The Physician Pharmacist: Respiratory

Lung Development:
-occurs in 5 stages = begins w/ formation of Lung buds from distal end of respiratory diverticulum during week 4 of development
-"Every Pulmonology Can See Alveoli" (EPCSA):

- **Embryonic** (Weeks 4-7):
  - Lung bud → trachea → bronchial buds → Mainstem bronchi → secondary (lobar) Bronchi → Tertiary (Segmental) Bronchi
  - Errors lead to **Tracheoesophageal Fistula**
- **Pseudoglandular** (weeks 5-17):
  - Endodermal tubules → terminal bronchioles (surrounded by modest capillary network)
  - **Respiration is Impossible at this stage and incompatible w/ Life**
- **Canalicular** (Weeks 16-25):
  - Terminal bronchioles → respiratory bronchioles → alveolar ducts (Surrounded by Prominent Capillary Network)
  - Airways increase in diameter
  - Pneumocytes develop starting at Week 20 of development
  - **Respiration capable at ~25 weeks**
- **Saccular** (Week 24-Birth):
  - Alveolar ducts → terminal sacs (separated by Primary Septae)
- **Alveolar** (week 36-8 years old)
  - Terminal sacs → Adult Alveoli (due to secondary septation)
  - In utero "Breathing" occurs via aspiration + expulsion of amniotic fluid → Pulmonary vascular resistance through gestation
  - Birth = air replaces fluid → Pulmonary Vascular Resistance

Club Cells:
-Non-ciliated, Low Columnar/Cuboidal Cells w/ Secretory Granules
-Located in Bronchioles
-Roles:

- Degrade toxins via CYP450
- Secrete components of Surfactant***
- Progenitor cells for Club + Ciliated Cells

Congenital Lung Malformations:

1. Pulmonary Hypoplasia:
-poorly developed bronchial tree w/ abnormal histology
-Associated w/ congenital **Diaphragmatic Hernia** (usually left-sided) or **Bilateral Renal Agenesis (Potter Sequence)**

2. Bronchogenic Cysts:
-abnormal budding of the foregut + 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 → airway compression, recurrent respiratory infections

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Alveolar Cell Types:

1. Type I Pneumocytes:
-Squamous, 97% of Alveolar surfaces
-Thinly line the Alveoli for Optimal Gas Exchange***

2. Type II Pneumocytes:
-Cuboidal + Clustered
-2 Functions:

1. Serve as Stem Cell Precursors for 2 Cell Types (Type I and Type II Cells); proliferation during lung damage
2. **Secrete Surfactant from lamellar bodies**

Surfactant:
- alveolar surface tension, alveolar collapse, lung recoil, lung compliance
-made of Lecithins (DPPC)
-Synthesis begins @ **20 weeks** gestation and achieves mature levels @ **35 weeks** gestation (Corticosteroids can fetal surfactant production; can be therapeutic in premature deliveries)
-Collapsing Pressure (P) = 2 (Surface tension) / Radius
-**Law of Laplace** = Alveoli have tendency to collapse on Expiration as radius

3. Alveolar Macrophages:
-phagocytose ofriegn materials + release cytokines/alveolar proteases
-Hemosiderin-Laden Macrophages (Heart-Failure Cells) may be found in setting of pulmonary edema or alveolar hemorrhage

Neonatal Respiratory Distress Syndrome (NRDS):
-Surfactant Deficiency = surface tension → alveolar collapse ("ground-glass" appearance of lung fields)
-RF = Prematurity, Gestational Diabetes (fetal insulin), C-section delivery (release of fetal glucocorticoids b/c less stressful than vaginal delivery)
-Tx = Maternal Steroids before birth + Exogenous surfactant to child

- Avoid Therapeutic Supplemental O2:
  - **Retinopathy of Prematurity**
  - **Intraventricular Hemorrhage (IVH)**
  - **Bronchopulmonary Dysplasia**

-Screening tests for Fetal Lung Maturity:

- **Lecithin-Sphingomyelin (L/S) Ratio** in Amniotic Fluid (≥ 2 is healthy, < 1.5 is predictive)
- Foam Stability Index
- Surfactant-Albumin Ratio

-Persistently low O2 Tension → risk of PDA

Respiratory Anatomy:
Conducting Zone:
-large airways = nose, pharynx, larynx, trachea and bronchi
-**Airway resistance is highest in the Large to medium sized bronchi**
-Small airways = bronchioles that further divide into terminal bronchioles (large numbers in Parallel → east airway resistance)
-Role = warms, humidifies, filters air BUT does not participate in gas exchange → **"anatomic dead space"**
-Cartilage + Goblet cells extend to the end of Bronchi
-Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus + extend to beginning of terminal bronchioles → transition to Cuboidal cells
-Clears mucus + debris from lungs via "Mucocilliary 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, alveoli** (gas exchange)
-Cuboidal cells in respiratory bronchioles → Simple squamous cells up to alveoli
-Cilia terminate in respiratory bronchioles
-Alveolar macrophages clear debris/provide immune response

Lung Anatomy;
-Right lung = 3 lobes; Left has 2 (and Lingula), Right has 3
-Relation of Pulmonary artery to bronchus at each lung hilum = RALS (**Right Anterior; Left Superior**)
-Carina is posterior to ascending aorta + anteromedial to descending aorta
-Right Lung = more common site for inhaled foreign bodies b/c Right Main stem bronchus is wider, more vertical, shorter than left
-Aspirate food;
- Supine = enters superior segment of Right lobe
- Lying on Right side = enters Right upper lobe
- Upright = enters right lower lobe

Diaphragm Structures:
-Perforating Diaphragm:
- **T8 = IVC, Right Phrenic Nerve**
- **T10 = Esophagus, Vagus (CN10 for T10)**
- **T12 = Aorta, Thoracic Duct, Azygos Vein (aortic hiatus)**

-Diaphragm innervated by **C3,4,5** ("keeps me alive") (Phrenic Nerve)
-Pain from Diaphragm irritation (air, blood, pus from peritoneal cavity) referred to Shoulder (C5), Trapezius Ridge (C3, C4)
-Other Bifurcations;
- Common Carotid "bifourcates" at C4
- Trachea "bifourcates" at T4
- Abdominal Aorta "bifourcates" at L4

Respiratory Physiology:
-Note: "Capacities" are sums of volumes

1. Tidal Volume:
-air that moves into lung with each quiet inspiration
-typically 500 mL

2. Inspiratory Reserve Volume:
-air that can still be breathed in after normal inspiration

3. Expiratory Reserve Volume:
-air that can still be breathed out after normal expiration

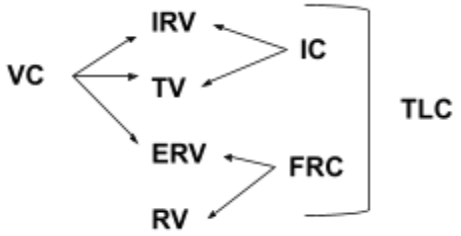
4. Residual Volume (RV);
-Air in lung after maximal expiration
-RV, and any capacity that uses RV Cannot be measured by Spirometry (Makes sense, since Spirometry measures maximal forced expiration)

5. Inspiratory Capacity:
-IRV + TV
-air that is breathed in after normal exhalation

6. Functional Residual Capacity (FRC):
-RV + ERV
-Volume of gas in lungs after normal expiration; outward pulling force of chest wall is balanced w/ inward collapsing force of lungs

7. Vital Capacity:
-IRV + TV + ERV
-Maximum volume of gas that can be expired after a maximal inspiration

8. Total Lung Capacity (TLC):
-IRV + TV + ERV + RV = VC + RV
-Volume of gas present in lungs after a max inspiration



Determination of Physiologic Dead Space:

$$V_D = V_T \times [(PaCO2 - PECO2) / PACO2]$$

-V_D = Physiological Dead Space = Anatomic Dead Space of conducting airways + 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
-**PACO2** = arterial PCO2
-**PECO2** = Expired air PCO2
-Physiologic Dead Space ~ Anatomic Dead Space in normal lungs (may be greater than anatomic dead space in lung diseases w/ V/Q Mismatch

Ventilation:

1. Minute Ventilation (V_E):
-Total volume of gas entering lungs per minute
-$V_E = V_T \times RR$

2. Alveolar Ventilation (V_A):
-volume of gas taht reaches alveoli each minute
- $V_A = (V_T - V_D) \times RR$

Normal Values:
-RR = 12-20 bpm
-V_T = 500 mL/breah
-V_D = 150 mL/breath

Lung and Chest Wall:

Elastic Recoil:
-Tendency for lungs to collapse inward + chest all to spring outward
-At FRC, airway + alveolar pressures equal atmospheric pressure (called Zero), and Intrapleural pressure is negative (preventing atelectasis)
-Inward pull of lung is balanced by the outward pull of the chest wall
-System pressure is atmospheric
-Pulmonary vascular resistance (PVR) is at a minimum

Compliance (Stretch):
-change in lung volume for a change in pressure (change Volume/ change Pressure)
-Inversely proportional to wall stiffness and is by Surfactant
- Compliance = Lung easier to fill (Emphysema, Aging)
- Compliance = Lung Harder to fill (Pulmonary Fibrosis, Pneumonia, ARDS, Pulmonary Edema)

Hysteresis:
-Lung inflation follows a different pressure volume curve than lung deflation due to need to overcome surface tensions forces in inflation
-Emphysema moves curve upwards (increasing slope), Fibrosis moves it downward (decreasing slope)

Respiratory System Changes in Elderly:
-Aging associated w/ progressive in lung function
-TLC remains the same
-Increased:
- Lung Compliance (Stretch) - Loss of elastic recoil
- RV (residual volume)
- V/Q Mismatch
- A-a Gradient

-Decreased:
- Chest wall compliance (chest wall stiffness)
- FVC and FEV1 (forced expiration)
- Respiratory Muscle Strength (impairs cough)
- Ventilatory Response to Hypoxia/Hypercapnia

Hemoglobin:
-Normal Hb composed of 4 Polypeptide subunits (2 alphas, 2 betas) that each bind 1 molecule of O2
-Hb is an allosteric protein that exhibits "Positive Cooperativity" when binding to O2;
- Oxygenated Hb has High affinity for O2
- Deoxygenated Hb has low affinity for O2 → promoting release/unloading of O2

-Protein component of Hb acts as a buffer for H+ ions
-**Myoglobin** = composed of single polypeptide chain associated w/ one heme Moiety (higher affinity for Oxygen than Hb)

Oxygen Content of Blood:

O2 Content = (1.34 x Hb x SaO2) + (0.003 x 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 15g/dL
-Normal O2 Binding capacity ~ 20 mL O2/dL of blood
-W/ Hb there is O2 content of arterial blood, but NO change in O2 saturation and PaO2
-O2 delivery to tissues = CO (cardiac output) x O2 content of blood

	CO Poisoning	**Anemia (RBC)**
[Hb]	Normal	
% O2 Sat of Hb	(CO competes w/ O2)	Normal
Dissolved O2 (PaO2)	Normal	Normal
Total O2 Content		
	Polycythemia (RBC)	**Cyanide Toxicity**
[Hb]		Normal
% O2 Sat of Hb	Normal	Normal
Dissolved O2 (PaO2)	Normal	Normal
Total O2 Content		Normal
	Methemoglobinemia	
[Hb]	Normal	
% O2 Sat of Hb	(Fe3+ is bad at binding O2)	
Dissolved O2 (PaO2)	Normal	
Total O2 Content		

Methemoglobin:
-Iron in Hb is normally in a reduced state (**Ferrous - Fe2+**) = "just the 2 of "us""
-Oxidized form of Hb (**Ferric - Fe3+**) does NOT bind O2 as readily as Ferrous does BUT does have affinity for Cyanide → tissue hypoxia from O2 Saturation and O2 Content
-**Methemoglobinemia** = presents w/ cyanosis (does not improve w/ supplemental Oxygen) or w/ Chocolate-colored blood
- Dapsone, Local anesthetics (Benzocaine), Nitrites (Diet, Polluted Water Sources) = cause poisoning by oxidizing Fe2+ to Fe3+

-Tx = **Methylene Blue +/- Vitamin C**

Oxygen-Hemoglobin Dissociation Curve:
-Sigmoidal shape due to positive cooperativity (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 Shape and is parabolic → far far left shift)
-Shift Right = P50 (higher PO2 required to maintain 50% saturation
-Shift Left = O2 unloading → renal hypoxia → EPO synthesis → compensatory erythrocytosis
-Fetal Hb (HbF)(2a, 2gamma) has higher affinity for O2 than adult Hb (due to affinity for 2,3-BPG) → dissociation curve is shifted left, driving diffusion of O2 across the placenta from pregnant pt to fetus

-**Right Shift: (O2 unloading to tissues)*****
- **H+ (pH)**
- **PCO2**
- **Exercise**
- **2,3-BPG**
- **High Altitude**
- **Temperature**

-**Left Shift: (O2 unloading to tissues)*****
- **H+ (pH - basic)**
- **PCO2**
- **2,3-BPG**
- **Temp**
- ** CO (Carbon Monoxide Poisoning)**
- ** MetHb (Methemoglobinemia)**
- ** HbF**

Note: Both CN and CO poisoning inhibit aerobic metabolism via inhibition of **Complex IV of the Electron Transport Chain (ETC) - "Cytochrome C Oxidase"** → Hypoxia that does not fully correct w/ supplemental O2 and Anaerobic Metabolism

Cyanide Poisoning:
-Exposure to synthetic product combustion, amygdalin ingestion (Apricot seeds), Purposeful Cyanide Ingestion, Fire Victims
-sxs = **HA, SOB, Drowsiness, Seizures, Coma Cherry Red Skin**, Bitter Almond Odorized Breath
-Labs:
- Normal PaO2
- Lactate (Anaerobic metabolism) → Metabolic Acidosis

-Oxygen/Hb Curve:
- "Curve Normal"
- O2 saturation may appear normal initially but despite plenty of O2 Supply, O2 is not used due to ineffective Oxidative Phosphorylation

-Tx:
- Decontamination (remove clothing)
- **Hydroxocobalamin** (Binds Cyanide → cyanocobalamin → renal excretion)
- **Nitrites** (Oxidize Hb → methemoglobin → binds cyanide → cyanmethemoglobin → Toxicity)
- **Sodium Thiosulfate** (CN conversion to Thiocyanate → Renal Excretion)

Carbon Monoxide Poisoning:
-Cause = Motor Exhaust, Gas Heaters, Fire Victims
-Sxs = **HA, Vomiting, Confusion, Visual Disturbances, Coma, Cherry Red Skin w/ Bullous Skin lesions** (multiple victims are often involved)
-Labs:
- Normal PaO2
- Carboxyhemoglobin on Co-Oximetry**
- **Bilateral Globus Pallidus Lesions on Brain MRI**

-Oxygen/Hb Curve:
- Left Shift*** (affinity for O2 → O2 unloading in tissues)
- Binds competitively to Hb w/ > 200x higher affinity than O2 (forming Carboxyhemoglobin → %O2 sat of Hb

-Tx = **100% O2 + Hyperbaric Oxygen (if severe)**

Pulmonary Circulation:
-normally a "Low-Resistance; High Compliance" system
-a in PAO2 causes a Hypoxic vasoconstriction that shifts blood AWAY from poorly ventilated regions of lung to well-ventilated regions
-Perfusion Limited = O2 (normal health), CO2, N2O → gas equilibrates early along the length of the capillary (exchange can be only if blood flow 's)
-Diffusion Limited = O2 (emphysema, Fibrosis, exercise), CO → gas does NOT equilibrate by the time blood reaches the end of the capillary
-O2 diffuses SLOWLY
-CO2 diffuses very rapidly across the alveolar membrane
-Disease states that lead to diffusion limitation (Pulmonary Fibrosis) are more likely to cause early hypoxia than Hypercapnia***
-Chronic Hypoxic Vasoconstriction may lead to Pulmonary HTN +/- Cor Pulmonale

Diffusion:

$$V_{GAS} = A \times D_K \times [(P_1 - P_2) / \text{Alveolar wall thickness}]$$

-A = area
-Dk = diffusion coefficient of Gas
-P1-P2 = difference in partial pressures

- A in Emphysema
- Alveolar wall thickness in Pulmonary Fibrosis

-DLCO = extent to which CO passes from air sacs of lungs into blood

Pulmonary Vascular Resistance (PVR):

$$PVR = [(P_{PA} - P_{LA}) / Q]$$

-**Q = P/ R**
-**R = 8nL/pie x r^4**
-P_{PA} = pressure in Pulmonary Artery
-P_{LA} = pressure in Left Atrium (PCWP)

Alveolar Gas Equation:

PAO2 = PIO2 - [PACO2 / R]
-R = respiratory quotient = CO2 produced/O2 consumed
A-a Gradient = PAO2 - PaO2
-normal A-a Gradient estimated as (age/4) + 4
-if pt is < 40 yo, their gradient should be < 14

Oxygen Deprivation;
1. Hypoxia (O2 delivery to tissue):
- CO

-Hypoxemia
-Ischemia
-Anemia
-CO/Cyanide Poisoning

2. Hypoxemia (PaO2):
-Normal A-a Gradient:
- High altitude (barometric pressure)
- Hypoventilation (opioid use, obesity hypoventilation syndrome)

- A-a Gradient:
- V/Q Mismatch
- Diffusion Limitation (Fibrosis)
- Right to Left Shunt (R→L)

3. Ischemia (loss of blood flow):
-Impeded arterial flow
- venous drainage

Ventilation/Perfusion Mismatch (V/Q Mismatch):
-ideally ventilation is matched to perfusion (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 (CO) there is vasodilation of apical capillaries → V/Q ratio approaching 1
-Bacteria (TB) thrive w/ high O2 (∴ flourishing in the apex of lung)
-**V/Q = 0** = Airway "0"bstruction (Shunt)
- In shunt, 100% O2 does not improve PaO2
- ex.) Aspiration

-V/Q = infinity = Blood flow obstruction (Physiologic Dead Space)
- Assuming < 100% dead space, 100% O2 improves PaO2
- ex.) Pulmonary Embolism

Zone 1 = PA ≥ Pa > P_V = [V/ Q] = V/Q
Zone 2 = Pa > PA > P_V = [V/Q ~ 1]
Zone 3 = Pa > P_V > PA = [V/ Q] = V/Q

Carbon Dioxide Transport (CO2):
-CO2 transported from tissues to lungs in 3 forms;

1. Bicarb (70%): Bicarb/Chloride Transporter on RBC membrane allows Bicarb to diffuse out of plasma and Cl- to diffuse into RBC (**"Chloride Shift"**)
    a. Co2 from tissue
    b. CO2 + H2O → Carbonic Anhydrase → H2CO3 → H+ and Bicarb → Bicarb leaves RBC for blood
2. Carbaminohemoglobin (**HbCO2**)(21-25%): CO2 bound to Hb at N-terminus of globin (not Heme) = CO2 favors deoxygenated form (O2 Unloaded)
3. CO2 dissolved in blood (5-9%)

-In lungs, **oxygenation of Hb** promotes dissociation of **H+** from Hb = shifts equilibrium toward CO2 formation; therefore, CO2 is release from RBCs **(Haldane Effect)**

- As Oxygen is bound in the lungs to RBCs, H+ dissociates allowing for H+ conc that shift Eq to the left, facilitating CO2 formation and release (to be expelled)

-Majority of Blood CO2 is carried as Bicarb in the plasma

High Altitudes:
- atmospheric oxygen (PiO2) → PaO2 → Ventilation → PaCO2 → respiratory alkalosis → altitude Sickness (HA, Nausea, Fatigue, Lightheadedness, Sleep Disturbances)

-Chronic exposure (Acclimatization) =

- EPO production → HCT and HB (due to chronic hypoxia)
- 2,3-BPG (binds to Hb → rightward shift of dissociation curve → O2 release
- Mitochondria in cells
- Renal excretion of Bicarb (compensating for Resp Alk) - Augmented w/ Acetazolamide

-Chronic Hypoxic Pulmonary Vasoconstriction (constricting areas w/ poor ventilation) → Pulmonary Vascular Resistance (PVR) → Pulmonary HTN or Right Ventricular Hypertrophy

Response to Exercise:
- CO2 production
- O2 consumption

-Right Shift in Curve (O2 delivery = affinity for O2)
- ventilation to meet O2 demand + remove excess CO2

-V/Q ratio from apex to base becomes more uniform
- Pulmonary blood flow due to CO
- pH during strenuous exercise (secondary to lactic acidosis)

-No change in PaO2 and PaCO2 (but in venous CO2 content and venous O2 content)

Rhinosinusitis:
-obstruction of sinus drainage into nasal cavity → inflammation + pain over affected area
-typically affects Maxillary Sinuses, which drain against gravity due to ostia location (superomedially)
-Superior Meatus = drains **sphenoid, posterior ethmoid**
-Middle Meatus = drains **frontal, maxillary sinus, anterior ethmoid**
-Inferior Meatus = drains **nasolacrimal duct**
-Acute Rhinosinusitis = most commonly caused by viruses (Rhinovirus)

- Potential for superimposed bacterial infxn (H flu, Strep Pnuemo, Mcat)

-Paranasal sinus infxns may extend to the orbits, Cavernous Sinus, Brain, causing complications (Orbital Cellulitis, Cavernous Sinus Syndrome, Meningitis)

Epistaxis: "Nose Bleed"
-Anterior segment of nostril (**Kiesselbach Plexus**)

- **Superior Labial a.**
- **Anterior Ethmoidal a.**
- **Posterior Ethmoidal a.**
- **Sphenopalatine a.**

-Lifethreatneing hemorrhages occur in Posterior segment (Sphenopalatine Artery = branch of Maxillary Artery)
-Causes = forigen body, trauma, allergic rhinitis, nasal angiofibromas

Head and Neck Cancer:
-Squamous Cell Carcinoma (SCC)
-RF = Tobacco, alcohol, **HPV-16 (Oropharyngeal), EBV (Nasopharyngeal)**
-Field Cancerization = carcinogen damages wide mucosal area → multiple tremors that develop independently after exposure
-**Nasopharyngeal Carcinoma**:

- Unilateral nasal obstruction
- Discharge
- Epistaxis
- Eustachian Tube Obstruction (Otitis Media +/- Effusion)
- Hearing Loss

Deep Venous Thrombosis (DVT):
-Blood clot within a deep vein → swelling, redness, warmth, pain
-RFs: "**Virchow's Triad"**

- **Stasis** (Post-op, long drive/flight)
- **Hypercoagulability** (defect in Coagulation cascade proteins, such as Factor V Leiden, Oral contraceptive use, Pregnancy)
- **Endothelial Damage** (Exposed Collagen triggers clotting cascade)

-Most pulmonary emboli arise from Proximal deep veins of lower extremity (Iliac, Femoral, Popliteus Veins)
-**D-dimer** = can rule out DVT (SnOUT, SpINS)

- High Sensitivity, Low Specificity

-Imaging test of choice = Compression US w/ Doppler
-Unfractionated Heparin or LMWH (Enoxaparin) for PPx and Acute Management
-Direct Anticoagulants (Rivaroxaban, Apixaban) for Tx and Long-Term Prevention

Pulmonary Emboli (PE):
-obstruction of Pulm. Artery /branches by foreign material (usually thrombus) that originated elsewhere
-Affected Alveoli are ventilated but NOT Perfused (**V/Q Mismatch**)
-sxs = Sudden onset SOB, Pleuritic chest pain, Tachypnea, Tachycardia, Hypoxemia, Respiratory Alkalosis
-Large emboli/Saddle Embolus = may cause sudden death due to electromechanical dissociation (Pulseless electrical activity)
-CT Pulmonary angio is imaging of choice (looking for filling defects)
-ECG shows sinus Tachycardia, or **S1Q3T3** Abnormality

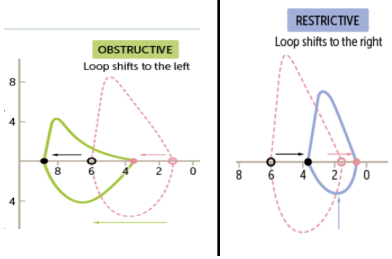
-**Lines of Zahn** = interdigitating areas of pink (Platelets, Fibrin) and Red (RBCs) found only in Thrombi formed <u>before</u> death (Helps distinguish Pre- and Post-mortem thrombi
-Tx = Anticoagulation (Heparin, Direct Thrombin/Factor Xa Inhibitors), IVC Filter (if anticoag contraindicated)
-Types = Fat, Air Thrombus, Bacteria, Amniotic Fluid, Tumor
-<u>Fat Emboli</u> = long bone fractures + Liposuction
- **Hypoxemia**
- **Neurologic Abnormalities**
- **Petechial rash**

-<u>Air Emboli</u> = Nitrogen Bubbles precipitate in ascending divers (Caisson Disease/Decompression Sickness)
- Tx w/ Hyperbaric O2

-<u>Amniotic Fluid Emboli</u> = during labor or postpartum leading to DIC (rare but high mortality)

<u>Flow-Volume Loops</u>:

	Obstructive Lung Disease	**Restrictive Lung Disease**
RV		
FRC		
TLC		
FEV1		
FVC		
FEV1/ FVC	**(**FEV1 decreased more than FVC)	**Normal or** (FEV1 proportionally to FVC)



<u>Mediastinal Pathology</u>:
-Normal mediastinum contains Heart, Thymus, Lymph nodes, Esophagus, Aorta

1. Mediastinal Masses:
-Anterior = 4 T's:
1. **Thyroid (Substernal Goiter)**
2. **Thymic Neoplasm**
3. **Teratoma**
4. **"Terrible" Lymphoma**

-Middle = Esophageal Carcinoma, Metastases, Hiatal Hernia, Bronchogenic Cysts
-Posterior = Neurogenic Tumor (Neurofibroma), Multiple Myeloma (MM)

2. Mediastinitis:
-Inflammation of mediastinal tissues
-Cause = postoperative complications of Cardiothoracic procedures (≤ 14 days), Esophageal Perforation, Contiguous Spread of Odontogenic/Retropharyngeal Infxn
-Chronic Mediastinitis = "Fibrosing Mediastinitis" → due to proliferation of CT in Mediastinum (**Histoplasma Capsulatum** = common cause)
-sxs = Fever, Tachycardia, Leukocytosis, Chest Pain, Sternal Wound Drainage

3. Pneumomediastinum:
-Presence of Gas (usually air) in the mediastinum
-cause = **spontaneous (due to rupture of Pulmonary Bleb)**, or secondary to trauma (Iatrogenic, Boerhaave Syndrome)
-Ruptured alveoli allow tracking of air into the mediastinum via Peribronchial + perivascular sheaths
-sxs =
- Chest pain, SOB
- **Voice Change**
- SQ Emphysema
- **(+) Hamman Sign (Crepitus on Cardiac Auscultation)**

<u>Obstructive Lung Diseases</u>:
-obstruction of airflow (FRC, RV, TLC) → **air trapping in lungs** w/ premature airway closure at high lung volumes (FEV1, FVC, FEV1/FVC Ratio)
-Leads to V/Q Mismatch

<u>1. Chronic Bronchitis</u>:
-sxs = wheezing, crackles, cyanosis (Hypoxemia due to shunting, CO2 Retention, secondary Polycythemia)
-Pathology = **Hypertrophy + Hyperplasia of mucus-secreting glands in bronchi** → Reid Index >50% (Thickness of Mucosal Gland Layer to Thickness of Wall btw Epithelium and Cartilage)
-DLCO may be normal
-ddx = productive cough for ≥ 3 months in a year for > 2 consecutive years

<u>2. Emphysema</u>:
-sxs = Barrel-shaped chest, expiration is prolonged and /or through pursed lips (increases airway pressure + prevents airway collapse)
-CXR = AP diameter, Flattened Diaphragm, Lung Field Lucency
-Chronic inflammation mediated by CD8+ T cells, PMNs, Neutrophils
-Types:
1. **Centriacinar:**
   a. Respiratory bronchioles (**sparring distal alveoli)**
   b. Tobacco/smoking*****
   c. Upper lobe predominance (smoke rises up)
2. **Panacinar**:
   a. Affects respiratory bronchioles + Alveoli
   b. a1-Antitrypsin Deficiency
   c. Lower Lobes

-Enlargement of Airspaces:
- Recoil
- compliance (stretch)
- **DLCO** from destruction of Alveolar walls
- blood volume in pulmonary capillaries

-Mech = Imbalance of proteases + antiproteases → Elastase activity → loss of Elastic Fibers → Lung Compliance

3. Asthma:
-Sxs = Asymptomatic baseline w/ intermittent episodes of coughing, wheezing, tachypnea, dyspnea, hypoxemia, inspiratory/expiratory ratio, mucus plugging
-Triggers = Viral URIs, Allergens, Stress
-Hyperresponsive Bronchi → reversible bronchoconstriction
-Smooth muscle hypertrophy + Hyperplasia, **Curschmann Spirals** (Shed epithelium forms whorled mucous plugs)
-**Charcot-Leyden Crystals** = Eosinophilic hexagonal, double pointed crystals formed from breakdown of eosinophils in sputum
-DLCO = normal/
-**Type I HSR**
-DDx = supported by Spirometry +/- **Methacholine** Challenge (Lung reactivity/stress challenge)
-**NSAID-Exacerbated respiratory disease is a combination of COX Inhibition** (Leukotriene Overproduction → Airway Constriction), Chronic sinusitis w/ nasal polyps, and asthma sxs

4. Bronchiectasis:
-sxs = daily purulent sputum, recurrent infections (most often Pseudomonas), Hemoptysis, **Digital Clubbing**
-path = chronic necrotizing infection of bronchi or obstruction → permanently dilated airways
-Associated w/ Bronchial obstruction, poor ciliary motility (Smoking, Kartagener Syndrome), CF, Allergic Bronchopulmonary Aspergillosis

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Restrictive Lung Diseases:
-may lead to lung volumes (FVC, TLC)
-PFTs normal or FEV1/FVC ratio
-sxs = Short shallow breaths
-Types:
1. Altered Respiratory Mechanics (Extrapulmonary, normal DLCO, normal A-a Gradient):
- **Respiratory Muscle Weakness**
  - Polio, Myasthenia Gravis, Guillain-barre Syndrome, ALS
- **Chest Wall abnormalities:**
  - Scoliosis, Severe Obesity

2. Diffuse Parenchymal Lung Diseases (Interstitial Lung Diseases) (Pulmonary, DLCO, A-a Gradient):
- Pneumoconiosis (Coal Workers' pneumoconiosis, Silicosis, Asbestosis)
- Sarcoidosis (Bilateral Hilar Lymphadenopathy, Noncaseating Granulomas, ACE and Ca2+
- Idiopathic Pulmonary Fibrosis
- Granulomatosis w/ Polyangiitis
- Pulmonary Langerhans Cell Histiocytosis (Eosinophilic Granuloma)
- Hypersensitivity Pneumonitis
- Drug Toxicity (Bleomycin, Busulfan, Amiodarone, MTX)
- Acute Respiratory Distress Syndrome (ARDS)
- Radiation Induced Lung Injury (RILI):
  - Due to proinflammatory cytokine release (TNF-a, IL-1, IL6)
  - May be asymptomatic but most common sxs are dry cough, SOB, Low-grade fever
  - Acute radiation pneumonitis develops within 3-12 weeks (exudative phase); radiation fibrosis may develop after 6-12 months

Idiopathic Pulmonary Fibrosis (IPF):
-Progressive fibrotic lung disease of unknown etiology
-May involve multiple cycles of lung injury, inflammation, and fibrosis
-Associated w/ Smoking, environmental pollutants, genetic defects
-Findings = Progressive SOB, Fatigue, Nonproductive cough, crackles, Clubbing
-Imaging = peripheral reticular opacities w/ traction bronchiectasis +/- "Honeycomb" appearance of lung (advanced disease)
-Histo = usual interstitial pneumonia
-Complications = Pulmonary HTN, Respiratory Failure, Lung Cancer, Arrhythmias

Hypersensitivity Pneumonitis:
-Mixed **Type III/IV HSR** reaction to environmental antigens
-Farmers + Bird owners
-Acute sxs = SOB, cough, chest tightness, fever HA
-Often self-limiting if stimulus removed
-Chronic sxs = irreversible fibrosis w/ Noncaseating granulomas, alveolar septal thickening, traction bronchiectasis

Sarcoidosis:
-Immune-mediated, widespread noncaseating granulomas, ACE levels, elevated CD4/CD8 ratio in BAL fluid
-Black females = most common population
-sxs = ASYMPTOMATIC except for Enlarge Lymph Nodes
-CXR = **bilateral adenopathy** + coarse reticular opacities
-CT = extensive **hilar** + **mediastinal Adenopathy**
-**Associated w/;**
- **Bell's Palsy**
- **Uveitis**
- **Granulomas** (Noncaseating epithelioid w/ 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 1a-Hydroxylase - mediated Vitamin D activation in Macrophages)

-Tx = Steroids (if symptomatic)

Inhalation Injury and Sequelae:
-Complication of inhalation of noxious stimuli (smoke)
-Caused by heat, particulates (< 1 micrometer), Irritants (NH3) → Chemical tracheobronchitis, Edema, Pneumonia, ARDS
-many present w/ Secondary burns, CO inhalation, Cyanide Poisoning, Arsenic Poisoning
-Singed nasal hairs or soot in oropharynx common on exam
-Bronchoscopy = severe edema, congestion of bronchus, soot deposition (18 hrs after inhalation injury) → Resolution at 11 days after injury

Pneumoconioses:
-**Asbestos** is from the roof (was common in insulation), but affects the base (lower lobes)
-**Silica, Coal, Berries** are from the base (earth) but affect the Roof (Upper lobes)

1. Asbestos-Related Disease:
-Asbestos causes asbestosis (Pulmonary Fibrosis), Pleural Disease, Malignancies
-Associated w/ Shipbuilding, Roofing, Plumbing
-"**Ivory White**" = Calcified, Supradiaphragmatic and Pleural Plaques are Pathognomonic
-Risk of **bronchogenic carcinoma w/** risk of **Mesothelioma**
- Risk of **Caplan Syndrome**:
  - **Rheumatoid Arthritis**
  - **Pneumoconiosis w/ Intrapulmonary Nodules**

-Affects lower lobes
-**Asbestos (Ferruginous) Bodies** are golden-brown fusiform rods resembling **dumbbells,** found in alveolar sputum sample, visualized using **Prussian Blue Stain**, often obtained by BAL
- Risk of Pleural Effusions

2. Berylliosis:
-Associated w/ exposure to beryllium in aerospace + manufacturing industries
-Granulomatous (Noncaseating) on Histology and therefore occasionally responsive to steroids
- Risk of cancer + Cor Pulmonale
-affects Upper Lobes

3. Coal Workers Pneumoconiosis:
-Prolonged coal dust exposure → macrophages laden w/ Carbon → inflammation and Fibrosis
-"Black Lung Disease"
- risk of Caplan Syndrome
-Affects Upper Lobes
-Small,rounded nodular opacities seen on Imaging
-**Anthracosis** = asymptomatic condition found in many urban dwellers exposed to sooty air

4. Silicosis:
-associated w/ Sandblasting, Foundries, Mines
-Macrophages respond to silica + release fibrogenic factors, leading to fibrosis
-Silica disrupts phagolysosomes + impairs macrophages, increasing susceptibility to TB
- risk of Cancer, Cor Pulmonale, and Caplan Syndrome
-Affects upper lobes
-**"Eggshell" Calcifications of Hilar Lymph nodes**

Mesothelioma:
-malignancy of the pleura associated w/ **Asbestosis**
-Results in **Hemorrhagic Pleural Effusion** (Exudative), Pleural Thickening
-Histology = **psammoma bodies**
-EM = show polygonal tumor cells w/ Microvilli, Desmosomes, Tonofilaments
-**Calretinin + Cytokeratin 5/6 (+)** in almost all Mesotheliomas, **(-) in Most Carcinomas**
-Tobacco smoking is NOT a risk factor

Acute Respiratory Distress Syndrome (ARDS):
-Pathogenesis:
1. alveolar insult → release of Pro-inflammatory cytokines
2. Neutrophil recruitment, activation, release of toxic mediators (Reactive Oxygen Species, Proteases)
3. Capillary endothelial damage and vessel permeability
4. Leakage of protein-rich fluid into alveoli → formation of intra-alveolar hyaline membranes + noncardiogenic pulmonary edema (Normal PCWP)

-Loss of Surfactant → Alveolar Collapse
-causes = Sepsis (most common), Aspiration, Pneumonia, Trauma, Pancreatitis
-DDx of Exclusion w/ 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

-Causes = Impaired gas exchange, Lung Compliance (Stiffness) → Pulmonary HTN
-Tx Underlying Cause + Mechanical Ventilation (TV,

Sleep Apnea:
-repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → Daytime somnolence
-ddx confirmed by sleep study
-Nocturnal hypoxia → Systemic + Pulmonary HTN, Arrhythmias (Afib/Flutter), Sudden Death
-Hypoxia → EPO release → Erythropoiesis

1. Obstructive Sleep Apnea:
-Respiratory effort against airway obstruction
-PaO2 is usually normal during the day
-associated w/ Obesity, loud snoring, daytime sleepiness
-Usually caused by excess parapharyngeal/oropharyngeal tissue in adults, Adenotonsillar Hypertrophy in children
-Tx = Weight loss, CPAP, Dental Devices, Hypoglossal nerve stimulation, Upper airway surgery

2. Central Sleep Apnea:
-Impaired respiratory effort due to CNS Injury/Toxicity, Congestive HF, Opioids
-Associated w/ **Cheyne-Stokes Respirations** = oscillations btw apnea and hyperpnea)
-Tx = Positive airway pressure

3. Obesity Hypoventilation Syndrome:
-"Pickwickian Syndrome"
-Obesity (BMI ≥ 30) → hypoventilation → PaCO2 during waking hours (Retention); PaO2 and PaCO2 during sleep
-Tx = weight loss, Positive airway pressure

PEEP (Keeps Alveoli open during expiration)

Pulmonary HTN:
- mean pulmonary artery pressure (>20 mmHg) at rest

-results in Arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions
- Pulmonary Vascular resistance → RV pressure → RVH, RV Failure

1. Pulmonary Arterial HTN (PAH):
-often idiopathic
-Females > Males
-Heritable PAH can be due to an inactivating mutation in **BMPR2 Gene** (normally inhibits vascular smooth muscle proliferation) → poor prognosis
-Pulmonary vascular endothelial dysfunction results in **Vasoconstrictors (Endothelin)** and **Vasodilators (NO and Prostacyclins)**
-Drug Induced (Amphetamines, Cocaine), Connective Tissue Disease, HIV infection, Portal HTN, Congenital Heart Disease, **Schistosomiasis**

2. Left Heart Disease:
-causes include systolic/diastolic dysfunction + valvular disease

3. Lung Diseases or Hypoxia:
-Destruction of Lung parenchyma (COPD)
-Lung inflammation/fibrosis (Interstitial lung diseases)
-Hypoxic vasoconstriction (obstructive sleep apnea, Living in high altitude)

4. Chronic Thromboembolic:
-Recurrent microthrombi → Cross-Sectional Area of Pulmonary Vascular beds

5. Multifactorial:
-hematologic, Systemic, Metabolic disorders, along w/ compression of Pulmonary vasculature by a tumor

	Breath Sounds	**Percussion**	**Tactile Fremitus: (Vibration = consolidation)**	**Tracheal Deviation**
Pleural Effusion		Dull		None if small (**AWAY** from side of lesion)
Atelectasis		Dull		**Toward** Lesion
Simple Pneumothorax		Hyperresonant (no lung)		None
Tension Pneumothorax		Hyperressonant		**AWAY** from side of lesion
Consolidation (Lobar Pneumonia, Pulmonary Edema)	Bronchial Breath sounds; late inspiratory crackles, egophony, whispered pectoriloquy	Dull		None

Digital Clubbing:
- angle btw nail bed + nail plate (>180 degrees)

-Mech = Pts w/ Intrapulmonary shunt → platelets + Megakaryocytes become lodged in digital vasculature → local release of PDGF and VEGF
-Hereditary or Acquired
-Causes = Respiratory disease (IPF, CF, BRonchiectasis, Lung Cancer), Cardiovascular Dx (Cyanotic COngenital heart Dx), Infxns (Lung Abscess, TB), Others (IBD)
-NOT usually associated w/ Asthma/COPD (Obstructive Lung Pattern)

Atelectasis:
-Alveolar collapse (Right upper lobe collapse against mediastinum
-Multiple Causes:
1. **Obstructive** = Airway obstruction prevents new air from reaching distal airways → Old air is Resorbed (Foreign Body, Mucous Plug, Tumor
2. **Compressive** = external compression on lung decreased lung volumes (Space-occupying lesion/pleural effusion)
3. **Contraction (Cicatrization)** = Scarring of lung

Pleural Effusions:
-excess accumulation of fluid btw pleural layers → restricted lung expansion during Inspiration
-Tx w/ Thoracentesis to remove/reduce fluid
-**Light Criteria**: "Fluid is Exudate if;"
- **Pleural Protein/Serum Protein > 0.5**
- **Pleural Fluid LDH/Serum LDH > 0.6**
- **Pleural Fluid LDH > 2/3rds ULN serum LDH**

Exudate:
-Cloudy fluid (Cellular)
-Due to malignancy, inflammation, infection (Pneumonia, Collagen Vascular Dx), Trauma (Occurs in states of **Vascular Permeability -"Fluid + Protein Leakage"**
-Often drained due to risk of infxn/source control

Transudate:
-Clear fluid (Hypocellular)
-Due to **Hydrostatic Pressure (HF, Na+ Retention) and/or Oncotic Pressure (nephrotic Syndrome, Cirrhosis**)

Lymphatic:
-"**Chylothorax**"

Pneumothorax:
-accumulation of air in pleural space
-sxs = SOB, Uneven chest expansion, chest pain, Tactile Fremitus, Hyperresonance, Diminished breath sounds on the affected side

1. Primary Spontaneous Pneumothorax:
-due to rupture of apical subpleural bleb or cysts
-occurs most frequently in **tall, thin, young males**
-associated w/ **Tobacco Smoking**

2. Secondary Spontaneous Pneumothorax:
-due to diseased lung (Bullae in Emphysema, Marfan Syndrome, Infxns), Mechanical Ventilation w/ use of High pressures → Barotrauma

3. Traumatic Pneumothorax:
-caused by blunt (Rib Fracture), Penetrating (Gunshot), Iatrogenic Trauma (Central Line Placement, Lung Biopsy, Barotrauma due to mechanical ventilation)

4. Tension Pneumothorax:
-Caused by any of the above
-Mech = Air enters pleural space but Cannot exit → increasing trapped air → tension
-Trachea deviates Away from affected lung
-may lead to Intrathoracic Pressure → mediastinal displacement → Kinking of IVC → Venous Return → Cardiac output, Obstructive shock (Hypotension, Tachycardia, Jugular Venous Distension (JVD))
-Tx = Immediate Needle Decompression + Chest Tube Placement

Lung Abscesses:
-Localized collection of pus within parenchyma
-caused by Aspiration of oropharyngeal contents (especially in pts predisposed to loss of consciousness = Alcohol overuse, Epilepsy), or Bronchial Obstruction (Cancer)
-**Air-fluid Levels** often seen on CXR; presence suggests cavitation (due to staph aureus, or Anaerobes = Bacteroides, Fusobacterium, Peptostreptococcus)
-Tx = Trainade, Abx, Surgery

parenchyma that distorts alveoli (Sarcoidosis)
4. **Adhesive** = due to lack of surfactant (NRDS)

Pneumonia:
1. Lobar Pneumonia:
-Organisms = Strep Pneumo > Legionella, Kleb
-Intra-alveolar exudate → consolidation (may involve whole lobe or entire lung)
-Pathogenesis:
1. **Congestion**: (Days 1-2)
   a. Red-purple, partial consolidation of Parenchyma
   b. Exudate w/ mostly bacteria
2. **Red Hepatization:** (Days 3-4)
   a. Red-Brown consolidation
   b. Exudate w/ Fibrin, Bacteria, RBCs, WBCs
   c. "Reversible"
3. **Gray Hepatization:** (Days 5-7)
   a. Uniformly gray
   b. Exudate full of WBCs + Lysed RBCs + fibrin
4. **Resolution**: (Days 8+)
   a. Enzymatic digestion of exudate by Macrophages

2. Bronchopneumonia:
-Orgs = Strep pneumo, Staph Aureus, H influ, Kleb
-Acute inflammatory infiltrates from Bronchioles into adjacent alveoli (Patchy distribution involving ≥ 1 Lobe)

3. Interstitial (Atypical) Pneumonia:
-Orgs = Mycoplasma, Chlamydophilia Pneumoniae, Chlamydophila Psittaci, Legionella, Coxiella Burnetii, Viral (RSV, CMV, Influenza, Adenovirus)
-Diffuse patchy inflammation localized to interstitial areas at alveolar walls
-CXR = bilateral multifocal opacities
-Generally follow a more indolent course ("Walking Pneumonia"

4. Cryptogenic Organizing Pneumonia:
-Cause = Unknown, (-) sputum/blood cultures, but often responds to steroids (not to Abx)
-Formally known as Bronchiolitis Obliterans Organizing Pneumonia (BOOP)
-Noninfectious pneumonia characterized by inflammation of bronchioles + Surrounding tissue

-Due to thoracic duct injury from trauma or malignancy
-Milky appearing fluid; Trigs

Lung Cancer:
-Leading cause of cancer death
-sxs = cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "Coin" lesion on CXR or noncalcified nodule on CT
-Common Mets =
- Liver (Jaundice, Hepatomegaly)
- Adrenals
- Bone (Pathologic Fractures)
- Brain

-Lung Metastases are more common than primary malignancy (usually from Breast, Colon, Prostate, Bladder cancer)
-SPHERE Complications:
- Superior Vena Cava/Thoracic Outlet Syndromes
- Pancoast Tumor
- Horner Syndrome
- Endocrine (Paraneoplastic)
- Recurrent Laryngeal Nerve Compression (Pleural or Pericardial)

-RF = Smoking, Second-hand smoke, Radiation, environmental exposures (Radon, Asbestos), Pulmonary Fibrosis, Family Hx
-"Squamous + Small Cell Carcinomas are Central and often caused by Smoking"

1. Small Cell Carcinoma (SCLC) (Oat Cell):
-Central location (by the Bronchus)
-Undifferentiated = "very aggressive"
-May Produce:
- **ACTH** (Cushing Syndrome)
- **ADH (SIADH)**
- Antibodies against presynaptic Ca2+ channels (**Lambert-Eaton Myasthenic Syndrome**) or Neurons (Paraneoplastic Myelitis, Encephalitis, Subacute Cerebellar Degeneration)
- **Amplification of *myc* oncogenes** common

-Managed w/ Chemo +/- Radiation
-Histo =
- neoplasm of "Neuroendocrine" **Kulchitsky Cells** → Small dark blue cells
- **Chromogranin A (+),** Neuron-Specific **Enolase (+), Synaptophysin (+)**

-Note: Lung abscess secondary to aspiration is most often found in Right Lung (RLL if upright, RUL or RML if Recumbent)

Non-Small Cell:

1. Adenocarcinoma:
-Peripheral locations
-MOST common primary lung cancer
-Most common subtype in people who do NOT smoke
-Females > Males
-Activating mutations include **KRAS, EGFR, ALK**
-Associated w/ Hypertrophic Osteoarthropathy (Clubbing)
-Bronchioloalveolar Subtype (Adenocarcinoma in situ) = CXR often show hazy infiltrates similar to pneumonia (better prognosis)
-Histo:
- Glandular pattern, often stains **mucin (+)**
- Bronchioloalveolar Subtype = grows along alveolar septa → apparent "thickening" of Alveolar walls (Tall, columnar cells containing mucus)

2. Squamous Cell Carcinoma (SCC):
-Central***
-Hilar mass arising from bronchus + **Cavitation** + Cigarettes (**Smoking**) + **HyperCalcemia (produces PTHrP)**
-"Keratin Pearls" + Intercellular Bridges (Desmosomes)

3. Large Cell Carcinoma:
-Peripheral
-Highly anaplastic undifferentiated tumor
-Strong association w/ **Smoking**
-can produce **hCG → Gynecomastia**
-Less responsive to Chemotherapy (often surgically removed) + Bad prognosis
-Histo = **Pleomorphic Giant Cells**

4. Bronchial Carcinoid Tumor:
-Central or Peripheral
-Excellent prognosis (metastasis very rare)
-sxs due to Mass effect or **Carcinoid Syndrome (Flushing, Diarrhea, Wheezing)**
-Nests of **Neuroendocrine Cells; Chromogranin A (+)**

Pancoast Tumor:
-"Superior Sulcus Tumor"
-Carcinoma that occurs in apex of lung + may cause pancoast syndrome by invading/compressing local structures
-Compression of Locoregional Structures can cause a variety of findings;
- Recurrent Laryngeal n. = **Hoarseness**
- Stellate Ganglion = **Horner Syndrome (Ipsilateral ptosis, Miosis, Anhidrosis)**
- SVC = **SVC Syndrome**
- Brachiocephalic Vein = **Brachiocephalic Syndrome (Unilateral Sxs)**
- Brachial Plexus = **Shoulder pain, sensorimotor deficits (atrophy of intrinsic muscles of hand)**
- Phrenic Nerve = **Hemidiaphragm paralysis (elevation seen on CXR)**

SVC Syndrome:
-"Medical Emergency"
-obstruction of SVC impairs blood drainage from the head
-sxs = **"facial Plethora"**, **non-blanching after fingertip pressure in neck, JVD, Upper-extremity edema, ICP if severe (HA, Dizziness, Aneurysm rupture)**
-Caused by Malignancy (Mediastinal Mass, Pancoast Tumor), Thrombosis of Indwelling Catheters

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H1 Blockers:
-Antihistamines = reversible inhibitors of H1 histamine receptors that function as neutral antagonists or inverse agonists

1st Gen:
-**Diphenhydramine, Dimenhydrinate, Chlorpheniramine, Doxylamine**
-use = allergy, motion sickness, vomiting in pregnancy, sleep aid
-ADRs = sedation, antimuscarinic, anti-alpha-adrenergic

2nd Gen:
-**Loratadine, Fexofenadine, Desloratadine, Cetirizine**
-Use = allergy

Dextromethorphan:
-Antitussive (**antagonizes NMDA** Glutamate Receptors)
-Synthetic codeine analog
-Mild opioid effect when used in excess
-Naloxone can be given for OD
-Mild Abuse potential
-Serotonin Syndrome Risk if combined w/ other serotonergic agents

Pseudoephedrine, Phenylephrine:
-mech = activation of a-adrenergic receptors in nasal mucosa (local vasoconstriction)
-use = reduce hyperemia, edema (used w/ nasal decongestants), opens obstructed eustachian tubes
-ADRs = **HTN, Rebound Congestion** (Rhinitis Medicamentosa) if used > 4-6 days
-Tachyphylaxis
-Can cause CNS stimulation/anxiety (Pseudoephedrine)

Pulmonary HTN Drugs:

Endothelin Receptor Antagonists: "Bosentan"
-Competitively antagonizes endothelin-1 receptors → decreasing pulmonary vascular Resistance (PVR)
-sxs = Hepatotoxic (monitor LFTs)

PDE-5 Inhibitors: "Sildenafil"
-inhibits PDE-5 → cGMP → prolonged vasodilatory effect of NO
-Tx ED (contraindicated when taking Nitroglycerin/other nitrates - risk of severe hypotension)

Prostacyclin Analogs: "Epoprostenol, Iloprost"
-PGI2 (Prostacyclin) w/ direct vasodilatory effects on pulmonary + systemic arterial vascular beds
-Inhibits platelet aggregation
-sxs = Flushing, Jaw pain

-Far less sedating than 1st gens b/c of entry into the CNS

<u>Asthma Drugs</u>:
-Bronchoconstriction is mediated by;
1. Inflammatory processes
2. PSNS tone

1. Inhaled B2-Agonists:
-**Albuterol** (SABA)= relaxes bronchial smooth muscle (short acting B2-agonist) used for acute exacerbations…sxs = Tremor, arrhythmia
-**Salmeterol, Formoterol** (LABA) = long acting agents for PPx (same sxs)

2. Inhaled Corticosteroids (ICS):
-Fluticasone, Budesonide = inhibit synthesis of virtually all cytokines (Activating NF-kB, the Transcription factor that induces production of TNF-a)
-1st Line therapy for Asthma
-use spacer + rinse mouth after use to avoid oral Thrush

3. Muscarinic ANtagonists:
-Tiotropium (LAMA), Ipratropium (SAMA) = competitively block muscarinic receptors, preventing bronchoconstriction
-Used for COPD

4. Antileukotrienes:
-Montelukast, Zafirlukast = block LT receptors (CysLT1) = very good for ASA-induced Asthma + Exorcist-Induced Asthma
-Zileuton = 5-Lipoxygenase Pathway Inhibitor (blocking conversion of AA to leukotrienes) but Hepatotoxic

5. Anti-IgE Monoclonal Therapy:
-**Omalizumab** = binds mostly unbound serum IgE + blocks binding to FcEpsionRI (used in allergic asthma w/ IgE levels resistant to inhaled steroids + Long-acting B2 agonists)

6. Methylxanthines:
-**Theophylline** = causes bronchodilation by inhibiting **phosphodiesterase** → cAMP levels due to cAMP hydrolysis

7. Cromolyn:
-prevents mast cell degranulation
-prevents acute asthma sxs
-rarely used

8. Anti-IL-5 Monoclonal Therapy:
-prevents eosinophil differentiation, maturation, activation, and survival mediated by IL-5 stimulation
-Maintenance therapy in severe eosinophilic asthma
-**Mepolizumab, Reslizumab = binds IL-5**
-Benralizumab = blocks IL-5 receptor alpha

References:

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-Limited use due to NTI (Cardiotoxicity, Neurotoxicity)
-Metabolized by CYP450
-Blocks actions of Adenosine