Boards & Beyond: Pulmonary Slides

Color slides for USMLE Step 1 preparation from the Boards and Beyond Website

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2022 Edition

Boards & Beyond provides a virtual medical school curriculum used by students around the globe to supplement their education and prepare for board exams such as USMLE Step 1.

This book of slides is intended as a companion to the videos for easy reference and note-taking. Videos are subject to change without notice. PDF versions of all color books are available via the website as part of membership.

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Pulmonary Embryology

Lung Anatomy
- Bronchi
- Hyaline cartilage
- Bronchioles
- No cartilage
- Terminal → respiratory
- Alveoli
- Capillaries
- Gas exchange

Tracheoesophageal Fistula
With Esophageal Atresia
- Abnormal septum formation
- Esophagus does not connect to stomach
- Accumulation of secretions
- Drooling, choking, vomiting
- Cannot pass NG tube into stomach
- Fistula esophagus → trachea
- Gastric distension
- Air in stomach on CXR
- Reflux → aspiration pneumonia
- Respiratory distress

Lung Maturation
Stages/Periods
- Pseudoglandular (5-16wk)
- Canalicular (16-26wk)
- Saccular (26wk -birth)
- Alveolar (after birth)

Lewis Spitz. Oesophageal atresia. Orphanet Journal of Rare Diseases
EA with TEF
Most Common

Lung Embryology
- Lung bud ("respiratory diverticulum")
- Outgrowth of foregut (future esophagus)
- Forms during 4th week of development

Lung Embryology

Pulmonary Embryology
Jason Ryan, MD, MPH
Canalicular Period
16-26 weeks
• Airway lumens become larger
• Type II pneumocytes form
• Produce surfactant
• Lower surface tension
• Keep alveoli open

Fetal Respiration
• Fetal breathing movements occur in utero
• Baby aspirates amniotic fluid
• Stimulates lung development
• Growth of respiratory muscles
• Important for growth during pseudoglandular phase

Pseudoglandular Period
5-16 weeks
• Lungs resemble a gland
• Branching to level of terminal bronchioles
• No respiratory bronchioles or alveoli present

Fetal Respiration
• Oligohydramnios:
• Pulmonary hypoplasia
• Part of Potter’s sequence
• Caused by fetal kidney abnormalities

Canalicular Period
16-26 weeks
• Terminal bronchioles divide
• Form respiratory bronchioles
• Respiratory bronchioles divide into alveolar ducts
• Survival after birth possible at end of period
Pulmonary Hypoplasia
- Oligohydramnios (Potter's sequence)
- Congenital diaphragmatic hernia
- Defective formation of pleuroperitoneal membrane
- Hole in diaphragm
- Abdominal organs herniate into chest
- In utero herniation → pulmonary hypoplasia
- Often fatal

Bronchopulmonary Dysplasia
- Occurs in premature infants
- Treated in NICU
- Surfactant, oxygen, mechanical ventilation
- Oxygen toxicity and lung trauma
- Alveolarization does not progress normally
- Respiratory problems during infancy
- Often improves during childhood

Alveolarization
- Airspaces subdivided
- New walls formed (septa)

Saccular Period
- 26 weeks - birth
  - Terminal sacs (primitive alveoli) form
  - Capillaries multiply in contact with alveoli

Bronchopulmonary Dysplasia
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Alveolar Period
- After birth
  - At birth, only about 1/3 of alveoli present
  - Following birth:
    - ↑ number of respiratory bronchioles and alveoli
    - Continued lung development through age 10

Pulmonary Hypoplasia
- Oligohydramnios (Potter's sequence)
- Congenital diaphragmatic hernia
  - Defective formation of pleuroperitoneal membrane
  - Hole in diaphragm
  - Abdominal organs herniate into chest
  - In utero herniation → pulmonary hypoplasia
  - Often fatal
Pulmonary Vascular Resistance

- In utero
  - PVR is high
  - Canalicular stage: few/no pulmonary capillaries
  - Later stages: hypoxemia → vasoconstriction
  - Umbilical venous blood: $P_{aO_2}$ 30 mmHg; $O_2$ sat=80%
  - Only about 10% of cardiac output to lungs
- At birth
  - PVR falls significantly
  - 100% cardiac output through lungs

Bronchogenic Cysts

- Abnormal budding of foregut
- Usually found in mediastinum
- Contain clear fluid
  - Air seen when infected
Pulmonary Anatomy

Zones
- **Conducting Zone**
  - No gas exchange
  - Large airways, nose, pharynx, trachea, bronchi
  - Filters, warms, humidifies air
  - Anatomic dead space
- **Respiratory Zone**
  - Gas exchange
  - Respiratory bronchioles, alveolar ducts, alveoli

Lung Anatomy

Bronchi and Bronchioles
- **Bronchi (cartilage)**
  - Primary (left and right)
  - Secondary/lobar
  - Tertiary/segmental
- **Bronchioles (no cartilage)**
  - Lobular/large
  - Terminal
  - Respiratory (feeds alveoli)
Airway Cells

- **Goblet cells**
  - Secrete mucus
  - Mostly glycoproteins and water
  - Protects against particulates, infection
- **Ciliated epithelial cells**
  - Beating cilia move mucus to epiglottis
  - Mucus swallowed
- **Club cells (bronchioles)**
  - Non-ciliated epithelial cells
  - Secrete protective proteins
  - Detoxification (P450 enzymes)

Respiratory Epithelium

- **Trachea and bronchi**
  - Ciliated pseudostratified columnar epithelial cells
  - Goblet cells
- **Bronchioles**
  - Epithelium transitions
  - Forms ciliated simple cuboidal epithelium
  - Club cells (terminal bronchioles)

Smooth Muscle

- **Conducting airway walls** contain smooth muscle
- Sympathetic activation (beta-2)
- Bronchodilation
- Parasympathetic activation (M3)
- Bronchoconstriction

Resistance to Air Flow

- Upper airways about 50% resistance
- Nose, mouth, pharynx
- Lower airway resistance
  - Highest in medium bronchi (turbulent flow)
  - Lowest in terminal bronchioles - slow laminar flow
Alveoli

- Small sacs
- Separated by septa
- Simple squamous epithelium (pneumocytes)
- Gas exchange
- Surrounded by capillaries

Pneumocytes

Alveolar Epithelial Cells

- Type 1
  - Most common (97% of cells)
  - Thin for gas exchange
- Type 2
  - Produce surfactant
  - Can proliferate to form other cell types
  - Key for regeneration after injury
  - Alveolar macrophages

Surfactant

- Exhale → alveoli shrink
- Collapse → atelectasis
- ↓ efficiency gas exchange
- Surfactant prevents collapse of alveoli

Surface Tension

- Alveoli lined with film of liquid
- Liquid-liquid forces shrink surface area into sphere
- Surface tension = liquid-liquid forces

Law of Laplace

- Determines collapsing pressure
  - Forces tending to collapse alveoli
  - Low collapsing pressure = easy to remain open
  - High collapsing pressure = difficult to remain open

Collapsing Pressure = \(2 \times \frac{\text{surface tension}}{\text{radius}}\)
Neonatal RDS

Complications

- Bronchopulmonary dysplasia
- Oxygen toxicity
- Oxygen promotes free radical formation
- Neovascularization in the retina
- Retinal detachment →blindness

Risk Factors

- Prematurity
- Maternal diabetes
- High insulin levels decrease surfactant production
- Cesarean delivery
- Baby spared stress response at delivery
- Reduced fetal cortisol
- Reduction in surfactant
Neonatal RDS
Prevention and Treatment

- Preterm delivery: **betamethasone**
  - Corticosteroid
  - Given to mother to stimulate surfactant production
- Treatment: surfactant
  - Administered via endotracheal tube

Right Upper Lobe

- Right Middle Lobe
- Right Lower Lobe
- Left Upper Lobe
- Left Lower Lobe

Right Upper Lobe

- Right Middle Lobe
- Right Lower Lobe
- Left Upper Lobe
- Left Lower Lobe

Right Lower Lobe

- Right Middle Lobe
- Right Upper Lobe
- Left Upper Lobe
- Left Lower Lobe

Left Upper Lobe

- Right Upper Lobe
- Right Middle Lobe
- Right Lower Lobe
- Left Lower Lobe

Image courtesy of Patrick J. Lynch, medical illustrator

Wikipedia/Public Domain
Mediastinal Compartments

- Mediastinum: space between lungs
- Divided into 3 anatomical compartments
  - Anterior
  - Middle
  - Posterior
- Differential diagnosis of mass varies by compartment

Foreign Body Aspiration

- Commonly occurs in children (peanuts)
- **Right lung** is more common site of aspiration
  - Right bronchus wider with less angle
  - More vertical path to lung
  - **Right lung**: 60% cases
    - Majority in main bronchus
    - Small number in right lower lobe bronchus
  - **Left lung**: 23% cases
    - Majority in main bronchus
    - Small number in left lower lobe bronchus

Muscles of Quiet Respiration

- **Diaphragm** → inspiration
- Exhalation is passive with normal (“quiet”) breathing

Public Domain

**Diaphragm**

- Innervated by **C3, C4, C5 (phrenic nerve)**
- Diaphragm irritation → “referred” shoulder pain
- Classic example: gallbladder disease
- Also lower lung masses
- Irritation can cause dyspnea and hiccups
- Cut nerve → diaphragm elevation, dyspnea
- “Paradoxical movement” → Moves up with inspiration
- Can see on fluoroscopy (“sniff test”)

**Diaphragm**

- **Caval opening**
  - T8
- **Inferior vena cava**
- **Esophageal hiatus**
  - T10
  - Esophagus, Vagus nerve
- **Aortic hiatus**
  - T12
  - Aorta, thoracic duct, azygous vein

**Anterior Mediastinal Masses**

- **Thymic masses**
  - Half of anterior masses derive from thymus
  - Thymoma: associated with myasthenia gravis
- **Teratoma or germ cell tumors** in adults
  - Mediastinum: most common location extra nodal GCT
- Teratomas, seminomas
- **Terrible lymphomas**
  - **Thyroid** growths
    - Enlarged or ectopic thyroid tissue may present as mass
    - Usually connected to thyroid gland

**Mediastinal Structures**

**Compartment** | **Major Structures** | **Masses**
--- | --- | ---
Anterior | Thymus, internal mammary arteries, lymph nodes | Thyroid, Thymic neoplasm, Teratoma, Lymphoma
Middle | Pericardium, heart, aorta, airway and esophagus | Lymphadenopathy: lymphoma, sarcoïd, or metastatic lung cancer
Posterior | Spine, nerves and spinal ganglia | Neurogenic tumors: schwannoma, neuroblastoma

**Anterior Mediastinal Masses**

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    - Enlarged or ectopic thyroid tissue may present as mass
    - Usually connected to thyroid gland
Exercise Breathing

- Inspiration (neck)
  - Scalenes – raise ribs
  - Sternocleidomastoids – raise sternum

- Exhalation (abdomen)
  - Rectus muscle
  - Internal/external obliques
  - Transverse abdominis
  - Internal intercostals
- Use of accessory muscles in respiratory distress
Lung Pressures
• Atmospheric pressure = 760 mmHg = 0 mmHg
• Alveolar pressure = pressure within alveoli
• Intrapleural pressure = pressure in pleural space
• Transpulmonary pressure = Alveolar pressure – Intrapleural pressure
• Necessary to keep alveoli open

Lung Capacities
Capacity = sum of two volumes
• Functional Residual Capacity
• Residual volume after quiet expiration
• RV + ERV
• Volume when system is relaxed
• Equilibrium: chest wall pulling out = lungs pulling in

Lung Volumes
• Tidal volume (TV)
• In/out air with each quiet breath
• Expiratory reserve volume (ERV)
• Extra air pushed out with force beyond TV
• RV remains in lungs
• Inspiratory reserve volume (IRV)
• Extra air can be drawn in with force beyond TV
• Lungs filled to capacity
• Residual volume (RV)
• Air that can’t be blown out no matter how hard you try

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Transpulmonary Pressure

- Alveolar Pressure – Intrapleural Pressure

\[ \text{TPP} = \text{P}_{\text{Alveoli}} - \text{P}_{\text{Intrapleural Space}} \]

Intrapleural Pressure

- **Negative** during normal quiet breathing
- Alveoli and lungs tend to **collapse**
  - Pull inward/recoil
  - Need outward force to keep walls open
- Chest wall tends to **expand**
  - Spring outward
  - Creates negative pressure in pleural space
  - Negative pressure "sucks" alveoli open

Pneumothorax

- Normal
- \[ \text{TPP} = 0 \]
- Lung collapses
- \[ \text{TPP} < 0 \]

Pneumothorax

- Patm = 0 mmHg
- \[ \Delta = 0 \text{ No Flow} \]
- \[ P_a = 0 \text{ mmHg} \]

Pressures and Air Flow
Air Flow and Pressure Changes

Quiet Breathing

- Inhalation
  - Intrapleural pressure becomes **more negative**
  - Alveolar pressure becomes negative
  - Air flow into lungs
- Exhalation
  - Intrapleural pressure becomes **less negative**
  - Alveolar pressure becomes positive
  - Air flow out of lungs

Lung Pressures

- Intrapleural Space
- Alveolus
- Chest Wall
- Air

Pressures and Air Flow

- Patm = 0 mmHg
- PA = \(-5\) mmHg
- \(\Delta = +5\) Flow In

Pressures and Air Flow

- Patm = 0 mmHg
- PA = \(+5\) mmHg
- \(\Delta = +5\) Flow Out
Lung Compliance

- For given pressure how much volume changes
- Compliant lung
  - Small amount of diaphragm effort
  - Generates small pressure change across lungs
  - Large volume change
  - Easy to move air in/out
- Non-compliant lung
  - Large amount diaphragm effort
  - Big pressure change across lung
  - Small volume change (lungs stiff)
  - Hard to move air in/out

\[ C = \frac{\Delta V}{\Delta P} \]

Functional residual capacity

- Lung in = chest out
- Volume where lungs rest after quiet exhalation
- Pressure inside system is zero
  - No \(1/4\) pressure from push/pull of lungs or chest wall
  - Pressure = atmospheric pressure
**Barrel Chest**
- Seen in patients with **emphysema**
- Increased lung compliance
- Increased FRC → larger volumes in chest

**Equal Pressure Point**
- Pleural pressure = airway pressure
- Beyond this point airway collapses
- In healthy lungs: EPP occurs in **cartilaginous** airways
- Prevents airway collapse

**Zones**
- Cartilage/Goblet Cells
- Smooth Muscle
- Cilia

**Forced Exhalation**
- Pleural pressure becomes **positive**
- Compresses airway
- Pressure on alveoli → positive pressure in airway
- Pushes air out → air flows from airways

**Equal Pressure Point**
- In disease: EPP moves toward alveoli
- Obstruction (bronchitis): more pressure drop
- Emphysema: loss of elastic recoil
- Can be reached in thin-walled bronchioles
- Result: Collapse, obstruction to airflow, air trapping

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**COPD**
Chronic Obstructive Pulmonary Disease
- **Slow exhalation**
  - Prevents large rise in pleural pressure
  - Forceful exhalation would ↑↑ intrapleural pressure
- **Pursed lips**
  - Increases airway (alveolar) pressure
  - Prevents collapse

**Hysteresis**
- Hysteresis = dependence of property on its history
- Different PV curves for inhalation and exhalation
- Slope PV curve = compliance
- Different compliance despite same lung structures

**Hysteresis**
- PV hysteresis caused by *surface tension*
- Inspiration begins with smallest volume
  - Molecules close together
  - Strongest surface tension
- Expiration begins at high lung volumes
  - Intermolecular forces low

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Hemoglobin

Oxygen Transport
- Dissolved O₂
  - Determined by Henry's law
  - \( P_{O_2} \times \text{solubility} = \text{dissolved O}_2 \)
  - Very small amount (2%) total blood O₂
- Bound to hemoglobin (98%)

Hemoglobin Types
- Hemoglobin A
  - Adult type
  - Most common type found (95%)
  - \( \alpha_2 \beta_2 \)
- Hemoglobin A₂
  - Adult type
  - Less common type (2-3%)
  - \( \alpha_2 \delta_2 \)
- Hemoglobin F
  - Fetal type
  - \( \alpha_2 \gamma_2 \)

Hemoglobin
- Globin chains
  - Proteins
  - Alpha (\( \alpha \))
  - Beta (\( \beta \))
  - Gamma (\( \gamma \))
  - Delta (\( \delta \))
- Heme
  - Molecule (non-peptide)
  - Contains iron (Fe)
  - Porphyrin ring
  - Oxygen binds iron

O₂-Hgb Dissociation Curves
- Y axis: percentage of hemoglobin bound to oxygen
- X-axis: partial pressure of oxygen (\( P_{O_2} \))

Oxygen-Hgb Binding
- Four heme groups do not simultaneous oxygenate
- First O₂ molecule INCREASES affinity for 2nd molecule
- Second O₂ molecule INCREASES affinity for 3rd molecule
- Third O₂ molecule INCREASES affinity for 4th molecule
- Affinity last O₂ = 300 times affinity for first O₂
- Positive cooperativity
  - Makes curve S shaped
Allosteric Proteins

- Allosteric = "other site"
- Binding at one site influenced by other sites
- Usually multi-subunit proteins
- Hemoglobin is an allosteric structure
- O₂ cooperativity is a positive allosteric effect

Hemoglobin Forms

- Globin chains can assume two formations
  - Taut form (T)
    - Tends to release O₂
    - Favored form in tissues
    - Allows more release of O₂
  - Relaxed form (R)
    - Holds on to O₂
    - Favored form in lungs
    - Allows more binding of O₂

Shifts in O₂-Hgb Curves

- Affinity of Hgb for O₂ can change — not fixed
- Hgb modified by environment within RBCs
- Dissociation curve shifts may occur to right or left

Rightward Shift

<table>
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<tr>
<th></th>
<th>Lungs PaO₂</th>
<th>Lungs %Sat</th>
<th>Tissues PaO₂</th>
<th>Tissues %Sat</th>
</tr>
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<tr>
<td>Normal</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>75%</td>
</tr>
<tr>
<td>Right Shift</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>50%</td>
</tr>
</tbody>
</table>

Normal: 100% → 75% Δ 25%
Right shift: 100% → 50% Δ 50%
**Left Curve Shifts**

- Latch on to O₂
- Lower metabolic activity
- ↓CO₂, ↑pH, ↓Temp

**Right Curve Shifts**

- Release O₂
- Favors taut form
- Causes of right shifts
  - Rising Metabolic Activity
  - ↑CO₂
  - ↓pH
  - ↑Temp
- Increases P₅₀

**2,3-Bisphosphoglycerate**

- Found in RBCs
- Promotes O₂ release from hemoglobin
- Negative allosteric effector
- Increasing levels:
  - Decrease oxygen affinity of hemoglobin
  - Increase delivery oxygen to tissues

**2,3 Bisphosphoglycerate**

- Created from diverted 1,3 BPG (glycolysis)
- Sacrifices ATP from glycolysis

**High Altitude**

- ↑ BPG with chronic hypoxia
  - COPD
  - High altitude
  - Chronic anemia

**Hemoglobin Saturation, %**

- PAO₂, mmHg

**Tissues**

- Machu Picchu
- Sea level

**Graphs**

- Normal Left shift
- Release O₂
- Taut
Carbon Monoxide

- Binds to iron in heme 240x the affinity of $O_2$
- Forms carboxyhemoglobin (HbCO)
- Blocks $O_2$ binding sites (less $O_2$ can be absorbed)
- "Functional anemia"
- Other binding sites cannot offload $O_2$
- Allosteric modification of hemoglobin
- Shifts dissociation curve left

\[ \text{C} \equiv \text{O} \]
Clinical Scenario

- Endoscopy patient
- **Benzocaine** spray used for throat analgesia
- Post procedure shortness of breath
- “Chocolate brown blood”
- O₂ sat (pulse oximetry) = variable (80s-90s)
- Oxygen does not improve shortness of breath
- PaO₂ (blood gas) = normal
- Diagnosis: ↑ methemoglobin level
- Other example:
- Premature babies given NO for pulmonary vasodilation

Methemoglobinemia

- Most iron in hemoglobin normally reduced (Fe²⁺)
- Small amount oxidizes iron: Fe³⁺
- Called methemoglobin
- Cannot bind O₂
- Excess methemoglobin: hypoxia

Fe³⁺

Methemoglobinemia

- Acquired methemoglobinemia from **drugs**
  - Local anesthetics (benzocaine)
  - Nitric oxide
  - Dapsone
- Treatment: **methylene blue**
  - Reducing agent
  - Fe³⁺ → Fe²⁺

Carbon Monoxide Poisoning

- Nonspecific symptoms
- Headache most common
- Malaise, nausea, dizziness
- Classic (but rare) sign: **cherry red lips**
  - Carboxyhemoglobin is red
  - Do not see blue lips (cyanosis)

::C≡O::

Carbon Monoxide Poisoning

- Standard pulse oximetry normal
- Cannot differentiate carboxyhemoglobin/oxyhemoglobin
- Diagnosis: **carboxyhemoglobin level**
  - Normal <3%
  - Smokers 10-15%
  - >15% suggest poisoning
- Treatment: **oxygen**

::C≡O::
**Pulmonary Circulation**

**Blood Oxygen Content**
- Systemic circulation
  - ↓ O₂ level (PaO₂) leads to vasodilation (↑blood flow)
- Pulmonary circulation
  - ↓ O₂ level (PaO₂) leads to vasoconstriction (↓blood flow)
  - "Hypoxic vasoconstriction"
  - Shunts blood away from poorly ventilated areas
  - More blood to well ventilated areas
- Key for fetal circulation
  - Low O₂ constricts pulmonary arteries in womb
  - At birth, arteries receive O₂ and dilate

**Blood O₂ Content**
- Low pressure system
  - Systemic: 120/80
  - Pulmonary artery: 24/12
- Walls of pulmonary artery very thin
  - Little smooth muscle
  - Low resistance to flow
  - Very distensible (compliant)

**Gas Exchange**
- Gasses classified by limiting factor for gas transfer
  - **Perfusion limited**
    - Gas transport limited by perfusion (blood flow)
    - More blood flow → more uptake of gas
  - **Diffusion limited**
    - Gas transport limited by diffusion

Inspired Air
(humidified, tracheal)

- O₂: 150 mmHg
- CO₂: 40 mmHg

Arterial Blood

- O₂: 90 mmHg
- CO₂: 40 mmHg

Venous Blood

- O₂: 40 mmHg
- CO₂: 40 mmHg
Low DLCO Disorders

- Emphysema
- Destruction of alveoli
- Decreased surface area
- Fibrosis or pulmonary edema
- Diffusion distance (thickness) increases

DLCO
Diffusing capacity of carbon monoxide
- Measures ability of lungs to transfer gas
- Patient inhales small amount (not dangerous) CO
- CO uptake is diffusion limited
- Amount taken up = diffusion capacity of lungs
- Machine measures CO exhaled
- Normal = 75 – 140 % predicted
- Severe disease <40% predicted

Gas Exchange: Oxygen
High Altitude

Gas Exchange: Carbon Dioxide

Gas Exchange
Length along capillary
Partial Pressure
N₂O: Perfusion limited
CO: Diffusion limited

Low DLCO Disorders

- Emphysema
- Destruction of alveoli
- Decreased surface area
- Fibrosis or pulmonary edema
- Diffusion distance (thickness) increases
Pulmonary Hypertension

- Arteriosclerosis
- Thickening of arterial walls
- Proliferation smooth muscle cells
- Thickening media
- Narrowing of the lumen

Medial Hypertrophy Normal

Gold standard diagnosis:

- Right heart catheterization
- Non-invasive diagnosis by echocardiography

Main symptom is dyspnea

- Untreated can lead to "cor pulmonale"
- Chronic high pressure in right ventricle
- Right ventricle hypertrophies
- Eventually dilates and fails
- Jugular venous distension
- Lower extremity edema
- Hepatomegaly
- Death from heart failure or arrhythmia

Normal PA pressure

- 24/12
- Mean 10-14mmHg

Pulmonary hypertension

- Mean pressure >25mmHg
- Loud P2 = pulmonary hypertension
- "Accentuated" or "loud" second heart sound
- Left upper sternal border

Pulmonary Vascular Resistance

- Resistance to blood flow
- Two vessels types:
  - Alveolar: capillaries
  - Extra-alveolar: arteries and veins
- Increased lung volumes:
  - Crushes alveolar vessels → high resistance
  - Pulls extra-alveolar vessels open

Pulmonary Hypertension

- Acute PA pressure
- Mean 26-40mmHg
- Pulmonary hypertension
- Mean pressure >25mmHg
- Loud P2 = pulmonary hypertension
- "Accentuated" or "loud" second heart sound
- Pulmonary stenosis
- Right ventricular hypertrophy

Arteriosclerosis

- Thickening of arterial walls
- Proliferation smooth muscle cells
- Thickening media
- Narrowing of the lumen

Medial Hypertrophy Normal
**Pulmonary Hypertension**

- High PVR
  - "Pulmonary Arterial HTN"
  - Primary or Secondary

\[ P_{PA} = CO \times PVR + P_{LA} \]

- High LA Pressure
  - Most common cause PHTN
  - "Pulmonary Venous HTN"
  - Heart Failure
  - Valve Disease

**Left Heart Disease**

- Most common cause of pulmonary hypertension
- "Pulmonary venous hypertension"
- Any cause of **high left atrial pressure**
  - Heart failure
  - Mitral stenosis
  - Mitral regurgitation

**High PVR**

- Pulmonary Arterial Hypertension

- Hypoxemia → vasoconstriction
  - COPD, other chronic lung diseases
  - Sleep apnea or high altitude (chronic hypoxia)

- Chronic pulmonary emboli
  - Decreased area for blood flow

**PAH**

- Pulmonary Arterial Hypertension

- High pulmonary vascular resistance
- No chronic lung disease or thrombosis
- Key associations:
  - Connective tissue disease (scleroderma)
  - Human immunodeficiency virus
  - Congenital heart disease (shunts)
  - Schistosomiasis
  - Drugs (amphetamines, cocaine)

**Idiopathic PAH**

- Rare disease
- Classically affects young women
- High pulmonary vascular resistance
- Increased activity vasoconstrictors
  - Endothelin
- Decreased activity vasodilators
  - Nitric oxide

**Left Heart Disease**

- Pulmonary Venous Hypertension

- PA: 25/12 mmHg

- O₂ CO₂

- Pulmonary Artery
  - Pulmonary Vein
  - Left Atrium

**Pulmonary Hypertension**

\[ P_{PA} = CO \times PVR + P_{LA} \]

- High LA Pressure
  - Most common cause PHTN
  - "Pulmonary Venous HTN"
  - Heart Failure
  - Valve Disease

**PAH**

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**Idiopathic PAH**

- Rare disease
- Classically affects young women
- High pulmonary vascular resistance
- Increased activity vasoconstrictors
  - Endothelin
- Decreased activity vasodilators
  - Nitric oxide
**PAH Treatments**

- All lower PVR
  - Epoprostenol: Prostacyclin (IV)
    - PGI₂
    - Potent vasodilator
  - Bosentan:
    - Antagonist endothelin-1 receptors (PO)
  - Sildenafil:
    - Inhibits PDE-5 in smooth muscle of lungs (PO)

**BMPR2 gene mutations**

- Bone morphogenic protein receptor type II
  - Inhibits smooth muscle proliferation
  - Mutations → abnormal growth (endothelium, smooth muscle)
  - Up to 25% of idiopathic cases
  - Up to 80% familial cases

**Plexiform Lesions**

- Unique to idiopathic PAH
- Endothelial proliferation forms multiple lumens
- Small arteries branch points from medium arteries

**Yale Rosen/Flikr**
Ventilation & Perfusion

Ventilation

• Ventilation = volume x frequency (respiratory rate)
  • 500cc per breath x 20 breaths per minute
  • 10,000cc/min
• Alveolar ventilation = useful for gas exchange
• Dead space ventilation = wasted ventilation

Dead Space

• Filled with air but no gas exchange
• Anatomic dead space
  • Volume of conducting portions of respiratory tract
  • Nose, trachea
• Physiologic dead space
  • Anatomic PLUS volume of alveoli that don’t exchange gas
  • Includes functional dead space
  • Insufficient perfusion
  • Apex is largest contributor
• Physiologic dead space increases in many diseases

Measuring Dead Space

• Bohr’s method
• Physiologic dead space (Vd) from:
  • Tidal volume (Vt)
  • PeCO2 (exhaled air)
  • PaCO2 (blood gas)

\[ V_d = \frac{P_{aCO2} - P_{eCO2}}{V_t} \]

Nomenclature

• PA = alveolar pressure
• PAO2 = alveolar O2
• PACO2 = alveolar CO2
• Pa = arterial pressure
• PaO2 = arterial O2
• PaCO2 = arterial CO2
• Pv = venous pressure
• Pe = expired pressure
• A = alveolar
  a = arterial

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Bohr Equation

\[ V_d = \frac{P_aCO_2 - P_CO_2}{V_t} \]

Zero Dead Space

\[ V_d = \frac{P_aCO_2 - P_CO_2}{V_t} \]

\[ 0 = \frac{P_aCO_2 - P_CO_2}{P_aCO_2} \]

\[ P_aCO_2 = P_aCO_2 \]

↑ dead space → \( P_aCO_2 \) approaches \( P_CO_2 \)

More gas exchange

Less retained CO2

100% Dead Space

\[ V_d = \frac{P_aCO_2 - P_CO_2}{V_t} \]

\[ 0 = \frac{P_aCO_2 - P_CO_2}{P_aCO_2} \]

\[ P_aCO_2 = P_aCO_2 \]

↑ dead space → \( P_aCO_2 \) approaches zero

Less gas exchange

More retained CO2

Dead Space

O2 = 100%

O2 = 70%

P_aCO_2 = 0

↓ dead space → \( P_aCO_2 \) approaches \( P_CO_2 \)

More gas exchange

Less retained CO2

Alveolar Ventilation Equation

Predicts Alveolar CO2

- Total ventilation (TV) = volume/min
  - **Volume in slightly > volume out due to O2 uptake**
  - Sometimes called minute ventilation

- Alveolar ventilation
  - TV minus “dead space”
  - Example: 500cc per minute
    - 150cc fills dead space
    - Only 350cc available for gas exchange
Lung Perfusion
• Upright position: Blood flow distribution is uneven
  • Caused by gravity
  • Apex: Lowest blood flow
  • Base: Highest blood flow
  • Lung divided into 3 zones to describe perfusion

Alveolar Gas Equation
Predicts Alveolar O2
• $P_{AO2} = P_{IO2} - \frac{P_{ACO2} \times K}{V}$

$P_{AO2} = \begin{array}{c|c|c}
40 & 150 & 100 \\
50 & 150 & 88 \\
60 & 150 & 75 \\
70 & 150 & 63 \\
80 & 150 & 50 \\
\end{array}$

Alveolar Ventilation Equation
Predicts Alveolar CO2
• $V = \text{alveolar ventilation}$
• $V_{CO2} = \text{rate of CO2 production}$
• $P_{ACO2} = \text{alveolar PCO2}$
• $Vt = \text{total ventilation}$
• $V_{ds} = \text{dead space ventilation}$
• $K = \text{constant}$

$P_{ACO2} = V_{CO2} \times K \div P_{AO2}$

Elevated Carbon Dioxide
• Hypercapnia
• Hypercarbia
• Causes acidosis
• Physiologic response: ↑ respiratory rate
  • Increased alveolar ventilation

Elevated Carbon Dioxide
• Hypercapnia
• Hypercarbia
• Causes acidosis
• Physiologic response: ↑ respiratory rate
  • Increased alveolar ventilation
**Lung Ventilation**
- Ventilation highest zone 3, lowest zone 1
- Also caused by gravity
- Upper lung compresses base \(\rightarrow\) pushes air out
- More room for filling of base with next breath
- Variations smaller (L/min) than blood flow

**Ventilation-Perfusion Ratio**
- \(V/Q\) ratio: alveolar ventilation/pulmonary blood flow
- Matching critical for gas exchange
- Under-ventilated or under-perfused alveoli inefficient
- **Normal \(V/Q\) ratio = 0.8**
- Alveolar ventilation (L/min)/pulmonary blood flow (L/min)
- Yields normal \(P_{aO2}\) (90 mmHg) and \(P_{aCO2}\) (40 mmHg)

**Zone 1**
- Lowest blood flow
- Lowest ventilation
- Highest \(V/Q\) ratio
- Highest \(P_{aO2}\)
- Lowest \(P_{aCO2}\)

**Zone 2**
- Lowest \(V/Q\) ratio

**Zone 3**
- Highest \(V/Q\) ratio
- Highest \(P_{aO2}\)
- Lowest \(P_{aCO2}\)

**Zone 3**
- Highest blood flow
- Highest \(V/Q\) ratio
- Highest \(P_{aO2}\)
- Lowest \(P_{aCO2}\)

**Tuberculosis**
- Tuberculosis
No change in mean PaO2 and PaCO2
• Increased venous CO2 (PVCO2)
• Decreased venous O2 (PVO2)

Venous Blood
PVCO2 46mmHg
PVO2 40mmHg

Arterial Blood
PaO2 90mmHg
PaCO2 40mmHg

Exercise
• No change in mean PaO2 and PaCO2
• Increased venous CO2 (PVCO2)
• Decreased venous O2 (PVO2)

Zone 1
• Lung apex: PA > Pa > PV
• Slight fall in Pa → capillary compression
• Hemorrhage/shock
• Zone 1 becomes dead space
  • Ventilation without perfusion

Zone 3 (Base)
Pa > PV > PA
Highest flow

Zone 2 (Mid)
PA > PA > PV

Pressures
PA Alveolar
P a Arterial
P v Venous

Exercise
• Increased O2 demand
• Ventilation rate increases
• Increased cardiac output
• V/Q ratio approaches 1
  • More blood flow
  • More ventilation
  • ↑ ventilation > ↑ blood flow
  • Becomes more even in zones

William Warby /Flikr

Pulmonary Blood Flow
• Normally, A-V pressure difference drives blood flow
• In lungs, alveolar pressure may determine blood flow
• High alveolar pressure → no blood flow → dead space

Zone 1
• Lung apex: PA > Pa > PV
• Slight fall in Pa → capillary compression
• Hemorrhage/shock
• Zone 1 becomes dead space
  • Ventilation without perfusion

Zone 2 (Mid)
PA > PA > PV

Zone 3 (Base)
Pa > PV > PA

Pressures
PA Alveolar
P a Arterial
P v Venous

Pulmonary Blood Flow
• PA constant
• At base, Pa and Pv highest
• At apex, Pa and Pv lowest

Zone 1 (Apex)
PA > Pa > Pv
Minimal flow

Zone 3 (Base)
Pa > Pv > PA
Highest flow
Oxygen Content

- Normal O₂ content requires:
  - Presence of hemoglobin
  - Sufficient saturation of hemoglobin
  - Normal PₐO₂

\[ \text{O₂ Content} = (\text{O₂ Binding Capacity}) \times (\% \text{ Sat}) + (\text{Dissolved O₂}) \] (ml O₂/dl)

- \( (1.39 \times \text{Hgb}) \times 0.003 \text{ PaO₂} \)

Pulse Oximetry

- Measures Hgb-O₂ saturation of blood
- Related to PaO₂
- Uses light and a photodetector

PaO₂

- Partial pressure oxygen in blood
- Obtained from an arterial blood gas
- Reflects amount of O₂ dissolved in blood
- Normal: >80mmHg

What determines O₂ content?

- O₂ binding capacity
  - How much O₂ blood can hold
  - Determined by hemoglobin
- Hemoglobin saturation
  - % Hemoglobin molecules saturated
- Dissolved O₂
  - O₂ directly dissolved in blood

Oxygen delivery to tissues

- Oxygen delivery to tissues depends on:
  - Cardiac output
  - O₂ content of blood
- For proper O₂ delivery need:
  - Normal cardiac output
  - Normal O₂ content

Oxygen Content

- Normal O₂ content requires:
  - Presence of hemoglobin
  - Sufficient saturation of hemoglobin
  - Normal PₐO₂

Pulse Oximetry

- Measures Hgb-O₂ saturation of blood
- Related to PaO₂
- Uses light and a photodetector
Hypoxemia, Hypoxia, Ischemia

- Hypoxemia: low oxygen content of blood
- Hypoxia: low O₂ delivery to tissues
- Ischemia: loss of blood flow

Heart Failure

- ↓ cardiac output
- ↓ blood flow to tissues → hypoxia
- O₂ content of blood may be normal
- PaO₂ and Hgb-O₂ sat may be normal

Anemia

- Oxygenation of blood by lungs is normal
- Oxygen carrying capacity of blood reduced
- Low O₂ content of blood
- PaO₂ and Hgb-O₂ sat normal

Carbon Monoxide

- Binds to iron in heme 240x the affinity of oxygen
- Blocks O₂ binding sites: "functional anemia"
- Alveolar O₂ (P_{A,O₂}) usually normal
- Amount of CO gas required for poisoning usually small
- Normal P_{A,O₂} → Normal P_{O₂}
- ↓ O₂ binding to Hb despite normal P_{O₂}

Hypoxemia, Hypoxia, Ischemia

- Low Hgb-O₂ sat or low PaO₂ = hypoxemia
- Hypoxemia → hypoxia
- Can have hypoxia without hypoxemia

Common Hypoxia Causes

- Hypoxemia
- Heart Failure
- Anemia
- Carbon Monoxide

Hypoxemia, Hypoxia, Ischemia

- Hypoxemia: low oxygen content of blood
- Hypoxia: low O₂ delivery to tissues
- Ischemia: loss of blood flow

Carbon Monoxide

- Low Hgb-O₂ sat (CO blocking O₂ binding sites)
- Pulse oximeter shows normal (100%) O₂ sat
- Can't distinguish Hb bound to CO from that bound to O₂
- O₂ content of blood reduced

Normal PaO₂
- Low O₂ % sat (reality)
- Normal O₂ % sat (detector)
- Hypoxia
A-a Gradient

- Difference between alveolar (A) and arterial (a) O₂
- Helpful for evaluating hypoxemia
- Step 1: Measure PₐO₂, PₐCO₂
- Step 2: Determine PₐO₂ from gas equation
- Step 3: A-a gradient = PₐO₂ – P_aO₂
- Normal 10-15 mmHg
  - Shunting from thebesian and bronchial veins

Hypoxemia

- Indicates defect oxygenating blood
- Causes categorized by A-a gradient
  - Alveolar O₂ (PₐO₂) - Arterial O₂ (P_aO₂)
  - PₐO₂ from alveolar gas equation
  - P_aO₂ from blood gas

Causes of Hypoxia

<table>
<thead>
<tr>
<th>O₂ Content</th>
<th>PaO₂</th>
<th>% Sat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Anemia</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>↓</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Alveolar Gas Equation

\[ P_{A\text{O}_2} = P_{I\text{O}_2} - P_{ACO_2} = 150 - \frac{P_{ACO_2}}{0.8} \]

A-a Gradient

- Low alveolar oxygen content (PₐO₂)
- Decreased oxygen content of air
  - High altitude
  - PₐO₂ sea level = 150 mmHg
  - PₐO₂ high altitude ~ 100 mmHg
- Hypoventilation
  - Reduced respiratory rate
  - Reduced tidal volume
  - Causes increase PₐO₂ → decreased PₐO₂
- Narcotics, neuromuscular weakness, obesity

Causes of Hypoxia

- Low alveolar oxygen content (PₐO₂)
- Decreased oxygen content of air
  - High altitude
  - PₐO₂ sea level = 150 mmHg
  - PₐO₂ high altitude ~ 100 mmHg
- Hypoventilation
  - Reduced respiratory rate
  - Reduced tidal volume
  - Causes increase PₐO₂ → decreased PₐO₂
- Narcotics, neuromuscular weakness, obesity
**Diffusion**

- Gases must diffuse from air to blood
- Rate of diffusion depends on:
  - Pressure difference (air-blood)
  - Area of alveoli for diffusion
  - Thickness of alveolar tissue

---

**Normal A-a Gradient**

- *Improves with oxygen*

\[ P_{AO2} = P_{IO2} - P_{ACO2} = 150 - P_{ACO2} \]

\[ R \]

\[ 0.8 \]

---

**Increased A-a Gradient**

- No problem with alveolar oxygen content (P_{AO2})
- **Low arterial oxygen content (P_{AO2})**
  - Most primary lung diseases: high A-a gradient
    - Pneumonia, pulmonary edema, etc.
  - Three basic mechanisms create the high A-a gradient
    - Diffusion defects
    - Shunt
    - V/Q Mismatch

---

**Alveolar Gas Equation**

\[ PAO2 = PIO2 - PaCO2 = 150 - PaCO2 \]

\[ R \]

\[ 0.8 \]

---

**A-a Gradient**

- Gases must diffuse from air to blood
- Rate of diffusion depends on:
  - Pressure difference (air-blood)
  - Area of alveoli for diffusion
  - Thickness of alveolar tissue
**Diffusion**

\[ V_{\text{gas}} = \frac{\text{Area} \times D \times (P_1 - P_2)}{\text{Thickness}} \]

- Surface area of alveoli falls in **emphysema**
- Diffusion distance (thickness) rises in:
  - Pulmonary fibrosis
  - Pulmonary edema
- Both lead to decreased diffusion \( \Rightarrow \) hypoxemia

**Ventilation-Perfusion Ratio**

- \( V/Q \) ratio: alveolar ventilation/pulmonary blood flow
- Matching critical for gas exchange
- Unventilated or unperfused alveoli inefficient

**Diffusion Limitation**

\[ V_{\text{gas}} = \frac{\text{Area} \times D \times (P_1 - P_2)}{\text{Thickness}} \]

**Shunting**

- No \( V \)
- Extreme reduction in \( V/Q \)
- \( V/Q = 0 \)
- Venous blood to arterial system without oxygenation
- Causes **hypoxemia**

**Shunting**

\[ V/Q = 0 \]
Mechanisms by Disease

- Most diseases (COPD, PNA, pulm edema) have hypoxemia from multiple mechanisms
- PNA may cause V/Q mismatch or shunt
- Some examples worth knowing
  - Intra-cardiac shunt: pure shunt mechanism
  - Inhale a peanut: V/Q = 0 (also pure shunt)
  - Pulmonary Embolism

V/Q Mismatch

- V/Q < 1
  - Reduced ventilation relative to perfusion
  - Perfusion wasted
  - Blood going where not enough O2 present
  - Hypoxemia with increased A-a gradient
  - Improves with oxygen

Carbon Dioxide

- Causes of hypercapnia
  - Hypoventilation
  - Increased dead space
  - Increased CO₂ production
  - Hypoxemia with high A-a gradient: no ↑ CO₂

Mechanisms of Hypoxemia

V-Q Mismatch

<table>
<thead>
<tr>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>PaO₂ using 100% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>--</td>
<td>↑</td>
</tr>
<tr>
<td>Shunt V/Q = 0</td>
<td>↓</td>
<td>--</td>
</tr>
<tr>
<td>V/Q Mismatch</td>
<td>↓</td>
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Mechanisms of Hypoxemia

Diffusion Limitation

- Reduced ventilation relative to perfusion
- Perfusion wasted
- Blood going where not enough O2 present
- Extreme version V/Q = 0 is shunt
- Hypoxemia with increased A-a gradient
- Improves with oxygen
Pulmonary Embolism

- Obstructed blood flow
- ↑ dead space
- Hypoxemia does occur in many patients
- V/Q mismatch
  - Blood flow forced through open vessels
  - Increased Q (working vessels)
  - Same V
  - Decreased V/Q (mismatch)
Carbon Dioxide

• Produced by cellular metabolism
• Transported to lungs via three mechanisms
  - Dissolved (5%)
  - Bound to hemoglobin (3%)
  - Bicarbonate (>90%)

Bicarbonate

• Most (>90%) CO₂ exists as bicarbonate
• Carrier form of CO₂
• Red cells contain large amounts carbonic anhydrase
  - Converts CO₂ to HCO₃⁻:

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

Dissolved CO₂

• Determined by Henry’s law
• \(P_{\text{CO}_2} \times \text{solubility} = \text{dissolved CO}_2\)
• Very small amount (5%) total blood CO₂

Bicarbonate Transport

• HCO₃⁻ inside RBCs leaves cell to plasma
• H⁺ remains in red cells
• Chloride (Cl⁻) enters cell
  - Maintains electrical neutrality
  - “Chloride shift”
• RBCs have high Cl⁻ content in venous blood

\[
\text{CO}_2 + \text{H}_2\text{O} \Leftrightarrow \text{H}_2\text{CO}_3 \Leftrightarrow \text{HCO}_3^- + \text{H}^+
\]
**Bohr Effect**

- Deoxyhemoglobin has high affinity for H^+.
- H^+ binds hemoglobin in low O_2/high CO_2 areas.
- Converts Hgb to "taut form" which releases O_2.
- Shifts O_2 curve to right.
- Hemoglobin releases more oxygen.

\[
CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+ 
\]

**Carbaminohemoglobin**

- Hemoglobin bound to CO_2.
- Binds at different site from O_2.
- CO_2 binding alters affinity for oxygen.
- More CO_2 → More O_2 release.
- CO_2 decreases affinity for oxygen.

**RBC Buffering H^+**

- H^+ produced when bicarbonate generated.
- Could cause dangerous fall in pH.
- Deoxyhemoglobin buffers (absorbs) H^+ in red cells.
- ↑ deoxyhemoglobin in RBCs when ↑ CO_2.
- Prevents H^+ from reducing pH.

**Bicarbonate**

- CO_2 produced by metabolism generates H^+ in RBCs.
- CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+.
- H^+ and low pH are *indicators of metabolism*.
- H^+ and low pH trigger release of O_2 by hemoglobin.

**RBC Buffering H^+**

- H^+ produced when bicarbonate generated.
- Could cause dangerous fall in pH.
- Deoxyhemoglobin buffers (absorbs) H^+ in red cells.
- ↑ deoxyhemoglobin in RBCs when ↑ CO_2.
- Prevents H^+ from reducing pH.
Exercise
• ↑ O2 consumption
• ↑ CO2 production
• ↑ Ventilation

High Altitude
• Lower atmospheric pressure
• Lower pO2
• Hypoxia → hyperventilation
• ↓ pCO2 → respiratory alkalosis (pH rises)
• After 24-48hrs, kidneys will excrete HCO3-
• pH will fall back toward normal

Haldane Effect
• O2 binding alters affinity for CO2
  • Low O2 environment Hgb binds more CO2
  • High O2 environment Hgb binds less CO2

Tissues versus Lungs

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low O2 (consumption)</td>
<td>High O2 (air)</td>
</tr>
<tr>
<td>High CO2 (metabolism)</td>
<td>Low CO2 (exhalation)</td>
</tr>
<tr>
<td>High H+</td>
<td>Low H+</td>
</tr>
<tr>
<td>Low pH</td>
<td>High pH</td>
</tr>
<tr>
<td>Favors O2 unloading</td>
<td>Favors O2 loading</td>
</tr>
<tr>
<td>Bohr Effect</td>
<td>Bohr Effect</td>
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CO2 Transport

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<tr>
<th></th>
<th>Lungs/Arteries</th>
<th>Tissues/Veins</th>
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</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.4</td>
<td>1</td>
</tr>
<tr>
<td>HCO3-</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>pCO2</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Hgb CO2 Content</td>
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High Altitude
• Lower atmospheric pressure
• Lower pO2
• Hypoxia → hyperventilation
• ↓ pCO2 → respiratory alkalosis (pH rises)
• After 24-48hrs, kidneys will excrete HCO3-
• pH will fall back toward normal

Haldane Effect
• Deoxyhemoglobin binds more CO2
  • Allows more CO2 loading with O2 consumption
  • Allows more CO2 unloading with high O2

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CO2 Transport

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<tr>
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<td>Hgb CO2 Content</td>
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Haldane Effect
• Deoxyhemoglobin binds more CO2
  • Allows more CO2 loading with O2 consumption
  • Allows more CO2 unloading with high O2

Tissues versus Lungs

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CO₂ and Breathing Control
• COPD patients: chronic retention of CO₂
  • Lose sensitivity to CO₂
  • Oxygen becomes major breathing stimulus
  • Excess oxygen therapy given → hypoventilation
• Theory: response to CO₂ blunted
  • Respiratory depression with high O₂
  • New data indicates more complex
    • Haldane effect

Cerebral Blood Flow

Panic Attacks
• Hyperventilation
  • Low CO₂
  • Hypocapnia → cerebral vasoconstriction
  • CNS symptoms (dizziness, blurred vision)

Exercise
• ↑ ventilation and blood flow
  • Normal PaO₂ and PaCO₂ despite metabolic changes
Veins: O₂ falls, CO₂ rises
Arteries: O₂ and CO₂ normal

Exercise
• More CO₂ produced by muscles
  • CO₂ levels in venous blood rise
  • More O₂ consumed by muscles
  • O₂ levels in venous blood fall

CO₂ and Breathing Control
• PaCO₂ is the major stimulus for breathing
  • Central chemoreceptors in medulla most important
  • Peripheral chemoreceptors: carotid and aortic bodies
    • Sense CO₂ but more sensitive to O₂
    • High PaCO₂ → increased respiratory rate
    • Low PaCO₂ → decreased respiratory rate

Cerebral Blood Flow

Cerebral Blood Flow
O₂ Content
Normal Range
Cerebral Blood Flow
CO₂ Content
Normal Range

Exercise
• More CO₂ produced by muscles
  • CO₂ levels in venous blood rise
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  • O₂ levels in venous blood fall

William Warby/Flikr
**CO₂ and Breathing Control**

- CO₂ level useful to determine **ventilation status**
  - High CO₂: hypoventilation
  - Low CO₂: hyperventilation
- Clinical scenario:
  - Patient with neuromuscular disease (ALS)
  - O₂ saturation on O₂ 95%
  - Blood gas: PaCO₂ = 60 (high)
  - Respiratory muscles failing
  - Symptoms of hypercapnia (high CO₂)
    - Lethargy
    - Confusion
    - Agitation

**CO₂ and Breathing Control**

- Clinical scenario
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**Lung Physical Exam**

**Percussion**
- Normal sounds = resonant
- Abnormal: dull or hyperresonant
  - Dull
    - Pleural effusion
    - Consolidation (pneumonia)
  - Hyperresonant → air trapped
    - Pneumothorax
    - Emphysema

**Adventitious Lung Sounds**
- Rales
- Wheezes
- Rhonchi
- Bronchial breath sounds
- Stridor

**Lung Auscultation**
- Normal breath sounds are vesicular
- Most all pathologic lung processes result in decreased lung sounds over affected area

**Lung Exam**
- Percussion
  - Finger against thorax → tap
- Auscultation
  - Stethoscope thorax
  - Upper, mid, lower lung fields
- Special techniques
  - Fremitus
  - Pectoriloquy

**Rales**
- Also called crackles
- Small airways “pop” open after collapse
- Early inspiratory, late inspiratory or expiratory
- Classic causes
  - Pulmonary edema (bases)
  - Pneumonia
  - Interstitial fibrosis
**Wheezes**
- Air flows through narrowed bronchi
- Usually expiratory or inspiratory/expiratory
- Classic cause is asthma
- Other causes:
  - Heart failure (cardiac asthma)
  - Chronic bronchitis
  - Obstruction (tumor; localized wheeze)

**Rhonchi**
- Secretions in large airways
- Coarse breath sounds
- Classic cause is COPD

**Bronchial Breath Sounds**
- High pitched lung sounds
- Like flow through tube
- Longer expiratory phase than normal
- Seen in pneumonia with consolidation

**Stridor**
- Wheeze that is almost entirely inspiratory
- Usually loudest over neck
- Indicates partial obstruction of larynx or trachea
- Some classic causes
  - Laryngotracheitis (croup)
  - Epiglottitis (Hib in children)
  - Retropharyngeal abscess
  - Diphtheria

**Pectoriloquy**
- Sounds over chest through stethoscope
- Bronchophony
  - Voice sounds are louder and clearer
- Whispered pectoriloquy
  - Whispered “99-99-99”
  - Should be muffled
  - Abnormal if clear
- Egophony: “Eeeeee” sounds like “Aaaay”
- All indicated fluid in lungs: Effusion, consolidation

**Wheezes**
- Place hands on patients back
- Patient says “ninety-nine”
- Vibrations travel through airways to back
- Varies with density of lung tissue
- Only common condition with increased fremitus is lobar pneumonia
- Decreased in most other processes
- Pleural effusion
- Pneumothorax
- Atelectasis
Nail Clubbing

- Associated with many pulmonary diseases
- Bronchiectasis
- Cystic Fibrosis
- Lung tumors
- Pulmonary fibrosis
- Also cyanotic congenital heart disease

Image courtesy of James Heilman, MD
Image courtesy of Jfdwolff
Pulmonary Function Tests

Spirometry

• Method for assessing pulmonary function
  - Pulmonary function tests (PFTs)
  - Patient blows into machine
  - Volume of air measured over time

Dyspnea

• Many, many causes
• Deconditioning
• Cardiac causes
• Anemia
• Pulmonary causes

Pulmonary Function Testing

• Determining flows, volumes in lung
• Helps determine cause of dyspnea
  - Sometimes unclear from history, exam, x-ray, etc.
• Helps determine disease severity/progression
  - Many diseases monitored by PFTs
  - COPD, Pulmonary Fibrosis

Pulmonary Dyspnea

• Obstruction
  - Can’t get air out of lungs
  - Air trapped
  - Poor oxygenation
• Restriction
  - Can’t get air into lungs
  - Poor oxygenation

Dyspnea

• Many, many causes
• Deconditioning
• Cardiac causes
• Anemia
• Pulmonary causes
Spirometry

- Must meet criteria for adequate test
- Sharp peak in flow curve
- Expiratory duration more than six seconds

Summary

- FEV1 and FVC fall in both obstructive and restrictive diseases
- FEV1 falls MORE than FVC in obstructive

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<th>FVC</th>
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<tr>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Restrictive</td>
<td>↓</td>
<td>↓</td>
<td>&gt;80%</td>
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Volumes

- Spirometry can measure
  - VC (FVC)
  - IRV
  - ERV
- Cannot measure
  - RV
  - FRC
- Residual volume rarely measured clinically
- Requires special techniques
Work of Breathing

- Work proportional to resistance
Work of Breathing

- Airflow resistance: Slower you breathe, less resistance

Work of Breathing

- Elastic resistance: Faster you breathe, less resistance

Work of Breathing

- Slower you breathe, less airflow resistance
  - Faster you breathe, less elastic resistance

Work of Breathing

- Increases in obstructive and restrictive disease
  - Different patterns
Obstructive Lung Disease

Chronic Bronchitis
- Chronic cough
- Productive of sputum
- At least 3 months over two years
- No other cause of cough present
- Strongly associated with smoking

Obstructive Lung Diseases
- Key points: Air trapping, slow flow out, less air out
- Reduced FEV1 (slow flow out)
- Reduced FVC (less air out)
- Reduced FEV1/FVC (hallmark)

Residual & Total Lung Volume
- Both go up in obstructive disease
  - From air trapping
- Both fall in restrictive disease
  - Less air fills the lungs due to restriction

Obstructive Lung Diseases
- Chronic bronchitis
- Emphysema
- Asthma
- Bronchiectasis
- Key differentiator: response to bronchodilators
  - Obstructive PFTs → administer bronchodilators
  - Improvement: asthma
  - No improvement: chronic lung disease

Chronic Bronchitis
- Hypertrophy of mucous secreting glands
- Reid Index
- Thickness of glands/wall
  - >50% in chronic bronchitis
- Lungs can plug with mucous “mucous plugging”
- Increased risk of infection

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Obstructive Lung Diseases
- Key points: Air trapping, slow flow out, less air out
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**Emphysema**
- Destruction of alveoli
  - Smoke activates macrophages
  - Recruitment of neutrophils
  - Release of proteases
  - Loss of elastic recoil
  - Small airways collapse on exhalation
  - Air “trapped” in lungs

**Chronic Bronchitis**
- Poor ventilation of lungs
- Increased CO2
- Decreased O2
- Hypoxic vasoconstriction
- Pulmonary hypertension
- Right heart failure (cor pulmonale)

**Shunting**
- O2 < 99%
- <99%
- 99%

**Emphysema**
- Smokers
  - Too many proteases created
  - Overwhelm anti-proteases
  - Upper lung damage
  - α1 anti-trypsin deficiency
    - Ineffective anti-proteases
    - Lower lobe damage

**Chronic Bronchitis**
- Cough
- Wheezing
- Crackles
- Dyspnea
- Cyanosis (shunting)

**Emphysema**
- Dyspnea
- Cough (less sputum than chronic bronchitis)
- Hyperventilation
- Weight loss
- Cor pulmonale
- Barrel Chest
Acinus

- Acinus = bronchiole + alveoli
- Smokers = centriacinar damage
- α1 anti-trypsin deficiency = panacinar

Chest Volumes and Pressures

- Chronic Bronchitis – Blue Bloater
  - Cyanosis from shunting (blue)
  - Air trapping (bloating)
- Emphysema – Pink Puffer
  - Loss of alveoli
  - Loss of surface area for O2 absorption (dead space)
  - Hyperventilation to compensate (puffer)
  - Initially this maintains O2 level (pink)

COPD

- Chronic Obstructive Pulmonary Disease
- Includes chronic bronchitis, emphysema, asthma
- Many similar symptoms (cough, dyspnea, wheezing)
- Many similar treatments

α1 Anti-trypsin Deficiency

- Inherited (autosomal co-dominant)
- Decreased or dysfunctional AAT
- AAT balances naturally occurring proteases
- Elastase found in neutrophils & alveolar macrophages
**Asthma Symptoms**
- Episodic symptoms
- Dyspnea, wheezing, cough
- Hypoxia during episodes
- Decreased I/E ratio
- Reduced peak flow
- Mucous plugging (airway obstruction/shunt)
- Death: Status asthmaticus

**AERD**
- Aspirin Exacerbated Respiratory Disease
- Asthma, chronic rhinosinusitis, nasal polyposis
- Chronic asthma/rhinosinusitis symptoms
- Acute exacerbations after ingestion aspirin or NSAIDs
- Dysregulation of arachidonic acid metabolism
- Overproduction leukotrienes
- Treatment: Leukotriene receptor antagonists
- Montelukast, Zafirlukast

**Asthma Triggers**
- URI
- Allergens (animal dander, dust mites, mold, pollens)
- Stress
- Exercise
- Cold
- Aspirin

**Asthma**
- Reversible bronchoconstriction
- Usually due to allergic stimulus
- Type I hypersensitivity reaction
- Airways are hyperresponsive
- Common in children
- Associated with other allergic (atopic) conditions
- Rhinitis, eczema
- May have family history of allergic reactions

**α1 Anti-trypsin Deficiency**
- Lung
  - Panacinar emphysema
  - Imbalance between neutrophil elastase (destroys elastin) and elastase inhibitor AAT (protects elastin)
  - Lower lung damage
- Liver cirrhosis
  - Abnormal α1 builds up in liver
  - Only occurs in phenotypes with pathologic polymerization of AAT in endoplasmic reticulum of hepatocytes
  - Some patients have severe AAT deficiency but no intra-hepatocytic accumulation
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**α1 Anti-trypsin Deficiency**
- Classic case
  - Typical COPD symptoms: cough, sputum, wheeze
  - Younger patient (40s)
  - Imaging: emphysematous changes most prominent at bases
  - Obstructive PFTs
  - Question often asks about panacinar involvement
  - These patients should NEVER smoke
  - Stimulates neutrophil elastase production

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Asthma Diagnosis
- Usually classic history/physical exam
- Methacholine challenge
  - Muscarinic agonist
  - Causes bronchoconstriction
  - Administer increasing amounts of nebulized drug
  - Spirometry after each dose
  - Look for dose at which FEV1 falls significantly
  - If dose is low → positive test

Asthma Pathology
- Recurrent episodes
- Smooth muscle hypertrophy
- Inflammation

Asthma Pathology
- Classic sputum findings
  - Curschmann’s spirals
  - Charcot-Leyden crystals

Pulsus Paradoxus
- Most frequent non-cardiac causes are asthma/COPD

Bronchiectasis
- Result of chronic, recurrent airway inflammation
- Airways become permanently dilated
- Obstruction
  - Large airways dilated
  - Small/medium airways thickened bronchial walls
ABPA
Allergic bronchopulmonary aspergillosis
• Hypersensitivity (allergic) reaction to aspergillus
• Lungs become colonized with Aspergillus fumigatus
• Low virulence fungus
• Only infects immunocompromised or debilitated lungs
• Occurs predominantly in asthma and CF patients
• ABPA patients:
  • Increases Th2 CD4+ cells
  • Synthesis interleukins
  • Eosinophilia
  • IgE antibody production

Kartagener’s syndrome
• Chronic sinusitis
• Bronchiectasis (chronic cough, recurrent infections)
• Male infertility
• Situs inversus

Primary Ciliary Dyskinesia
Immotile-cilia syndrome
• Cilia unable to beat, beat normally, or absent
• Inherited (autosomal recessive)
• Gene mutations dynein structure/formation
• Dynein = motor protein creates movement

Bronchiectasis Symptoms
• Recurrent infections
• Cough, excessive sputum (foul smelling)
• Hemoptysis
• Cor pulmonale
• Amyloidosis

Bronchiectasis Etiologies
• Obstruction (tumor)
• Smoking
• Cystic fibrosis
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Kartagener’s syndrome
• Classic case:
  • Child
  • Recurrent sinus/ear infections
  • Chronic cough
  • Bronchiectasis on chest CT
  • Obstruction on PFTs
  • Situs inversus
• Question often asks about dynein protein

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• Allergic bronchopulmonary aspergillosis
ABPA
Allergic bronchopulmonary aspergillosis
- Classic case
  - Asthma or CF patient
  - Recurrent episodes cough, fever, malaise
  - Brownish mucus plugs, hemoptysis
  - Peripheral blood eosinophilia
  - High IgE level
  - Bronchiectasis on imaging
  - PFTs with obstruction
- Diagnosis: Skin testing aspergillosis
- Treatment: Steroids

Summary
Lung Diseases
- Restrictive
- Obstructive
- Chronic Bronchitis
- Emphysema
- Asthma
- Bronchiectasis
- Smoking
- α1-antitrypsin
- OBPA
Restrictive Lung Disease

Causes
- #1: Poor breathing mechanics
- #2: Interstitial lung diseases

Poor Breathing Mechanics
- Not a primary pulmonary issue
- Under-ventilation of lungs
- Alveoli working: A-a gradient normal
- Neuromuscular
  - ALS, Polio, myasthenia gravis
- Structural
  - Scoliosis
  - Morbid obesity

Interstitial Lung Disease
- Bilateral, diffuse pattern
- Small, irregular opacities (reticulonodular)
  - "Honeycomb" lung appearance.

DLCO
- Diffusing capacity in lung of carbon monoxide
- DLCO separates cases restrictive disease
- Restriction with normal DLCO
- Extra-pulmonary cause: obesity
- Restriction with low DLCO
  - Interstitial lung disease
**DLCO**

- DLCO = diffusing capacity of carbon monoxide
- Measures ability of lungs to transfer gas to RBCs
- Patient inhales small amount (not dangerous) CO
- CO uptake is diffusion limited
  - Amount taken up = diffusion function lungs
- Machine measures CO exhaled
- Normal = 75 – 140% predicted
- Severe disease <40% predicted

**Low DLCO Conditions**

- Intstitial lung disease
- Emphysema
- Abnormal vasculature
  - Pulmonary hypertension
  - Pulmonary embolism
- Prior lung resection
- Anemia
  - Corrects when adjusted for Hb level

**Interstitial Diseases**

- "Diffuse parenchymal lung diseases"
- Large group of disorders
- Similar clinical, radiographic, physiologic, or pathologic manifestations

**Interstitial Diseases**

- Idiopathic pulmonary fibrosis
- Systemic diseases with interstitial lung features
  - Scleroderma
  - Rheumatoid arthritis
  - Goodpasture’s (anti-GBM disease)
  - Wegener’s (granulomatosis with polyangiitis)
  - Sarcoidosis
- Pneumoconiosis
  - Drug toxicity (amiodarone, methotrexate)
  - Hypersensitivity pneumonitis

**Idiopathic pulmonary fibrosis**

- Most common type: Idiopathic interstitial pneumonia
- Slow onset dyspnea
- Typically affects adults over the age of 40
Asbestosis
- Inhalation of asbestos fibers
- Shipbuilding, roofing, plumbing
- Classically affects lower lobes
- Three clinical problems:
  - Interstitial lung disease (asbestosis)
  - Pleural plaques
  - Lung cancer

Silicosis
- Inhalation of silica in quartz, granite, or sandstone
- Most widespread pneumoconiosis in US
- Foundries (metal production facilities)
- Sandblasting (abrasive blasting)
- Mines

Silicosis
- Macrophages react to silica
- Inflammation → fibroblasts → collagen
- Impaired macrophage killing
- High prevalence of bronchogenic carcinoma

Coal miner’s lung
- Inhalation of coal dust particles
- CXR or Chest CT:
  - Small, rounded, nodular opacities
  - Preference for the upper lobes

Silicosis
- Affects upper lobes
- Eggshell calcifications of lymph nodes

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Hypersensitivity pneumonitis

- Classic case
- Farmer or bird handler
- Cough, dyspnea, chest tightness
- Diffuse crackles
- Diagnosis (challenging):
  - Bronchoalveolar lavage
  - Inhalation challenge
  - Lung biopsy
- Treatment:
  - Avoid exposure
  - Steroids

Drug toxicity

- Bleomycin
- Busulfan
- Amiodarone
- Methotrexate

Asbestosis

- Bronchogenic carcinoma
- Mesothelioma
  - Asbestos is the only known risk factor for mesothelioma
  - Occurs decades after exposure
  - Pleural thickening and pleural effusion
  - Slow onset symptoms (dyspnea, cough, chest pain)
  - Poor prognosis

Hypersensitivity pneumonitis

- Hypersensitivity reaction to environmental antigen
  - Agricultural dusts
  - Microorganisms (fungal, bacterial, or protozoa)
  - Chemicals
  - Mixed type III/IV hypersensitivity
  - Classic case is a farmer's lung
    - Moldy hay, grain exposure
  - Also common in bird/poultry handlers
    - Waste from birds → dried, finely dispersed dust

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Treatment of COPD/Asthma

β2 Agonists
- Activate adenylate cyclase →↑cAMP
- Relax bronchiolar smooth muscle
- Short acting: Albuterol
  - Nebulizer or inhaler
  - Use during acute attacks (prn)
- Long acting: Salmeterol, Formoterol
  - Not used as monotherapy for asthma (always with ICS)
- Systemic side effects (rare)
  - Tremor, arrhythmia

Muscarinic Antagonists
- Vagal nerve →Ach →Bronchoconstriction
- MA drugs block M receptors: smooth muscle
- Prevents bronchoconstriction

Muscarinic Antagonists
- Short acting: Ipratropium
- Long acting: Tiotropium

Steroids
- Inhaled: Beclomethasone, Fluticasone, Budesonide
- Oral: Prednisone
- IV: Methylprednisolone (Solumedrol)
**Theophylline**
- Methylxanthines
- Multiple, complex mechanisms
  - Bronchodilation
  - Likely through inhibition of PDE
  - Less hydrolysis (breakdown) of cAMP
  - ↑cAMP
- Also down-regulates inflammatory cell functions

**Special Asthma Drugs**
- Leukotriene receptor antagonists (PO)
  - Montelukast (Singulair)
  - Useful in aspirin sensitive asthma
- Zileuton (PO)
  - 5-lipoxygenase inhibitors
  - Blocks conversion of arachidonic acid to leukotrienes

**Eicosanoids**
- Lipids (cell membranes)
- Arachidonic acid
- Leukotrienes
- Lipoxygenase
- Thromboxanes
- Prostaglandins
- Cyclooxygenase
- Phospholipase A2
- Montelukast
- LTD4
- Zileuton

**Steroids**
- Inhibit synthesis of cytokines
- Bind to glucocorticoid receptor (GR)
- Many, many immunosuppressive effects
- ↓ expression of many interleukins, IFN-γ, TNF-α, GM-CSF
- Inactivation of NF-κB
  - Transcription factor
  - Induces production of TNF-α
- Common side effect is oral candidiasis (“thrush”)
- Patients instructed to rinse after inhalation

**Special Asthma Drugs**
- Omalizumab (SQ injection)
  - IgG monoclonal antibody
  - Inhibits IgE binding to IgE receptor on mast cells & basophils
- Cromolyn (inhaler/nebulizer)
  - Inhibits mast cell degranulation
  - Blocks release of histamine, leukotrienes

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Theophylline

- Narrow therapeutic index
- Levels must be monitored
- Dose must be titrated
- Goal is a peak serum concentration 10 to 20 mg/L.

- Cardiotoxicity
  - Blocks adenosine receptors
  - Increased heart rate
  - Arrhythmias (atrial tachycardia, atrial flutter)
  - Cause of death in overdose/poisoning
- Key clinical scenario
  - Patient on theophylline for asthma/COPD
  - SVT
  - Adenosine fails to slow heart rate

- GI toxicity
  - Nausea, vomiting
- Neurotoxicity
  - Seizures
- Overdose scenario: Nausea, vomiting, seizures

- Metabolized by P450
- Many drug-drug interactions
- Common culprits:
  - Cimetidine
  - Ciprofloxacin
  - Erythromycin
  - Clarithromycin
  - Verapamil

- Narrow therapeutic index
- Levels must be monitored
- Dose must be titrated
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Asthma

- Avoidance of Triggers
- Steroids
- Zileuton
- Cromolyn
- Omalizumab

- Mast Cell
  - Leukotrienes
  - Histamine
  - IgE

- Bronchoconstriction

- β agonists
- M antagonists
- Theophylline
- LRAAs

Special COPD Drugs

- Theophylline
- Roflumilast (PO)
- Phosphodiesterase-4 (PDE-4) inhibitor
- Decreases inflammation
- May relax airway smooth muscle

Roflumilast is a phosphodiesterase-4 inhibitor.
### Asthma: Acute Exacerbations
- Oxygen
- Nebulized albuterol +/- ipratropium (Combivent)
- IV or oral corticosteroids
  - Prednisone 60mg daily
  - Methylprednisolone 80mg IV q8hrs
- Antibiotics (severe, hospitalized patients)
  - Fluoroquinolones
  - Amoxicillin/clavulanate
- Rarely used:
  - Ipratropium
  - IV Magnesium sulfate

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### COPD: Chronic Therapy
- Oxygen
- Associated with increased survival
- PaO2 < 55mmHg or O2 sat <88%
- Pulmonary rehabilitation
  - Improves exercise capacity, quality of life
  - Decrease dyspnea
- Vaccinations
- Smoking cessation

### GOLD Criteria
Global Initiative for Chronic Obstructive Lung Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
<th>FEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold 1</td>
<td>Mild</td>
<td>FEV1 &lt;80%</td>
</tr>
<tr>
<td>Gold 2</td>
<td>Moderate</td>
<td>FEV1 50-79%</td>
</tr>
<tr>
<td>Gold 3</td>
<td>Severe</td>
<td>FEV1 30-49%</td>
</tr>
<tr>
<td>Gold 4</td>
<td>Very Severe</td>
<td>FEV1 &lt;30%</td>
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### Surgical Treatment

- For advanced "end-staged" COPD
- Lung volume reduction surgery/Bullectomy
  - Remove diseased lung tissue
  - Allow healthy lung tissue more room to expand
- Lung transplant

### Asthma: Chronic Therapy

1. **Step 1**: SABA as needed
2. **Step 2**: Add Low dose ICS
3. **Step 3**: Medium ICS or Low ICS + LABA
4. **Step 4**: Medium ICS + LABA
5. **Step 5**: High ICS + LABA
6. **Step 6**: High ICS + LABA + Oral Steroids
Lobar Pneumonia

- Classic form of pneumonia (S. pneumoniae)
- Bacteria acquired in nasopharynx
- Aerosolized to alveolus
- Enter alveolar type II cells
- Pneumococci multiply in alveolus
- Invade alveolar epithelium
- Pass from one alveolus to next (pores of Cohn)
- Inflammation/consolidation of lobes
- Can involve entire lung

Four Lobar Stages

- #1: Congestion (1st 24 hours)
  - Alveolar capillaries dilate
  - Exudate of bacteria develops
- #2: Red hepatization (2-3 days)
  - Exudate of RBCs, neutrophils, fibrin
  - "Fresh" exudate: RBCs/WBCs intact
  - Pneumococci alive
  - Lobes look red
- #3: Gray hepatization (4-6 days)
  - Gray, firm lobe
  - Exudate with neutrophils/fibrin
  - RBCs disintegrate
  - Dying pneumococci
- #4: Resolution
  - Return to normal (little scarring)
  - Enzymes digest exudate
  - Type II pneumocyte key for regeneration
Causes of Pneumonia

Adults

• Gram-negative rods
  • Klebsiella, E. Coli, Pseudomonas
  • Uncommon unless severe PNA
  • Often isolated in hospitalized patients
• S. Aureus (postinfluenza pneumonia)
• Anaerobes (aspiration PNA; lung abscess)
• Viruses
  • Influenza
  • RSV (children)

Children

• S. pneumoniae – most common
• Haemophilus influenzae
• Mycoplasma pneumoniae
• Chlamydia pneumoniae
• Usually milder than strep pneumonia
• Respiratory distress rare
• Interstitial infiltrates on CXR
• “Walking pneumonia”

Causes of Pneumonia

Bronchopneumonia

• Patchy inflammation of multiple lobules
• Primary involvement airways and surrounding interstitium
• Staphylococcus aureus

Interstitial Pneumonia

• Inflammatory infiltrate of alveolar walls only
• More indolent course
• Viruses
  • Legionella pneumophila
  • Mycoplasma pneumoniae
  • Chlamydia pneumoniae

Atypical Pneumonia

• Pneumonia caused by:
  • Legionella pneumophila
  • Mycoplasma pneumoniae
  • Chlamydia pneumoniae
  • Usually milder than strep pneumonia
  • Respiratory distress rare
  • Interstitial infiltrates on CXR
  • “Walking pneumonia”

Causes of Pneumonia

Children

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<th>Neutones Age</th>
<th>Children Age</th>
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<tr>
<td>&lt;4 weeks</td>
<td>4wk-1yr</td>
</tr>
<tr>
<td>Group B Strep</td>
<td>Viruses (RSV)</td>
</tr>
<tr>
<td>E. Coli</td>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
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</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Pneumonia</td>
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Nosocomial PNA
• Lots of resistance to antibiotics
• Gram negative rods
• E. coli, Klebsiella, Enterobacter, Pseudomonas, Acinetobacter
• Staph Aureus including MRSA
• Often cover for pseudomonas, MRSA
• Sometimes multi-drug combinations
• Cefepime or Ceftazidime
• Imipenem or Meropenem
• Piperacillin-tazobactam (Zosyn)

Community Acquired PNA
• Complicated
  • COPD, CKD, Diabetes, CHF, Alcoholism
  • Recent antibiotic use
  • Fluoroquinolone (levofloxacin)
  • Amoxicillin plus azithromycin

• Uncomplicated
  • No co-morbidities
  • No recent antibiotic use
  • Low community rates resistance
  • Azithromycin, Clarithromycin, or Doxycycline
  • Three to five day course
  • Patient should be afebrile 48-72 hrs and clinically stable

Clinical Classes of Pneumonia
• Community acquired
  • Usually S. Pneumoniae, H. Influenza, S. Aureus
  • Sometimes Mycoplasma, Chlamydia, Legionella (atypicals)
• Nosocomial
  • Bad bugs
  • Often gram negatives (Pseudomona, Klebsiella, E. Coli)
  • Hospital Acquired
  • Ventilator-associated pneumonia (VAP)
  • Healthcare-associated pneumonia (HCAP; nursing homes)

Diagnosis
• Usually:
  • History
  • Physical exam
  • X-ray (sometimes CT scan)
• Rarely
  • Sputum culture
  • Bronchoalveolar lavage

Signs/Symptoms
• High Fever
• Cough
• Sputum production
• Elevated WBC
• Pleuritic chest pain

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Legionella

- First identified at American Legion convention
- Infection from inhalation of aerosolized bacteria
- Outbreaks at hotels with contaminated water
- Can cause nosocomial pneumonia in nursing homes

Legionella Symptoms
- Initially mild pneumonia symptoms
  - Fever; mild, slightly productive cough
  - Can progress to severe pneumonia
- GI symptoms
  - Watery diarrhea, nausea, vomiting, and abdominal pain
- Hyponatremia (Na<130 meq/L) common
  - Can occur in any PNA but more common Legionella

ARDS

Acute Respiratory Distress Syndrome
- Triggered by various lung injuries
- Injury → release of pro-inflammatory cytokines
  - TNF, interleukins
  - Cytokines recruit neutrophils to lungs
  - Neutrophils release toxic mediators
    - Reactive oxygen species, proteases
  - Damage to capillary endothelium and alveolar epithelium
  - Protein escapes from vascular space
  - Fluid pours into the interstitium

ARDS Triggers
- Sepsis (most common)
- Infection (PNA)
- Aspiration
- Trauma
- Acute pancreatitis
- Transfusion-related acute lung injury (TRALI)

ARDS Treatment
- Mechanical ventilation
- Low tidal volume
- Supportive care (fluids, nutrition)
- VAP pneumonia is serious complication

ARDS

Complications
- Sepsis
- Respiratory failure
- Lung abscesses
- Pleural effusion
- ARDS

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Complications
- Sepsis
- Respiratory failure
- Lung abscesses
- Pleural effusion
- ARDS
CMV
- Pneumonia in transplant patients on immunosuppressive drugs
- “Owl eye” intranuclear inclusions

Influenza Virus
- Atypical pneumonia
- Influenza A or B viruses
- Fever, headache, myalgia, and malaise
- Nonproductive cough, sore throat, runny nose
- Major complication is secondary pneumonia
- Strain pneumoniae, Staph aureus, H. influenzae
- Worsening symptoms after initial improvement
- Cause of death

Mycoplasma Pneumonia
- Atypical pneumonia
- Can’t see on gram stain (no cell wall)
- Classically causes outbreaks in young adults
- College dorm residents
- Military recruits
- CXR looks worse than symptoms
- Can cause autoimmune hemolytic anemia
- IgM antibody → RBC antigen
- “Cold” hemolytic anemia
- Stevens-Johnson syndrome

Pontiac Fever
- Mild form of Legionella infection
- Fever, malaise, chills, fatigue, and headache
- No respiratory complaints
- Chest radiograph usually normal

Legionella
- Diagnosis
  - Special culture requirements
  - Does not gram stain well
  - Buffered charcoal yeast extract agar (BCYE)
  - Iron and cysteine added for growth
  - Supplemented with antibiotics and silver dyes
    - Antimicrobials prevent overgrowth by competing organisms
    - Dyes give distinctive color to Legionella
  - Urinary antigen test
    - Rapid test available in minutes
    - Does not test for all Legionella types

- Classic Case
  - Mild cough
  - Watery diarrhea
  - Confusion (low Na)
  - Negative bacteria on gram stain
  - Diagnose with urinary antigen test
  - Treatment: Fluoroquinolone or Azithromycin

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Klebsiella Pneumonia
• Can cause lobar pneumonia
• Often from aspiration
• Marked inflammation/necrosis
• Thick, mucoid and blood-tinged sputum
• “Currant jelly”

Aspiration Pneumonia
• Klebsiella
• Staph Aureus
• Anaerobic bacteria
• Peptostreptococcus
• Fusobacterium
• Prevotella
• Bacteroides
• Clindamycin first-line therapy

Aspiration Pneumonia
• Aspiration of microorganisms
• Bugs from oral cavity and nasopharynx to lungs
• Risk factors:
  • Reduced consciousness (anesthesia)
  • Seizures
  • Alcoholics
  • Dysphagia from neuromuscular weakness
• Classic patients:
  • Debilitated nursing home patient
  • Alcoholic

RSV
• Respiratory Syncytial Virus
• Viral respiratory infection in infants
• Often seasonal outbreaks (Nov – April)
• Most common cause lower respiratory tract illness in children
• Bronchiolitis, pneumonia, acute respiratory failure
• Often starts as upper airway infection
• Runny nose
• Few days later, lower tract symptoms
• Wheezing often present

RSV
• Treatment: Ribavirin
• Inhibits synthesis of guanine nucleotides
• Prevention: Palivizumab
• Monoclonal antibody against F protein
• RSV contains surface F (fusion) protein
• Causes respiratory epithelial cell fusion
• Used in pre-term infants (high risk RSV)
• Sometimes congenital heart disease

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Lung Abscess

- Contained, fluid-filled space in lungs
- "Air fluid level" on imaging
- Usually a consequence of aspiration
- Rarely due to bronchial obstruction from cancer
- Predominantly anaerobes
  - Peptostreptococcus
  - Prevotella
  - Bacteroides
  - Fusobacterium
- Sometimes S. Aureus, Klebsiella
- Treatment: Clindamycin

PCP

Pneumocystis jirovecii

- Diffuse interstitial pneumonia
- Requires immunocompromise
- Classically HIV
- AIDS-defining illness
- Yeast → inhaled
- Usually no symptoms if immune system intact

Diagnosed by microscopy
- Sputum sample or BAL
- Staining required → cannot be cultured
- Special stains used
  - Silver stains often used

Image courtesy of Yale Rosen

PCP

Pneumocystis jirovecii

- Treatments
  - TMP-SMX (first line)
  - Dapsone
  - Pentamidine
- Prophylaxis
  - TMP-SMX when CD4 <200 cells/μL
  - High dose steroid or other immunosuppressant

Image courtesy of Yale Rosen

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Image courtesy of Yale Rosen
Pneumothorax

- Air in pleural space
- Two types to know about
  - Spontaneous
  - Tension

Spontaneous PTX

- Primary
  - Rupture of subpleural bleb
  - Common in tall, thin young males
- Secondary
  - Older patients with underlying pulmonary disease
  - COPD

What are the pleura?

- Two layers of tissue surrounding lungs
  - Visceral pleura - attached to lung
  - Parietal pleura - attached to chest wall
- Pleural space/cavity - between layers
- Pleural lined by mesothelial cells
- Secrete small amount pleural fluid for lubrication

Pleural Disease

Jason Ryan, MD, MPH
Pleural Effusion
• Accumulation of fluid in pleural space

Image courtesy of James Heilman, MD

Pneumothorax
Treatment
• 100% Oxygen
  • Displaces nitrogen from capillary blood
  • ↑gradient for nitrogen reabsorption from pleural space
• Chest tube
  • Larger pneumothoraces (>15% lung volume)

Tension PTX
• Usually from trauma
• Air enters pleural space but cannot leave
• Medical emergency
• Emergent thoracentesis/chest tube placement
• Trachea deviates AWAY from affected side

Transudative Effusion
• Something driving fluid into pleural space
• Most commonly due to CHF (High pressure)
• Other causes:
  • Nephrotic syndrome (low protein)
  • Carcinosis (low albumin)
• Mostly fluid in effusion
• Very little protein in effusion
• Usually treat for underlying cause (no drainage)

Exudative Effusion
• Fluid leaking into pleural space
• High vascular permeability
• Many causes
• Malignancy
• Pneumonia
• More protein in pleural fluid vs. transudative
• Usually requires drainage
Mesothelioma

• Pleural tumor
• Asbestos is only known risk factor
• Decades after exposure
• Imaging: Pleural thickening and pleural effusion
• Slow onset symptoms (dyspnea, cough, chest pain)
• Poor prognosis
• Median survival 4 to 13 months untreated
• 6 to 18 months treated with chemo

Other Effusions

• Hemothorax
  • High Hct in fluid
• Empyema
  • Infected pleural fluid
  • Pus, putrid odor, positive culture
• Malignant effusion
  • Positive cytology

Transudate vs. Exudate

• Thoracentesis to obtain fluid sample
• Test for protein, LDH
• Light's Criteria – Exudate if:
  • Pleural protein/serum protein greater than 0.5
  • Pleural LDH/serum LDH greater than 0.6
  • Pleural LDH greater than 2/3 upper limits normal LDH

Lymphatic Effusions

“Chylothorax”

• Lymphatic fluid effusion
• From thoracic duct obstruction/injury
• Malignancy most common cause
• Trauma (usually surgical)
• Milky-appearing fluid
• Very high triglycerides
  • TG usually > 110 mg/dL

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Benign Pulmonary Nodules
• Granulomas (80% benign nodules)
• Hamartomas
• Lung tissue and cartilage (with scattered calcification)

Diagnosis
• Pulmonary nodule
• “Coin lesion”
• Compare with prior
• Biopsy for diagnosis

Common Cancers
• Breast
• Prostate
• Lung (most deadly)
• Colorectal

Symptoms
• Usually advanced at presentation
• Cough, dyspnea, rarely hemoptysis
• Usually leads to chest imaging

Lung Cancer Risk Factors
• Cigarette smoking
• Polycyclic Aromatic Hydrocarbons (PAHs)
• Radiation Therapy
• Hodgkin’s and breast cancer survivors
• Environmental toxins
  • Asbestos
  • Radon

Lung Cancer
Jason Ryan, MD, MPH

Lung Cancer
Common Cancers
Symptoms
Lung Cancer Risk Factors
Diagnosis
Benign Pulmonary Nodules

Image courtesy of Lange123
Lung Cancers

- Small cell (15%)
  - Fast growing; Early mets
  - Non amenable to surgical resection
  - Smokers
  - Treated with chemo
  - Poor prognosis
- Non-small cell (Most Common: 85%)
  - Can sometimes be resected
  - Better prognosis
  - Smokers and non-smokers

Small Cell Cancer

- Poorly differentiated small cells
- Classic in male smokers
- Neuroendocrine tumor
- Central tumor

Paraneoplastic Syndromes

- ACTH
  - Cushing syndrome
  - Progressive obesity
  - Hyperglycemia
- ADH
  - SIADH
  - Hyponatremia (confusion)
- Antibodies
  - Antibodies against pre-synaptic Ca channels in neurons
  - Block release of acetylcholine
  - Lambert-Eaton syndrome
  - Main symptom is weakness

Non-Small Cell Cancers

- Squamous Cell Carcinoma
- Adenocarcinoma
- Large cell carcinoma
- Bronchioloalveolar Carcinoma
- Carcinoid tumor

Squamous Cell Carcinoma

- Hilar mass arising from bronchus
- Key pathology
  - Keratin production (“pearls”) by tumor cells
  - Intercellular desmosomes (“intercellular bridges”)
- Male smokers
- Can produce PTHrP
  - Hypercalcemia
  - Stones, bones, groans, psychiatric overtones
  - Bone and abdominal pain, confusion

Granulomas

- Fungi
  - Histoplasmosis (patient from Midwest, Miss/Ohio river valley)
  - Coccidioidomycosis (southwest, California)
- Mycobacteria
  - Usually tuberculosis

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  - Lambert-Eaton syndrome
  - Main symptom is weakness

Non-Small Cell Cancers

- Squamous Cell Carcinoma
- Adenocarcinoma
- Large cell carcinoma
- Bronchioloalveolar Carcinoma
- Carcinoid tumor

Squamous Cell Carcinoma

- Hilar mass arising from bronchus
- Key pathology
  - Keratin production (“pearls”) by tumor cells
  - Intercellular desmosomes (“intercellular bridges”)
- Male smokers
- Can produce PTHrP
  - Hypercalcemia
  - Stones, bones, groans, psychiatric overtones
  - Bone and abdominal pain, confusion

Granulomas

- Fungi
  - Histoplasmosis (patient from Midwest, Miss/Ohio river valley)
  - Coccidioidomycosis (southwest, California)
- Mycobacteria
  - Usually tuberculosis

Small Cell Cancer

- Paraneoplastic Syndromes
  - ACTH
  - Cushing syndrome
  - Progressive obesity
  - Hyperglycemia
  - ADH
  - SIADH
  - Hyponatremia (confusion)
  - Antibodies
    - Antibodies against pre-synaptic Ca channels in neurons
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Lung Cancers

- Small cell (15%)
  - Fast growing; Early mets
  - Non amenable to surgical resection
  - Smokers
  - Treated with chemo
  - Poor prognosis
- Non-small cell (Most Common: 85%)
  - Can sometimes be resected
  - Better prognosis
  - Smokers and non-smokers

Small Cell Cancer

- Poorly differentiated small cells
- Classic in male smokers
- Neuroendocrine tumor
- Central tumor

Paraneoplastic Syndromes

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Adenocarcinoma

- Glandular tumor
- Most common lung cancer: nonsmokers/females
- Peripheral

Bronchioloalveolar Carcinoma

- Subtype of adenocarcinoma
- Many similar features to adeno:
  - Nonsmokers, Peripheral
  - Mucinous type: Derived from goblet cells
  - Nonmucinous: Clara cells or type II pneumocytes
- Looks like PNA on CXR
  - Lobular consolidation
- Excellent prognosis
  - Surgery, radiotherapy, sometimes adjuvant chemotherapy

Carcinoid tumor

- Neuroendocrine
- Well-differentiated cells
- Chromogranin positive
- Non-smokers
- Rarely causes carcinoid syndrome
- Secretion of serotonin
  - Flushing, diarrhea

Large Cell Carcinoma

- Poorly differentiated
- Lacks glandular or squamous differentiation
- Lacks small cells
- Smokers cancer
- Central or peripheral
- Poor prognosis

Complications

- Pleural effusions
  - Tap fluid, send for cytology
- Phrenic nerve compression
  - Diaphragm paralysis
  - Dyspnea
  - Hemidiaphragm elevated on CXR
  - Sniff test
- Recurrent laryngeal nerve compression
  - Hoarseness
- Bronchioloalveolar Carcinoma

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SVC Syndrome

- Obstruction of blood flow through SVC
  - Can be caused by compression from tumor
- Mediastinal Masses: Lymphoma
- Other causes in crude thrombosis
  - Indwelling catheters, pacemaker wires
- Facial swelling or head fullness
- Arm swelling
  - Can cause increased ICP
  - Headaches, confusion, coma
  - Cranial artery rupture
**Metastasis to Lung**
- More common than primary lung tumors
- Most commonly from breast or colon cancer
- Usually multiple lesions on imaging

**SVC Syndrome**
- Usually diagnosed CXR or CT Chest
- Various treatment options:
  - Anticoagulation for thrombus
  - Steroids (lymphoma)
  - Chemo/Radiation
  - Endovascular stenting

**Pancoast Tumor**
- Carcinoma at apex of lung
- Involve superior sulcus
  - Groove formed by subclavian vessels
  - Arm edema affected side
  - Shoulder pain radiating toward axilla/scapula
  - Arm paresthesias, weakness
  - Can compress sympathetic nerves
  - Horner’s syndrome
    - Miosis
    - Ptosis
    - Anhidrosis

**Metastasis from Lung Cancer**
- Adrenals
  - Usually found on imaging without symptoms
- Brain
  - Headache, neuro deficits, seizures
- Bone
  - Pathologic fractures
- Liver
  - Hepatomegaly, jaundice

**Image courtesy of Jmarchn**

**SVC Syndrome**
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**Image courtesy of Jmarchn**
Sleep Apnea

Central Sleep Apnea
- Patients with marginal ventilation when awake
  - Hypoventilate when awake
  - Fall asleep → apnea periods
  - Central nervous system disease (encephalitis)
  - Neuromuscular diseases (polio, ALS)
  - Severe kyphoscoliosis
  - Narcotics

Sleep Apnea Types
- Central sleep apnea
  - No effort to breathe
- Obstructive sleep apnea
  - Decreased air flow despite effort to breathe

Sleep Apnea Symptoms
- Unrestful sleep
- Daytime somnolence
- Loud snoring

Sleep Apnea
- Apnea = cessation of breathing
- Sleep apnea = cessation of breathing during sleep
- Usually >10 seconds
- Multiple episodes per night are typical

Sleep Apnea
• Central sleep apnea
• No effort to breathe
• Obstructive sleep apnea
• Decreased air flow despite effort to breathe

Central Sleep Apnea
• Cheyne-Stokes breathing
  - Cyclic breathing
  - Delayed detection/response to changes in PaCO₂
  - Common in heart failure and stroke patients
Obstructive Sleep Apnea

- Recurrent soft tissue collapse in the pharynx
- Strongest risk factor is obesity

Sleep Apnea Complications

- HTN
- Pulmonary HTN
- Arrhythmias
- Sudden death

Erythropoiesis

- Chronic hypoxia
- EPO release

Sleep Apnea Diagnosis

- Polysomnography
- “Sleep study”
- Patient sleeps in monitored setting
- EEG, eye movements
- O2 level, HR, respiratory rate
- Number of apnea episodes recorded

Sleep Apnea Treatments

- Weight loss
- Takes time; not best option for exhausted patients
- CPAP
  - First line for symptomatic patients
  - Upper airway surgery
  - Severe disease

CPAP

- Nasal Insert
- Full Face Mask
- Nasal Mask

Image courtesy of Aslam Calicut
Cystic Fibrosis

CF Pathophysiology

- Thick mucous in lungs
  - Recurrent pulmonary infections (Pseudomonas, S. Aureus)
  - Chronic bronchitis
  - Bronchiectasis
- Thick mucous in GI tract
  - Impaired flow of bile and pancreatic secretions
  - Malabsorption especially fats
  - Loss of fat soluble vitamins (A, D, E, K)
  - Steatorrhea

CFTR

- ATP ion transporter
- Epithelial Cell Functions
  - Pumps Cl⁻ out of epithelial cells
  - Against concentration gradient (uses ATP)
  - Creates a membrane potential that draws out Na⁺/H₂O
  - Hydrates mucosal surfaces (lungs, GI tract)
- Sweat gland functions
  - Removes NaCl from sweat (makes sweat hypotonic)
  - CF patients have high NaCl in sweat

CFTR Mutations

- Many mutations identified
- Most common mutation: delta F508
  - Deletion of 3 DNA bases
  - Codes for 508th AA acid: phenylalanine
- Most common consequence: abnormal processing
  - Abnormal protein folding
  - Prevents protein trafficking to correct cellular location

CFTR

- Cystic Fibrosis Transmembrane Regulator
- CFTR protein is abnormal in CF
- CFTR gene encodes for the abnormal protein

Cystic Fibrosis

- Inherited genetic disease
- Autosomal recessive pattern
- Both parents must be carriers
- Results in thick, sticky mucus in lungs/GI tract
- Common cause chronic lung disease in children

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Cystic Fibrosis

Jason Ryan, MD, MPH
CF Presentation
- Usually diagnosed <2yo
- Respiratory disease (45%)
- Failure to thrive (28%)
- Meconium ileus (20%)

CF Lung Disease
- Productive cough
- Hyperinflation of lungs on CXR
- Obstructive pattern
- Later disease
  - Chronic bronchitis
  - Bronchiectasis
  - Acute exacerbations
  - Pseudomonas aeruginosa: major pathogen in CF

Pancreatic insufficiency
- Chronic pancreatitis
- CF-related diabetes
- Fat malabsorption
- Steatorrhea:
  - Frequent stools
  - Foul-smelling stools
  - Oily or greasy
  - Stools may float

Pancreatic insufficiency
- Deficiencies of fat-soluble vitamins: A, D, E, and K
- Vitamin K: coagulopathy
- Vitamin D: rickets
- Vitamin A: Night blindness
- Vitamin E: Ataxia, hemolysis

Meconium ileus
- Meconium
  - Meconium: first stool of newborn
  - Very thick and sticky
  - Meconium ileus = bowel obstruction
  - Meconium too thick/sticky
  - Meconium plug forms
  - Abdominal distension
  - Vomiting
  - Air fluid levels of X-ray
  - Failure to pass meconium

Other symptoms
- Biliary disease
  - Bile duct obstruction
  - Pale or clay-colored stool
  - Elevation of LFTs
  - Hepatomegaly
  - Cirrhosis
  - Gallstones
Other symptoms

- Infertility
  - 95 percent males with CF are infertile
  - Absent vas deferens
  - Problem is sperm transport not spermatogenesis
  - Can have children with assisted techniques

Diagnosis

- Sweat chloride test
- Pilocarpine iontophoresis
- Pilocarpine gauze placed on skin
- Electrode placed over gauze
- Small electrical current drives pilocarpine into skin
- Sweating occurs
- Sweat collected on filter paper
- Chloride content analyzed
- High chloride level suggests CF
- DNA testing done if sweat test abnormal

Treatment

- Promote clearance of airway secretions
  - Inhaled DNase (dornase alfa)
  - Inhaled saline
  - N-acetylcysteine
  - Ivacaftor (tablets)
    - Increased chloride ion flux
    - Only for patients with G551D mutation
  - Exacerbations are treated with antibiotics
  - Lung transplantation

Other Treatments

- Pancreatic enzyme replacement
- Vitamins (A, D, E, K)
- Vaccinations
Prognosis

- Average life span ~ 37 years
- Death from lung complications

Screening

- Prenatal
  - Test for 23 most common CF mutations in US
  - Often test mother first and stop if negative
- Newborn
  - ↑ blood levels immunoreactive trypsinogen (IRT)
  - Blood test → if positive → sweat test


**Virulence Factors**
- Trehalose dimycolate ("cord factor")
- Helps evade immune response
- Causes granuloma formation
- Triggers cytokine release
- Sulfatides
  - Glycolipids
  - Inhibits fusion of phagosomes/lysosomes
- Catalase-peroxidase
  - Resists host cell oxidation

**Acid Fast**
- Cell walls impermeable to many dyes
- Stain with very concentrated dyes plus heat
  - Lipid soluble; contain phenols
  - Once stained, plate rinsed with acid decolorizer
    - "Acid fast stain"
  - TB resists decolorization with acid solvents
  - Some other bacteria (Nocardia) also do this

**Culture of TB**
- Difficult to culture
  - Special media used
  - Lowenstein-Jensen agar
  - Slow growing
  - Does not stain well with Gram stain
  - This is due to mycolic acids in cell wall
  - Also fatty acids and complex lipids

**Mycobacterium tuberculosis**
- Obligate aerobes
- Prefer lungs
- Reactivation disease prefers upper lobes
- Facultative intracellular pathogens
  - Infect macrophages

**Tuberculosis**
- Ancient disease: Found in mummies!
- Old name: Consumption
  - Tubercle = round nodule
  - Tuberculosis = multiple round nodules

**Tuberculosis**
Jason Ryan, MD, MPH
Granulomas
- Granulomatous inflammation
- Caseating necrosis
- Macrophages transform to:
  - Epithelioid cells
  - Langhans giant cells
  - Fibroblasts activated → collagen
- T-cell mediated delayed type hypersensitivity reaction
- Type IV hypersensitivity reaction

Primary TB
Pathophysiology
- Two to four weeks
  - Cell-mediated immune system controls TB
  - TH1 response
  - Activation of CD4+ T cells
  - Interferon-γ secreted
  - Activated macrophages and cytotoxic T lymphocytes

Primary TB
Clinical Picture
- Mainly a disease of childhood or chemo patients
  - Ineffective immune response
  - Gradual onset: weeks
  - Fever
  - Cough
  - Pleuritic chest pain
  - Fatigue, arthralgias

Primary TB
Pathophysiology
- First week
  - TB infects macrophages
  - Phagocytosed
  - Intracellular bacterial proliferation

Exposure to TB
- Most patients will not develop active disease
  - Infection can clear or remain "latent"
  - Small proportion patients develop active disease

Spread of TB
- Spreads through the air
- Active TB patient's cough, sneeze, etc.
- Inhaled by uninfected person
- Can spread rapidly in crowded areas

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Pathophysiology
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- T-cell mediated delayed type hypersensitivity reaction
- Type IV hypersensitivity reaction
**Hilar Lymphadenopathy**
- CXR often normal
- Classic finding is hilar lymphadenopathy
- Occurs as early as 1 week after infection
- Resolve slowly over months to years

**Ghon Foci**
- Ghon foci form
  - Granulomas
  - Subpleural
  - Mid to lower lungs
  - Ghon foci plus lymph node is Ghon complex
  - Calcified Ghon complex is a Ranke complex

**Primary TB Resolution**
- Most (90%) patients control infection
  - Disease heals leaving fibrosis
  - Sometimes completely clear
  - Usually enters latent phase ("walled off")
  - Immunity develops
  - PPD positive
- Rare (10%) patients have expanded illness
  - Miliary dissemination
  - More common with HIV, CKD, DM (impaired immunity)

**Miliary TB**
- Hematogenous spread of TB
- Progressive primary infection or reactivation
  - Nearly any organ system can be involved
  - Bones
  - Liver
  - CNS (meningitis)
  - Heart (pericarditis)
  - Skin

**Miliary TB**
- Pott's disease
  - Spine infection (osteomyelitis)
  - Back pain, fever, night sweats, weight loss
  - Constrictive pericarditis

**Reactivation TB**
- Reactivation of dormant TB
  - Cough, weight loss, fatigue
  - Fever
  - Night sweats
  - Chest pain
  - Often cavitation (caseous and liquefactive necrosis)
  - Hemoptysis (erode pulmonary vasculature)
  - CXR classically shows upper lobe lesions
Diagnosis of Latent TB
• Identification of latent TB crucial to infection control
• Diagnosis: Tuberculin skin testing (TST)
  • Skin injection purified protein derivative (PPD)
  • 5 tuberculin units (0.1 mL)
  • Wait 48 hours
  • Measure diameter of induration (not erythema)

Diagnosis of Active TB
• Not necessary to hospitalize just for TB suspicion
• Outpatients: Remain at home, avoid visitors, mask
• Inpatients: Respiratory isolation
  • Private room
  • Negative air pressure
  • Persons entering must wear a respirator
  • Tight seal over the nose and mouth

Reactivation TB
• Can occur when immune compromise develops
• HIV infection
• TNF-α inhibitors
  • Used in autoimmune diseases
  • Etanercept, Infliximab
• Diabetes

Aspergilloma
• Fungus ball
  • Caused by Aspergillus fumigatus
  • Non-invasive form of aspergillosis
  • Grows in pre-formed cavities
  • Pulmonary TB is most common association
  • Often asymptomatic
  • Can cause hemoptysis
  • Diagnosis: Imaging plus sputum culture
  • Treatment: Observation vs. surgery

TB Infection Summary
Exposure
Infection
Clears
Infection
Contained
"Latent"
Primary
TB
Reactivation
TB
Miliary
TB

Diagnosis of Active TB
• Usual method: 3 sputum samples
  • Usually about 8hrs apart
  • Spontaneous or induced
  • Induced: Inhalation of aerosolized saline by nebulizer
• Acid-fast smear and culture

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Aspergillus
ABPA
Invasive Aspergillus
Aspergilloma

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**PPD Testing**

<table>
<thead>
<tr>
<th>Induration</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5mm</td>
<td>Negative</td>
</tr>
<tr>
<td>&gt;5mm</td>
<td>Positive, if HIV, Immunosuppressed</td>
</tr>
<tr>
<td>&gt;10mm</td>
<td>High-risk individual*</td>
</tr>
<tr>
<td>&gt;15mm</td>
<td>Healthy patient &gt;5yo with low likelihood of TB</td>
</tr>
</tbody>
</table>

* Silicosis, CKD, DM, IV drug users, homeless, prison employees, others

**BCG Vaccine**

- Bacille Calmette-Guérin
- Live strain of *Mycobacterium bovis*
- More effective in patients with no TB exposure
  - About 80% effective in children
  - Less effective in adults
- Used in children in areas with high prevalence of TB
- Creates false positive PPD

**Treatment of Active TB**

- Requires multi-drug regimens
- Typical regimen:
  - Isoniazid
  - Rifampin
  - Pyrazinamide
  - Ethambutol
  - Sometimes streptomycin
  - Sometimes direct observation therapy (DOT)
  - Risk of Multi-drug resistant (MDR) TB

**Isoniazid**

- Blocks synthesis of mycolic acids
- Bacteria lose their acid fastness
- katG-encoded catalase-peroxidase
- Converts INH to active form
- Mutations lead to INH resistance
- Monotherapy produces resistance

**Treatment of Positive PPD**

- Most patients with latent TB will not develop disease
- Small proportion may reactivate
- Prophylaxis lowers risk
  - Isoniazid (INH) for 9 months
  - Further PPD testing not indicated
  - Will remain positive for life

**PPD Testing**

- False negatives can occur
- Immunosuppressive drugs
  - Corticosteroids
  - TNF-α inhibitors
- Immunocompromised
  - HIV
  - CKD
  - Malignant disease
  - Disseminated lymph system
  - Sarcoidosis
  - Some lymphomas or leukemias

**PPD Testing**

- Silicosis, CKD, DM, IV drug users, homeless, prison employees, others
**Isoniazid**
- Neurotoxic
  - Neuropathy, ataxia, and paresthesia
  - Competes with B6 as co-factor neurotransmitter synthesis
  - Pyridoxine (B6) co-administered
  - Limits neurotoxicity
- Hepatotoxic (check LFTs)
  - Probably related to metabolites of INH
- Drug-induced lupus

**Rifampin**
- Inhibit bacterial DNA-dependent RNA polymerase
- Blocks RNA synthesis
- Main side effects are liver, GI
  - Increased LFTs
  - GI upset: nausea, cramps, diarrhea
- Red/orange discoloration fluids (not dangerous)
  - Urine
  - Saliva
  - Sweat, tears
  - CSF

**Pyrazinamide**
- Mechanism unknown
- Converted to pyrazinoic acid (PZA)
- May be more active in acidic environment inside macrophages
- Hepatotoxic
  - Can raise LFTs
- Competes with uric acid for excretion in kidneys
  - Can raise uric acid levels
  - Hyperuricemia
  - Gout exacerbations

**Ethambutol**
- Inhibits arabinosyl transferase
- Polymerizes arabinose for mycobacteria cell walls
- Key side effect: optic neuropathy
  - Red-green color blindness
  - Difficulty discriminating red and green hues
  - Loss of visual acuity
  - Reversible

**Streptomycin**
- Older, aminoglycoside drug
- Inhibits bacterial 30S ribosomal subunit
  - Prevents protein synthesis
- Lots of resistance
  - Mutations of genes for ribosomal proteins

**Rifampin**
- Other uses
  - Leprosy
  - Meningococcal prophylaxis
  - Chemoprophylaxis in contacts of children HiB

**Pyrazinamide**
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Tuberculosis Key Points

• Mycolic acid cell walls → acid fast
• Infects macrophages (intracellular)
• Delayed type hypersensitivity reaction
• Hilary lymphadenopathy: Ghon complex
• Reactivation in upper lobes (immunosuppressed)
• Latent infection diagnosed with PPD
• Treat latent disease with INH
• Treat active disease with multidrug regimen
Sarcoidosis

Jason Ryan, MD, MPH

**Pathology**
- Cell mediated immune process
- Accumulation of TH1 CD4+ helper T cells
- High CD4:CD8 ratio
- Secrete IL-2 and interferon-γ
- IL-2 stimulates TH1 proliferation
- IFN-γ activates macrophages
- Ultimately leads to granuloma formation
- Key players: CD4 T cells, IL-2, IFN-γ

**Organ Involvement**
- Lungs (most common)
- Skin
- Eye
- Heart
  - Conduction disease (heart block)
  - Cardiomyopathy
- Many other systems rarely involved
  - Renal: Renal failure
  - CNS: Neurosarcoid, Bell’s Palsy, Motor loss
- Any system can be involved

**Lung Involvement**
- Classic finding is hilar lymphadenopathy
- Classic symptom is cough, dyspnea
- Can cause infiltrates
- Can cause pulmonary fibrosis

**Sarcoidosis**
- Hallmark is widespread non-caseating granulomas
- Tightly packed central area of macrophages, epithelioid cells, multinucleated giant cells
- Surrounded by lymphocytes, monocytes, mast cells, fibroblasts

**Sarcoidosis**
- Granulomatous disease
- Granulomas form many places in the body
- Immune-mediated
  - Immune cells play major role
  - Unknown cause

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Skin Involvement

- Many lesions possible
  - Plaques, maculopapules, subcutaneous nodules
  - Classic lesion is erythema nodosum
  - Inflammation of fat cells under skin
  - Tender red nodules
  - Usually on both shins

Eye Involvement: Uveitis

- Can involve many parts of eye
- Classic is uveitis
- Uvea:
  - Iris, ciliary body, choroid
- Uveitis Types
  - Anterior (iris, ciliary)
  - Posterior (choroid)
- Often mild symptoms
  - Dry eye, blurry vision
  - Often detected on routine exam

Other Sarcoidosis Features

- Hypercalcemia
  - Elevated 1-α hydroxylase activity in alveolar macrophages
  - Increased vitamin D levels (calcitriol)
- High ACE levels
  - Non-specific finding
  - Elevated in many lung diseases

Skin Involvement

- Many lesions possible
  - Plaques, maculopapules, subcutaneous nodules
  - Classic lesion is erythema nodosum
  - Inflammation of fat cells under skin
  - Tender red nodules
  - Usually on both shins

Eye Involvement: Uveitis

- Can involve many parts of eye
- Classic is uveitis
- Uvea:
  - Iris, ciliary body, choroid
- Uveitis Types
  - Anterior (iris, ciliary)
  - Posterior (choroid)
- Often mild symptoms
  - Dry eye, blurry vision
  - Often detected on routine exam

Other Sarcoidosis Features

- Hypercalcemia
  - Elevated 1-α hydroxylase activity in alveolar macrophages
  - Increased vitamin D levels (calcitriol)
- High ACE levels
  - Non-specific finding
  - Elevated in many lung diseases

Classical Presentation

- Hilary lymphadenopathy
- Cough, dyspnea
- Often asymptomatic, detected on routine chest x-ray

Treatment

- Steroids
- Other immunosuppressants
  - Methotrexate
  - Azathioprine
  - Mycophenolate
Pulmonary Embolism

- Chest pain
- Classic presentation is pleuritic

- Respiratory distress
  - Dypnea
  - Hypoxemia
  - Tachypnea

- Massive PE can cause sudden death
  - Obstruction to flow through pulmonary arteries
- Small, chronic emboli: pulmonary hypertension

- Can be “unprovoked”
- Often secondary to a hypercoagulable state
  - Secondary: Malignancy, surgery, etc.
  - Primary: Protein C/S deficiency, ATIII deficiency, etc.

Thrombus in pulmonary artery
- Rarely formed in heart or pulmonary vasculature
- Majority come from femoral vein or deep leg veins
- Travels to lung via IVC → RA → RV

CT Angiogram
Deep Vein Thrombosis

- Often asymptomatic until PE
- Calf pain
- Palpable cord (thrombosed vein)
- Unilateral edema
- Warmth, tenderness, erythema
- Homan’s sign: calf pain with dorsiflexion of foot
- Diagnosis: Lower extremity ultrasound

Pulmonary Embolism

- Ventilation-Perfusion
  - Dead space
  - Ventilation without perfusion
  - V/Q mismatch
  - Hyperventilation
  - Blood gas findings variable
  - Classic findings: low PaO₂ and low PCO₂

Deep Vein Thrombosis

- Similar treatment to PE
  - "DVT/PE"
  - "Venous thromboembolism" (VTE)
  - Prevention important in hospitalized patients
  - Hypercoagulable
  - Immobility, stasis of blood, inflammation
  - Prophylaxis: SQ heparin, LMWH

IVC Filter

- Used in high-risk DVT patients
- Placed to prevent pulmonary embolism

Deep Vein Thrombosis

- Thrombus within a deep vein
- Usually occurs in calf or thigh
- Commonly femoral/popliteal veins
- Can extend or “grow”
- Precedes pulmonary embolism
- Often 2° hypercoagulable state

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Patent Foramen Ovale

- Found in ~25% adults
- Failure of foramen ovale to close after birth
- Can allow venous clot to reach arterial system (brain)
- Rarely causes stroke in patients with DVT/PE

Treatment DVT/PE

- Initial treatment with heparin or LMWH
- Transition to warfarin (oral)
- Massive PE: thrombolysis (tPA)

Pulmonary Embolism

Diagnosis

- CT angiogram
- VQ Scan – used in patients with elevated creatinine

Wells Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
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Score >=3 High Probability
1-2 Mod Probability
0 Low Probability

D-dimer

- Degradation product of fibrin
- Sensitive but not specific (unidirectional)
- Levels elevated in DVT/PE
- Levels also elevated in many, many other conditions
- Useful when normal in setting of low-mod Wells score

Pulmonary Embolism

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S1Q3T3

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Amniotic Fluid Embolism

- During labor or shortly after
- Amniotic fluid, fetal cells, fetal debris enter maternal circulation
- Inflammatory reaction
- Often fatal

Wikipedia/Public Domain

Fat Embolism

- Often occurs after a long bone fracture
- Fat may cross lungs → small artery infarctions
- Fat embolism syndrome: pulmonary, neuro, skin

Wikipedia/Public Domain

Amniotic Fluid Embolism

- Phase II (hemorrhagic phase)
  - Massive hemorrhage
  - DIC
  - Key feature: bleeding
  - Seizures also often occur

Wikipedia/Public Domain

Fat Embolism

- Lung
  - Dyspnea, hypoxemia
  - Diffuse capillary leak (ARDS)
  - Often requires mechanical ventilation
- Neurological
  - Usually confusion
  - May develop focal deficits
  - Petechiae

James Heilman, MD/Wikipedia

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Hellerhoff/Wikipedia
Chest X-rays

Jason Ryan, MD, MPH

Chest X-ray

- Difficult to see different structures
- Many, many normal variants
- Many, many pathologic findings
- Reasonable goals:
  - Basic chest anatomy
  - Classic examples of pathology

Chest Anatomy

Pulmonary Edema

Pulmonary Edema

Normal, Kerley B

Pleural Effusion

Image courtesy of James Heilman, MD
Pneumothorax

Lobar Pneumonia

Interstitial Fibrosis

Hilar Lymphadenopathy

Pulmonary Nodule