Boards & Beyond: Pulmonary Slides

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

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2021 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

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)

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

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

Pulmonary Embryology
Jason Ryan, MD, MPH

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

**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
- Airway lumens become larger
- **Type II pneumocytes** form
- Produce surfactant
- Lower surface tension
- Keep alveoli open
**Pulmonary Hypoplasia**
- Oligohydramnios (Potter's sequence)
- Congenital diaphragmatic hernia
- Defective formation 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

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

**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

**Alveolarization**
- Airspaces subdivided
- New walls formed (septa)

**Pulmonary Hypoplasia**
- Oligohydramnios (Potter’s sequence)
- Congenital diaphragmatic hernia
  - Defective formation 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: PaO₂ 30mmHg; O₂sat=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

- Do not communicate with lungs
- Lined by respiratory epithelium
  - Columnar, ciliated
- Walls contain cartilage (diagnostic criteria)
- Often asymptomatic
- May lead to pneumonia, compression of airway

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 (β-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
**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 = \(2 \times \frac{\text{surface tension}}{\text{radius}}\)

**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
Law of Laplace

- Lungs contain many small alveoli
- Small radius = high distending pressure
- Need low surface tension to remain open
- Surfactant reduces surface tension
- Increases lung compliance (less stiff, more floppy)

\[
\text{Collapsing Pressure} = 2 \times \frac{\text{surface tension}}{\text{radius}}
\]

Fetal Lung Maturity

- Lungs "mature" when adequate surfactant present
- Occurs around 35 weeks
- Lecithin-sphingomyelin ratio (L/S ratio)
  - Both produced equally until ~35 weeks
  - Ratio > 2.0 in amniotic fluid suggests lungs mature

Neonatal RDS

- **Surfactant deficiency**
  - High surface tension
  - Atelectasis
  - Decreased lung compliance
  - Hypoxemia/↑ pCO2 (poor ventilation)
  - Poorly responsive to O2
    - Lungs collapsed (alveoli)
    - Intrapulmonary shunting

Neonatal RDS

- **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

- **Complications**
  - Bronchopulmonary dysplasia
    - Oxygen toxicity
    - Atelectasis does not progress normally
  - Respiratory problems during infancy
  - Patent ductus arteriosus
    - Hypoxia keeps shunt open
  - Retinopathy of prematurity
    - Oxygen → free radical formation
    - Neovascularization in the retina
    - Retinal detachment → blindness
Neonatal RDS
Prevention and Treatment

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

Wikipedia/Public Domain

Right Upper Lobe

Right Middle Lobe

Right Lower Lobe

Left Upper Lobe
Mediastinal Compartments

Mediastinal Structures

- 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**
  - 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”)

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

- **Diaphragm irritation** → "referred" shoulder pain
- **Classic example**: gallbladder disease
- **Also** lower lung masses
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- **Exhalation** is passive with normal (“quiet”) breathing

- **Public Domain**

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**Anterior Mediastinal Masses**

**Terrible Ts**

- **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

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<th>Compartments</th>
<th>Major Structures</th>
<th>Masses</th>
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- **Caval opening**
  - T8
  - Inferior vena cava
- **Esophageal hiatus**
  - T10
  - Esophagus, Vagus nerve
- **Aortic hiatus**
  - T12
  - Aorta, thoracic duct, azygous vein

**Mediastinal Structures**

**Compartment** | **Major Structures** | **Masses** |
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**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
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- Can see on fluoroscopy (“sniff test”)

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

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

- Total lung capacity = sum of all volumes
- RV + ERV + IRV + TV
- Inspiratory capacity
  - Most air you can inspire
  - TV + IRV
- Vital capacity
  - Most you can exhale
  - TV + IRV + ERV

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
Transpulmonary Pressure
- Alveolar Pressure – Intrapleural Pressure

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

Transpulmonary Pressure
- Alveolar Pressure – Intrapleural Pressure

Pressures and Air Flow
- \( \Delta = 0 \) No Flow
- \( P_{\text{atm}} = 0 \text{mmHg} \)
- \( P_A = 0 \text{mmHg} \)

Pneumothorax
- Normal
  - TPP = 5 – 5 = 0
- Pneumothorax
  - Lung collapses
  - TPP = 0 – (-5) = +5

Transpulmonary Pressure
- Alveolar Pressure – Intrapleural Pressure

Pneumothorax
- Normal
  - TPP = 5 – 5 = 0
- Pneumothorax
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Transpulmonary Pressure
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Transpulmonary Pressure
- Alveolar Pressure – Intrapleural Pressure

Transpulmonary Pressure
- Alveolar Pressure – Intrapleural Pressure
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

Patm = 0 mmHg

PA = -5 mmHg

Δ = +5 Flow In

Patm = 0 mmHg

PA = +5 mmHg

Δ = +5 Flow Out

Pressures and Air Flow

Patm = 0 mmHg

Δ = +5 Flow Out

Patm = 0 mmHg

Δ = +5 Flow In

Patm = 0 mmHg

Inhalation

Resting State

Inhalation

Resting State

Inhalation

Resting State

Inhalation

Resting State

Inhalation

Resting State

Inhalation

Resting State
Alveoli and Pleural Pressures

- Quiet (tidal) breathing

- Inhale
  - Alveolar Pressure (cm H2O): +5
  - Intrapleural Pressure (cm H2O): -5
  - FRC: 0.5 liters

- Exhale
  - Alveolar Pressure (cm H2O): +5
  - Intrapleural Pressure (cm H2O): -5
  - FRC: 0.5 liters

Lung Volumes and Pressures

- Volume
  - Airway Pressure

Chest Volumes and Pressures
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 of diaphragm effort
    - Big pressure change across lungs
    - Small volume change (lungs stiff)
    - Hard to move air in/out

C = \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

Chest Volumes and Pressures
- Volume
  - Chest Wall
  - Lungs

System
- FRC

Airway Pressure
- - 0 + +
Barrel Chest
- Seen in patients with **emphysema**
- Increased lung compliance
- Increased FRC → larger volumes in chest

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

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

Barrel Chest
- Seen in patients with ** emphysema**
- Increased lung compliance
- Increased FRC → larger volumes in chest

Zones
- Cartilage/Goblet Cells
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Forced Exhalation
- Pleural pressure becomes **positive**
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Barrel Chest
- Seen in patients with **emphysema**
- Increased lung compliance
- Increased FRC → larger volumes in chest
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

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
### Hemoglobin

#### Oxygen Transport
- **Dissolved O$_2$**
  - Determined by Henry’s law
  - $\text{PaO}_2 \times \text{solubility} = \text{dissolved O}_2$
  - Very small amount (2%) total blood O$_2$
- **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

#### O$_2$-Hgb Dissociation Curves
- **Y axis:** percentage of hemoglobin bound to oxygen
- **X-axis:** partial pressure of oxygen ($\text{PaO}_2$)

#### Oxygen-Hgb Binding
- Four heme groups do not simultaneous oxygenate
- First O$_2$ molecule INCREASES affinity for 2nd molecule
- Second O$_2$ molecule INCREASES affinity for 3rd molecule
- Third O$_2$ molecule INCREASES affinity for 4th molecule
- Affinity last O$_2$ = 300 times affinity for first O$_2$
- **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
- \( O_2 \) cooperativity is a positive allosteric effect

Hemoglobin Forms

- Globin chains can assume two formations
  - Taut form (T)
    - Tends to release \( O_2 \)
    - Favored form in tissues
    - Allows more release of \( O_2 \)
  - Relaxed form (R)
    - Holds on to \( O_2 \)
    - Favored form in lungs
    - Allows more binding of \( O_2 \)

Shifts in \( O_2 \)-Hgb Curves

- Affinity of Hgb for \( O_2 \) 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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<th></th>
<th>Lungs PaO2</th>
<th>Lungs %Sat</th>
<th>Tissues PaO2</th>
<th>Tissues %Sat</th>
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<td>Normal</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>75%</td>
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<tr>
<td>Right Shift</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>50%</td>
</tr>
</tbody>
</table>

Normal: 100% \( \rightarrow \) 75% \( \Delta 25\% \)
Right shift: 100% \( \rightarrow \) 50% \( \Delta 50\% \)
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

2,3-Bisphosphoglycerate

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

High Altitude

- ↑ BPG with chronic hypoxia
  - COPD
  - High altitude
  - Chronic anemia
**Carbon Monoxide**

- Binds to iron in heme 240x the affinity of O₂
- Forms carboxyhemoglobin (HbCO)
- Blocks O₂ binding sites (less O₂ can be absorbed)
- "Functional anemia"
- Other binding sites cannot offload O₂
- Allosteric modification of hemoglobin
- Shifts dissociation curve left

\[
\text{HbCO} = \text{Hb + CO}
\]

**Fetal Hemoglobin**

HgbF(α₂γ₂)

- After 8 weeks HgbF is predominant Hgb
  - Up to 90% fetal hemoglobin
  - Levels fall in weeks/months after birth
  - In adult HgbF <1% total hemoglobin
- Higher O₂ affinity than HgbA
  - Necessary because fetal pO₂ = 40 mmHg

**Myoglobin**

- Found in skeletal muscle and heart
- Single peptide chain
- Binds one molecule of O₂

**2,3-Bisphosphoglycerate**

- Left shift caused by altered 2,3 BPG binding
- 2,3 BPG binds γ chains poorly (binds β chains avidly)
- Less 2,3-BPG binding → O₂ affinity increases (left shift)

**Fetal Hemoglobin**

HgbF(α₂γ₂)

- After 8 weeks HgbF is predominant Hgb
- Up to 90% fetal hemoglobin
- Levels fall in weeks/months after birth
- In adult HgbF <1% total hemoglobin
- Higher O₂ affinity than HgbA
- Necessary because fetal pO₂ = 40 mmHg

**Myoglobin**

- Found in skeletal muscle and heart
- Single peptide chain
- Binds one molecule of O₂
- Higher O₂ affinity at all pressures

**Hemoglobin**

Higher O₂ affinity

**Fetal Hemoglobin**

HgbF(α₂γ₂)

- Left shift caused by altered 2,3 BPG binding
- 2,3 BPG binds γ chains poorly (binds β chains avidly)
- Less 2,3-BPG binding → O₂ affinity increases (left shift)

**2,3-Bisphosphoglycerate**

- Left shift
- Higher O₂ affinity
Clinical Scenario
- Endoscopy patient
- Benzocaine spray used for throat analgesia
- Post procedure shortness of breath
- “Chocolate brown blood”
- $O_2$ sat (pulse oximetry) = variable (80s-90s)
- Oxygen does not improve shortness of breath
- $P_{aO_2}$ (blood gas) = normal
- Diagnosis: ↑ methemoglobin level
- Other example:
  - Premature babies given NO for pulmonary vasodilation

Methemoglobinemia
- Most iron in hemoglobin normally reduced ($Fe^{2+}$)
- Small amount oxidizes iron: $Fe^{3+}$
  - Called methemoglobin
  - Cannot bind $O_2$
  - Excess methemoglobin: hypoxia

Fe$^{3+}$

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)

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

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)

Methemoglobinemia
- Acquired methemoglobinemia from drugs
  - Local anesthetics (benzocaine)
  - Nitric oxide
  - Dapsone
- Treatment: methylene blue
  - Reducing agent
    - $Fe^{3+} \rightarrow Fe^{2+}$
**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

**Blood Oxygen Content**

- **Systemic circulation**
  - ↓ O₂ level (PaO₂) leads to vasodilation (↑blood flow)
- **Pulmonary circulation**
  - ↓ O₂ level (PaO₂) leads to vasocstriction (↓blood flow)
  - "Hypoxic vasocstriction"
  - 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

**Pulmonary Circulation**

- **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)
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
- Hypoxemia

Gas Exchange: Carbon Dioxide
- Healthy Lung
- Fibrosis
- Diffusion limited

Low DLCO Disorders

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

Area = \( \frac{D \times (P1 - P2)}{\text{Thickness}} \)
Pulmonary Hypertension

- 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

- 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

- Gold standard diagnosis: right heart catheterization
- Non-invasive diagnosis by echocardiography
  - Estimate PA pressure
  - Visualize right heart structures

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

- Medial Hypertrophy
- Normal
**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)
    - Potent vasodilator
  - Bosentan:
    - Antagonist endothelin-1 receptors (PO)
  - Sildenafil:
    - Inhibits PDE-5 in smooth muscle of lungs (PO)

**BMPR2 gene mutations**
- Bone morphogenetic 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

**BMPR2 gene mutations**
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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 many diseases

Measuring Dead Space

- Bohr's method
- Physiologic dead space ($V_d$) from:
  - Tidal volume ($V_t$)
  - $P_{eCO2}$ (exhaled air)
  - $P_{aCO2}$ (blood gas)

$$V_d = \frac{P_{aCO2} - P_{eCO2}}{V_t}$$

Nomenclature

- $P_A$ = alveolar pressure
- $P_{aCO2}$ = arterial $CO_2$
- $P_a$ = arterial pressure
- $P_{aO2}$ = arterial $O_2$
- $P_v$ = venous pressure
- $P_{eCO2}$ = expired pressure

Ventilation & Perfusion

Jason Ryan, MD, MPH

Pixabay/Public Domain
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

Bohr Equation

\[
\frac{V_d}{V_t} = \frac{P_{a}CO_2 - P_{CO_2}}{P_{CO_2}}
\]

Zero Dead Space

\[
\frac{V_d}{V_t} = \frac{P_{a}CO_2 - P_{CO_2}}{P_{CO_2}}
\]

0 = \frac{P_{a}CO_2 - P_{CO_2}}{P_{CO_2}}

0 = P_{a}CO_2 - P_{CO_2}

\[P_{a}CO_2 = P_{CO_2}\]

↓ dead space \(P_{a}CO_2\) approaches \(P_{CO_2}\)
More gas exchange
Less retained CO2

100% Dead Space

\[
\frac{V_d}{V_t} = \frac{P_{a}CO_2 - P_{CO_2}}{P_{CO_2}}
\]

1 = \frac{P_{a}CO_2 - P_{CO_2}}{P_{CO_2}}

\[P_{a}CO_2 = P_{CO_2} - P_{CO_2}\]

\[P_{CO_2} = 0\]

↑ dead space \(P_{a}CO_2\) approaches zero
Less gas exchange
More retained CO2

Dead Space

Main problem: ↑ CO2
Hypercapnia
Response: ↑ RR

02 = 100%

Flow
Obstructions

02 = 70%

100%

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
**Elevated Carbon Dioxide**

- Hypercapnia
- Hypercarbia
- Causes acidosis
- Physiologic response: ↑ respiratory rate
  - Increased alveolar ventilation

**Alveolar Ventilation Equation**

Predicts Alveolar CO2

- \( V_a \) = alveolar ventilation
- \( V_{CO2} \) = rate of CO2 production
- \( P_{ACO2} \) = alveolar PCO2
- \( V_t \) = total ventilation
- \( V_{ds} \) = dead space ventilation
- \( K \) = constant

\[
P_{ACO2} = \frac{V_{CO2} \cdot K}{V_t}
\]

**Three Major Causes of ↑ CO₂**

↑ CO₂ production
↑ \( V_a \) (hypoventilation)
↑ \( V_{ds} \) (dead space)

**Alveolar Gas Equation**

Predicts Alveolar O2

- \( P_{AO2} \) = alveolar O2
- \( P_{IO2} \) = inspired O2
- \( PACO2 \) = alveolar CO2
- \( R \) = respiratory exchange ratio
  - \( \frac{CO_2 \text{ production}}{O_2 \text{ consumption}} \)
  - Varies with diet, metabolic state

\[
P_{AO2} = P_{IO2} - \frac{P_{ACO2} \cdot K}{V_t - V_{ds}}
\]

**Alveolar Ventilation Equation**

Predicts Alveolar O2

- \( VA \) = alveolar ventilation
- \( VCO2 \) = rate of CO2 production
- \( PACO2 \) = alveolar PCO2
- \( Vt \) = total ventilation
- \( Vds \) = dead space ventilation
- \( K \) = constant

\[
VCO2 \cdot K = \frac{VA - Vds}{Vt}
\]

**C02 production↑ V (hypoventilation)
C02 production↑ Vds (dead space)**

**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
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 $P_{o2}$ (90 mmHg) and $P_{co2}$ (40 mm Hg)

Ventilation highest zone 3, lowest zone 1
- Also caused by gravity
- Upper lung compresses base → pushes air out
- More room for filling of base with next breath
- Variations smaller (L/min) than blood flow

Zone 1
- Lowest V
- Lowest Q
- Lowest blood flow
- Lowest ventilation
- Highest V/Q
- Wasted V

Zone 2
- Most V
- Most Q
- Most blood flow
- Most ventilation
- Lowest V/Q
- Wasted Q

Zone 3
- Highest V
- Highest Q
- Highest blood flow
- Highest ventilation
- Lowest V/Q

Both decrease bottom to top
- Blood flow decreases more
- V/Q ratio changes

V/Q V/Q PaO2 PaCO2
↓ ↓ ↑ 130 30
↑ ↑ ↓ 90 42

Zone 1
Zone 2
Zone 3
(3.0)
(0.6)

Lung Ventilation

- Ventilation highest zone 3, lowest zone 1
- Also caused by gravity
- Upper lung compresses base → pushes air out
- More room for filling of base with next breath
- Variations smaller (L/min) than blood flow

Zone 1
- Lowest V
- Lowest Q
- Lowest blood flow
- Lowest ventilation
- Highest V/Q
- Wasted V

Zone 2
- Most V
- Most Q
- Most blood flow
- Most ventilation
- Lowest V/Q
- Wasted Q

Zone 3
- Highest V
- Highest Q
- Highest blood flow
- Highest ventilation
- Lowest V/Q
- Wasted Q

Zone 1
(40EC)

Tuberculosis
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

Exercise

- No change in mean P\textsubscript{aO2} and P\textsubscript{aCO2}
- Increased venous CO\textsubscript{2} (P\textsubscript{vCO2})
- Decreased venous O\textsubscript{2} (P\textsubscript{vO2})
Oxygen Content

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

\[
O₂ \text{ Content} = (O₂ \text{ Binding Capacity}) \times (% \text{ Sat}) + (\text{Dissolved } O₂) \\
(1.39 \times Hgb) 0.003 \text{ PaO₂}
\]

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

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

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

Pulse Oximetry

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

Oxygen Content

\[
O₂ \text{ Content} = (O₂ \text{ Binding Capacity}) \times (% \text{ Sat}) + (\text{Dissolved } O₂) \\
(1.39 \times Hgb) 0.003 \text{ PaO₂}
\]

- Normal O₂ content requires:
  - Presence of hemoglobin
  - Sufficient saturation of hemoglobin
  - Normal PaO₂
Hyoxemia, Hypoxia, Ischemia

- Hyoxemia: 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 (PₐO₂) usually normal
- Amount of CO gas required for poisoning usually small
- Normal PₐO₂ → Normal PₐO₂
- ↓ O₂ binding to Hb despite normal PₐO₂

Hypoxemia, Hypoxia, Ischemia

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

Common Hypoxia Causes

- Hyoxemia
- Heart Failure
- Anemia
- Carbon Monoxide

Hypoxemia, Hypoxia, Ischemia

- 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
Normal A-a Gradient

- Low alveolar oxygen content ($P_{A\text{O}_2}$)
- Decreased oxygen content of air
  - High altitude: $P_{A\text{O}_2}$ sea level = 150 mmHg
  - $P_{A\text{O}_2}$ high altitude ~ 100 mmHg
- Hypoventilation
  - Reduced respiratory rate
  - Reduced tidal volume
  - Causes increase $P_{ACO2}$ → decreased $P_{A\text{O}_2}$
  - Narcotics, neuromuscular weakness, obesity
Normal A-a Gradient
- Improves with oxygen

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

A-a Gradient
- No problem with alveolar oxygen content (\(P_{A\text{O}_2}\))
- Low arterial oxygen content (\(P_{a\text{O}_2}\))
- 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

\[ \text{PAO}_2 = \text{PIO}_2 - \text{PaCO}_2 = 150 - \text{PaCO}_2 \]

Increased A-a Gradient
- Hypoventilation
- High CO2

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
Diffusion

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

Diffusion Limitation

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

- 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

Shunting

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

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

(diff. coefficient)
**V/Q Mismatch**

- $V/Q < 1$
  - Reduced ventilation relative to perfusion
  - Perfusion wasted
  - Blood going where not enough $O_2$ present
  - Extreme version $V/Q = 0$ is shunt
- Hypoxemia with increased A-a gradient
- Improves with oxygen

**Carbon Dioxide**

- Causes of hypercapnia
  - Hypoventilation
  - Increased dead space
  - Increased $CO_2$ production
- Hypoxemia with high A-a gradient: no ↑ $CO_2$

**Mechanisms of Hypoxemia**

<table>
<thead>
<tr>
<th></th>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>PaO₂ using 100% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion Limitation</td>
<td>↓</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Shunt V/Q = 0</td>
<td>↓</td>
<td></td>
<td>No change</td>
</tr>
<tr>
<td>V/Q Mismatch</td>
<td>↓</td>
<td></td>
<td>↑</td>
</tr>
</tbody>
</table>

**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
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

Carbon Dioxide

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

CO₂ + H₂O ⇌ H₂CO₃ ⇌ HCO₃⁻ + H⁺

Dissolved CO₂

• Determined by Henry's law
• P × solubility = dissolved CO₂
• Very small amount (5%) total blood CO₂

Bicarbonate

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

CO₂ + H₂O ⇌ H₂CO₃ ⇌ HCO₃⁻ + H⁺

Bicarbonate

CO₂ + H₂O ⇌ H₂CO₃ ⇌ HCO₃⁻ + H⁺

RBC 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

CO₂ + H₂O ⇌ H₂CO₃ ⇌ HCO₃⁻ + H⁺
Bohr Effect

- Deoxyhemoglobin has high affinity for H⁺
- H⁺ binds hemoglobin in low O₂/high CO₂ areas
- Converts Hgb to "taut form" which releases O₂
- Shifts O₂ curve to right
- Hemoglobin releases more oxygen

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

Cellular Metabolism

↑ H⁺   ↓ pH
↑ CO₂

Richard Wheeler and Zephyris

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 ↑ CO₂
- Prevents H⁺ from reducing pH

H⁺ and low pH are indicators of metabolism
- H⁺ and low pH trigger release of O₂ by hemoglobin

Richard Wheeler and Zephyris

Carbaminohemoglobin

- Hemoglobin bound to CO₂
- Binds at different site from O₂
- CO₂ binding alters affinity for oxygen
- More CO₂ → More O₂ release
- CO₂ decreases affinity for oxygen

H⁺ produced when bicarbonate generated
- Could cause dangerous fall in pH
- Deoxyhemoglobin buffers (absorbs) H⁺ in red cells
- ↑ deoxyhemoglobin in RBCs when ↑ CO₂
- Prevents H⁺ from reducing pH

Richard Wheeler and Zephyris

Bicarbonate

↑ venous HCO₃⁻
**Haldane Effect**

- O₂ binding alters affinity for CO₂
  - Low O₂ environment Hgb binds more CO₂
  - High O₂ environment Hgb binds less CO₂

**CO₂ Transport**

<table>
<thead>
<tr>
<th></th>
<th>Lungs/Arteries</th>
<th>Tissues/Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO₂</td>
<td>100</td>
<td>↓</td>
</tr>
<tr>
<td>pCO₂</td>
<td>40</td>
<td>↑</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>24</td>
<td>↑</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>↓</td>
</tr>
</tbody>
</table>

**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>
</tr>
<tr>
<td>Favors CO₂ loading</td>
<td>Favors CO₂ unloading</td>
</tr>
<tr>
<td>Haldane Effect</td>
<td>Haldane Effect</td>
</tr>
</tbody>
</table>

**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

**Exercise**

- ↑ O₂ consumption
- ↑ CO₂ production
- ↑ Ventilation
**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

**Exercise**

- ↑ ventilation and blood flow
- Normal PaO₂ and PaCO₂ despite metabolic changes

**Panic Attacks**

- Hyperventilation
- Low CO₂
- Hypocapnia → cerebral vasoconstriction
- CNS symptoms (dizziness, blurred vision)

**Cerebral Blood Flow**

- O₂ Content
- CO₂ Content

**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

**Exercise**

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

**Panic Attacks**

- Hyperventilation
- Low CO₂
- Hypocapnia → cerebral vasoconstriction
- CNS symptoms (dizziness, blurred vision)

**Cerebral Blood Flow**

- O₂ Content
- CO₂ Content

**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

**Exercise**

- ↑ ventilation and blood flow
- Normal PaO₂ and PaCO₂ despite metabolic changes

**Panic Attacks**

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**Cerebral Blood Flow**

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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: 95%
  - Blood gas: PaCO₂ = 60 (high)
  - Respiratory muscles failing
  - Symptoms of hypercapnia (high CO₂)
    - Lethargy
    - Confusion
    - Agitation

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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

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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

Pulmonary Function

Tests

Jason Ryan, MD, MPH

Spirometry

Volume (L)
Time (s)
1
FEV1
FVC
Normal
FVC = 5L
FEV1 = 4L
FEV1/FVC = 0.8

Image courtesy of Jmarchn

Pulmonary Function Testing

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Pulmonary Function Tests

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Image courtesy of Jmarchn
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

<table>
<thead>
<tr>
<th></th>
<th>FEV1</th>
<th>FVC</th>
<th>FEV1/FVC</th>
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<tbody>
<tr>
<td>Obstructive</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Restrictive</td>
<td>↓</td>
<td>↓</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

Volumes

- Spirometry can measure
  - VC (FVC)
  - ERV
  - RV
  - FRC
- Cannot measure
- 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
• 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

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
• 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

Obstructive Lung Disease
Jason Ryan, MD, MPH

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
Chronic Bronchitis

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

Chronic Bronchitis

- Cough
- Wheezing
- Crackles
- Dyspnea
- Cyanosis (shunting)

Shunting

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

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

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

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

**Blue Bloater – Pink Puffer**
- 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)

**Chest Volumes and Pressures**
- Volume
- -40 -20 0 20 40
- System
- Chest Wall
- Lungs
- FRC

**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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  - Panacinar emphysema
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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
Bronchiectasis Symptoms
- Recurrent infections
- Cough, excessive sputum (foul smelling)
- Hemoptysis
- Cor pulmonale
- Amyloidosis

Bronchiectasis Etiologies
- Obstruction (tumor)
- Smoking
- Cystic fibrosis
- Kartagener’s syndrome
- Allergic bronchopulmonary aspergillosis

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

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

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

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
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
    - Obstruction
    - Smoking
    - α1-antitrypsin
    - Cystic Fibrosis
    - Kartagener’s
    - ABPA
Restrictive Lung Disease

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

Restrictive Lung Diseases
- Key points: Can’t get air in → less air out
  - Reduced FVC (less air in/out)
  - Reduced FEV1 (less air in/out)
  - Normal (>80%) FEV1/FVC (hallmark)

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
Pneumoconiosis
Occupational lung diseases
• Coal miner’s lung
• Silicosis
• Asbestosis

Idiopathic pulmonary fibrosis
• Most common type: Idiopathic interstitial pneumonia
• Slow onset dyspnea
• Typically affects adults over the age of 40

Interstitial Diseases
• “Diffuse parenchymal lung diseases”
• Large group of disorders
• Similar clinical, radiographic, physiologic, or pathologic manifestations

Low DLCO Conditions
• Intstitial lung disease
• Emphysema
• Abnormal vasculature
• Pulmonary hypertension
• Pulmonary embolism
• Prior lung resection
• Anemia
• Corrects when adjusted for Hb level

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

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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
- High prevalence of TB
- 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

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  - Occurs decades after exposure
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  - Slow onset symptoms (dyspnea, cough, chest pain)
- Poor prognosis

Drug toxicity

- Bleomycin
- Busulfan
- Amiodarone
- Methotrexate

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Treatment of COPD & Asthma

COPD and Asthma Drugs
- Short-acting bronchodilators
  - Albuterol
  - Ipratropium
- Long-acting bronchodilators
  - Salmeterol, Formoterol
  - Tiotropium
- Steroids

β2 Agonists
- Activate adenylate cyclase → ↑cAMP
- Relax bronchiole 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

Steroids
- Inhaled: Beclomethasone, Fluticasone, Budesonide
- Oral: Prednisone
- IV: Methylprednisolone (Solumedrol)

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

Treatment of COPD/Asthma
Jason Ryan, MD, MPH
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

Steroids
• Inhibit synthesis of cytokines
• Bind to glucocorticoid receptor (GR)
• Many, many immunosuppressive effects
• ↓ expression 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

Eicosanoids
• Lipids (cell membranes)
  • Arachidonic acid
• Leukotrienes
• Lipoxygenase
• Thromboxanes
• Prostaglandins
• Cyclooxygenase
• Phospholipase A2

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Image courtesy of James Heilman, MD

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

Theophylline
• Methylxanthines
• Multiple, complex mechanisms
• Bronchodilation
• Likely through inhibition of PDE
• Less hydrolysis (breakdown) of cAMP
• ↑cAMP
• Also down-regulates inflammatory cell functions
Theophylline

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

Theophylline

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

Theophylline

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

Theophylline

- 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

Theophylline

- Narrow therapeutic index
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Asthma

- Avoidance of Triggers
- Steroids
- Zileuton
- Cromolyn
- Theophylline
- β agonists
- M antagonists
- LRAs

Special COPD Drugs

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

**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 &gt;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>
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<tr>
<td>Gold 4</td>
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- Vaccinations
- Smoking cessation
Asthma: Chronic Therapy

- **Step 1**: SABA as needed
- **Step 2**: Add low dose ICS
- **Step 3**: Medium ICS or Low ICS + LABA
- **Step 4**: Medium ICS + LABA
- **Step 5**: High ICS + LABA + Oral Steroids
- **Step 6**: LTRA, Ileostomy, Theophylline, Omalizumab

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
Pneumonia

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**
- S. pneumoniae – most common
- Haemophilus influenzae
- Mycoplasma pneumoniae
- C. pneumoniae
- Legionella

**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)

**Viruses**
- Influenza
- RSV (children)

**Atypical Pneumonia**
- Pneumonia caused by:
  - Legionella pneumophila
  - Mycoplasma pneumoniae
  - Chlamydophila pneumoniae
- Usually milder than strep pneumonia
- Respiratory distress rare
- Interstitial infiltrates on CXR
- “Walking pneumonia”

**Interstitial Pneumonia**
- Inflammatory infiltrate of alveolar walls only
- More indolent course
- Viruses
  - Legionella pneumophila
  - Mycoplasma pneumoniae
  - Chlamydophila pneumoniae

**Bronchopneumonia**
- Patchy inflammation of multiple lobules
- Primary involvement airways and surrounding interstitium
- Staphylococcus aureus

### Causes of Pneumonia

**Children**
- Group B Strept
- E. Coli
- Viruses (RSV)
- Mycoplasma
- Chlamydia Pneumonia
- Strepoccocus Pneumoniae
Signs/Symptoms
- High Fever
- Cough
- Sputum production
- Elevated WBC
- Pleuritic chest pain

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

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

Community Acquired PNA
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

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

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)
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

ARDS Treatment

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

ALDS Triggers

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

**Pontiac Fever**

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

**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

**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
  - Strep pneumoniae, Staph aureus, H. influenzae
- Worsening symptoms after initial improvement
- Cause of death

**CMV**

- Pneumonia in transplant patients on immunosuppressive drugs
- “Owl eye” intranuclear inclusions
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

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

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

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PCP
Pneumocystis jirovecii
- Diagnosed by microscopy
  - Sputum sample or BAL
  - Staining required → cannot be cultured
- Special stains used
  - Silver stains often used
- Treatments
  - TMP-SMX (first line)
  - Dapsone
  - Pentamidine
- Prophylaxis
  - TMP-SMX when CD4 < 200 cells/μL
  - High dose steroid or other immunosuppressant

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

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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

Spontaneous PTX

- Sudden onset dyspnea
- Sometimes pleuritic chest pain
- CXR for diagnosis

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

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

Pleural Effusion
- Three general etiologies
  - Transudative
  - Exudative
  - Lymphatic

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

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

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

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

Diagnosis
- Pulmonary nodule
- "Coin lesion"
- Compare with prior
- Biopsy for diagnosis

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

Common Cancers
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Lung Cancer
Jason Ryan, MD, MPH
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

Non-Small Cell Cancers
- Squamous Cell Carcinoma
- Adenocarcinoma
- Large cell carcinoma
- Bronchioloalveolar Carcinoma
- Carcinoid tumor

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

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

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
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
SVC Syndrome
- Obstruction of blood flow through SVC
- Can be caused by compression from tumor
- Lung Masses: NSCLC, SCLC
- Mediastinal Masses: Lymphoma
- Other causes include thrombosis
  - Indwelling catheters, pacemaker wires
- Facial swelling or head fullness
- Arm swelling
- Can cause increased ICP
  - Headaches, confusion, coma
  - Cranial artery rupture

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

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

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
  - Lobar consolidation
  - Excellent prognosis
  - Surgery, radiotherapy, sometimes adjuvant chemotherapy

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

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

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Adenocarcinoma
- Glandular tumor
- Most common lung cancer: nonsmokers/females
- Peripheral
Metastasis to Lung
• More common than primary lung tumors
• Most commonly from breast or colon cancer
• Usually multiple lesions on imaging

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

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 paresthesia, weakness
• Can compress sympathetic nerves
• Horner’s syndrome
  • Miosis
  • Ptosis
  • Anhidrosis

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

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

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

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

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

Cystic Fibrosis
Jason Ryan, MD, MPH

Cystic Fibrosis

Cystic Fibrosis

Cystic Fibrosis

Cystic Fibrosis

Cystic Fibrosis

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

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

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

- Digital clubbing
- Nasal polyps

Diagnosis

- Rare CF patients have negative sweat test
- Usually have milder disease
- Often recurrent pulmonary and sinus infections
- If symptoms highly suggestive, can test nasal transepithelial potential difference
- Measure nasal voltage
- CF patients: more negative voltage
- Due to abnormal sodium processing

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
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

Prognosis

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

• 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

• 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

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

Clinical Picture

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

Exposure to TB

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

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

Spread of TB

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

**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

**Primary TB Resolution**
- Most (90%) patients control infection
  - Disease heals leaving fibrosis
  - Sometimes completely clears
  - 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)

**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

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

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- Most (90%) patients control infection
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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)

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"
  - Reactivation TB
  - Miliary TB
  - Primary 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

Reactivation TB
- Can occur when immune compromise develops
- HIV infection
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- Diabetic
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Aspergillus
- ABPA
- Invasive Aspergillus
- Aspergilloma

Reactivation TB
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**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 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

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

**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

**PPD Testing**

<table>
<thead>
<tr>
<th>Induration</th>
<th>Interpretation</th>
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</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 patients &gt;5yo with low likelihood of TB</td>
</tr>
</tbody>
</table>

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

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**PPD Testing**
- False negatives can occur
- Immunosuppressive drugs
  - Corticosteroids
  - TNF-α inhibitors
- Immunocompromised
  - HIV
  - CKD
  - Malnutrition
  - Diseased 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
Tuberculosis Key Points

- Mycolic acid cell walls → acid fast
- Infects macrophages (intracellular)
- Delayed type hypersensitivity reaction
- Hilar 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

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

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

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

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

Jason Ryan, MD, MPH
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
  25-OH Vitamin D → 1α-hydroxylase → 1,25-OH2 Vitamin D

Classic Presentation

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

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

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

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
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)

Wells Score

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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
Diagnosis
• CT angiogram
• VQ Scan – used in patients with elevated creatinine

Pulmonary Embolism in a Woman Taking Oral Contraceptives and Valdecoxib.
Westgate EJ, FitzGerald GA

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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

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

Fat Embolism

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

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

- Phase I
  - Pulmonary artery vasospasm → pulmonary hypertension
  - Right heart failure
  - Hypoxia
  - Myocardial capillary damage → left heart failure
  - Pulmonary capillary damage → ARDS
  - Acute respiratory distress syndrome
  - Key features: respiratory distress, ↓O₂, hypotension

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Chest X-rays

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

Pleural Effusion
Pneumothorax

Lobar Pneumonia

Interstitial Fibrosis

Hilar Lymphadenopathy

Pulmonary Nodule