells CD1 cells are negative for CD5 and are often positive for CD23. Additionally, CDS is a tumor marker for mantle cell lymphoma, which is caused by the BCL-1 (centrosome) -centrosome. Mantle cell lymphomas express high levels of CD5-2 and tend to manifest in men in their 50s and 60s as panleukopenia/lymphopenia.

- E is not correct. 11% choose 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 cell histiocytosis stain positive for 5-10 and CD2a.

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 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 epithymas: 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 α1-antitrypsin. Normally, α1-antitrypsin is released into the bloodstream and travels to the lung, where it protects the lungs from destruction via excessive proteolysis. 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 PNG! This lack of normal α1-antitrypsin leads to progressive and unregulated proteolysis.

- A is not correct. 12% choose this - panacinar 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. 11% choose 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 heavy smoking.

- D is not correct. 15% choose 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 ≤ 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. 24% choose 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 dyspsis or 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: Panacinar deficiency manifests as paraseptal 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-C-Lateral body wall
d-D-Pleuroperitoneal Folds
E-Septum transversum

- The correct answer is D. The ulnar fold reveals a congenital diaphragmatic hernia (CDH) in the fetus. The diaphragm is derived from four embryologic structures: the septum transversum, the pleuropertitoneal folds, the dorsal mesentery of the esophagus, and a muscular outgrowth of the lateral body wall. The pleuropertitoneal folds form a large portion of the fetal diaphragm; if they fail to form completely, the thorax and the abdomen are incompletely separated posteriorly, and the abdominal contents often herniate into the thorax (known as a Bochdalek hernia). Pressure from abdominal organs results in lung hypoplasia. The polyhydramnios can 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 receptive surface for the recycling of amniotic fluid. Newborns with CDH typically have a flat stomach and a heart displaced to the right.

- E is not correct. 1% choose 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. 0% choose this. OA through the foramen is displaced from the abdomen into the thorax in the presence of a congenital diaphragmatic hernia, its formation is normal. The foramen 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 lung is from the celiac trunk.

- C is not correct. 10% choose 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% choose 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 rare causes of congenital diaphragmatic hernia.

- Bottom Line: Polyhydramnios is common with congenital diaphragmatic hernia due to failure of the pleuropertitoneal folds to form.
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