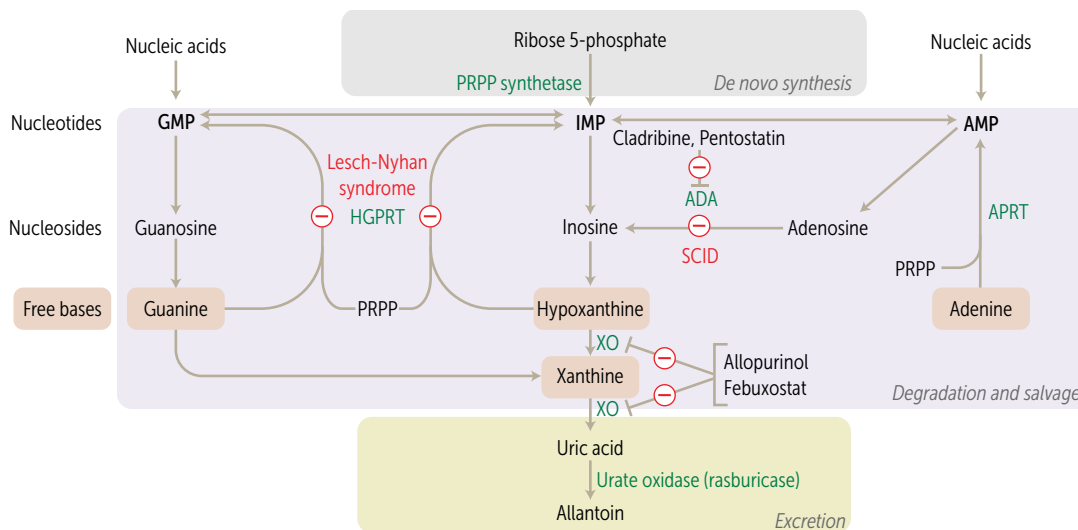


## Purine salvage deficiencies



ADA, adenosine deaminase; APRT, adenosine phosphoribosyltransferase; HGPRT, hypoxanthine guanine phosphoribosyltransferase; XO, xanthine oxidase; SCID, severe combined immune deficiency (autosomal recessive inheritance)

### Adenosine deaminase deficiency

ADA is required for degradation of adenosine and deoxyadenosine.  $\downarrow$  ADA  $\rightarrow$   $\uparrow$  dATP  $\rightarrow$   $\downarrow$  ribonucleotide reductase activity  $\rightarrow$   $\downarrow$  DNA precursors in cells  $\rightarrow$   $\downarrow$  lymphocytes.

One of the major causes of autosomal recessive SCID.

### Lesch-Nyhan syndrome

Defective purine salvage due to absent **HGPRT**, which converts hypoxanthine to IMP and guanine to GMP.  $\uparrow$  purine synthesis ( $\uparrow$  PRPP aminotransferase activity)  $\rightarrow$  excess uric acid production. X-linked recessive.

Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (red/orange "sand" [sodium urate crystals] in diaper), gout, dystonia, macrocytosis.

### HGPRT:

Hyperuricemia

Gout

Pissed off (aggression, self-mutilation)

Red/orange crystals in urine

Tense muscles (dystonia)

Treatment: allopurinol or febuxostat (2nd line).

## Genetic code features

### Unambiguous

Each codon specifies only 1 amino acid.

### Degenerate/redundant

Most amino acids are coded by multiple codons. **Wobble**—codons that differ in 3rd ("wobble") position may code for the same tRNA/amino acid. Specific base pairing is usually required only in the first 2 nucleotide positions of mRNA codon.

Exceptions: methionine (AUG) and tryptophan (UGG) encoded by only 1 codon.

### Commaless, nonoverlapping

Read from a fixed starting point as a continuous sequence of bases.

Exceptions: some viruses.

### Universal

Genetic code is conserved throughout evolution.

Exception in humans: mitochondria.

**Influenza viruses**

Orthomyxoviruses. Enveloped,  $\ominus$  ssRNA viruses with segmented genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*.  
Treatment: supportive +/- neuraminidase inhibitor (eg, oseltamivir, zanamivir).

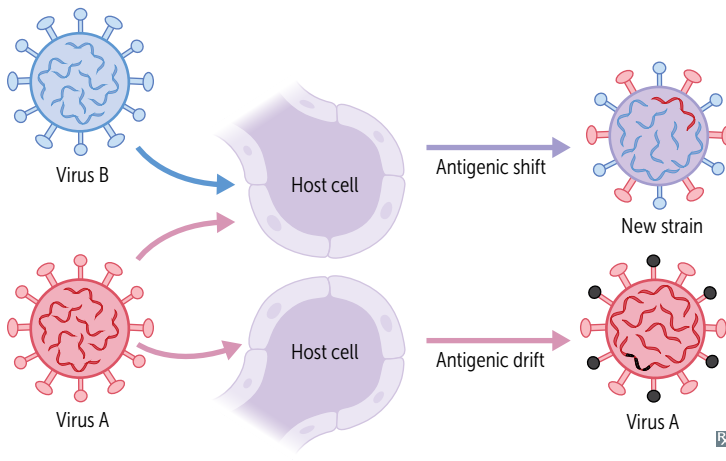
Hemagglutinin: lets the virus in  
Neuraminidase: sends the virus away  
 Reformulated vaccine (“the flu shot”) contains viral strains most likely to appear during the flu season, due to the virus’ rapid genetic change. Killed viral vaccine is most frequently used. Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally.  
Sudden shift is more deadly than gradual drift.

**Genetic/antigenic shift**

Infection of 1 cell by 2 different segmented viruses (eg, swine influenza and human influenza viruses) → RNA segment reassortment → dramatically different virus (genetic shift) → major global outbreaks (pandemics).

**Genetic/antigenic drift**

Random mutation in hemagglutinin (HA) or neuraminidase (NA) genes → minor changes in HA or NA protein (drift) occur frequently → major global outbreaks (pandemics).



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**Rubella virus**

A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities **A**.

Causes mild disease in children but serious congenital disease (a TORCH infection). Congenital rubella findings include classic triad of sensorineural deafness, cataracts, and patent ductus arteriosus. “Blueberry muffin” appearance may be seen due to dermal extramedullary hematopoiesis.

**Paramyxoviruses**

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus. All subtypes can cause respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants. Palivizumab for paramyxovirus (RSV) prophylaxis in preemies.

**Expressing empathy****PEARLS**

<b>Partnership</b>	<u>Reassure the patient that you will work together through difficult times, and offer appropriate resources.</u>
<b>Empathy</b>	<u>Acknowledge the emotions displayed and demonstrate understanding of why the patient is feeling that way.</u>
<b>Apology</b>	Take personal responsibility when appropriate, or offer condolences for the patient's situation.
<b>Respect</b>	<u>Commend the patient for coming in to discuss a problem, pushing through challenging circumstances, keeping a positive attitude, or other constructive behaviors.</u>
<b>Legitimization</b>	<u>Assure the patient that emotional responses are understandable or common.</u>
<b>Support</b>	Offer to help the patient through difficult times.

**Delivering bad news****SPIKES**

<b>Setting</b>	Offer in advance for the patient to bring support. Eliminate distractions, ensure privacy, and sit down with the patient to talk.
<b>Perception</b>	<u>Determine the patient's understanding and expectations of the situation.</u>
<b>Invitation</b>	<u>Obtain the patient's permission to disclose the news and what level of detail is desired.</u>
<b>Knowledge</b>	Share the information in small pieces without <u>medical jargon</u> , allowing time to process. Assess the patient's understanding.
<b>Emotions</b>	Acknowledge the patient's emotions, and provide opportunity to express them. Listen and offer empathetic responses.
<b>Strategy</b>	If the patient feels ready, discuss treatment options and goals of care. Offer an agenda for the next appointment.

**Gender- and sexuality-inclusive history taking**

Avoid making assumptions about sexual orientation, gender identity, gender expression, and behavior (eg, a patient who identifies as heterosexual may engage in same-sex sexual activity). Use gender-neutral terms (eg, refer to a patient's "partner" rather than assuming a spouse's gender). A patient's sex assigned at birth and gender identity may differ. Consider stating what pronouns you use when you introduce yourself (eg, "I'm Dr. Smith, and I use she/her pronouns") and asking patients how they would like to be addressed. Reassure them about the confidentiality of their appointments and be sensitive to the fact that patients may not be open about their sexual orientation or gender identity to others in their life. Do not bring up gender or sexuality if it is not relevant to the visit (eg, a gender-nonconforming patient seeking care for a hand laceration).

**Trauma-informed communication**

Patients with a history of a traumatic experience should receive thorough behavioral health screenings. Regularly assess mood, substance use, social supports, and suicide risk. Focus assessments on trauma-related symptoms that interfere with social and occupational function. Do not ask invasive questions requiring the patient to describe trauma in detail. Before the physical exam, reassure patients that they may signal to end it immediately if they experience too much physical or emotional discomfort. Offer the presence of additional staff for support.

**Motivational interviewing**

Counseling technique to facilitate behavior modification by helping patients resolve ambivalence about change. Useful for many conditions (eg, nicotine dependence, obesity). Helpful when patient has some desire to change, but it does not require that the patient be committed to making the change. May involve asking patients to examine how their behavior interferes with their life or why they might want to change it. Assess barriers (eg, food access, untreated trauma) that may make behavior change difficult.

Assessing a patient's readiness for change is also important for guiding physician-suggested goals. These goals should be **S**pecific, **M**easurable, **A**chievable, **R**elevant, and **T**ime bound (**SMART**).

**Communicating with patients with disabilities**

Use "person-first" language, which refers to "a person with a disability" rather than "a disabled person." Consider asking patients what terms they use to describe themselves. Under most circumstances, talk directly to the patient. Do not assume that nonverbal patients do not understand. Accompanying caregivers can add information to any discussion as needed. Ask if assistance is desired rather than assuming the patient cannot do something alone. Most people, including people with disabilities, value their independence. For patients with speech difficulties, provide extra time for the interview. If their speech is difficult to understand, consider asking them to write down a few words or ask them to rephrase their sentence. Repeat what they said to ensure you understood it correctly. For patients with a cognitive impairment, use concrete, specific language. Ask simple, direct questions. Eliminate background noise and distractions. Do not assume the patient can read. Adjust to how the patient understands best (eg, use hand gestures or ask them to demonstrate a task). Ask patients who are deaf or hard of hearing their preferred mode of communication. Use light touch or waving to get their attention. For patients who prefer to speak and lipread, eliminate background noise, face the patient, and do not change your mode of speaking. As with other parts of a medical history, do not bring up a disability if it is not relevant to a visit (eg, a patient in a wheelchair with an ear infection). Do not skip relevant parts of the physical exam even if the disability makes the exam challenging.

**Use of interpreters**

Visits with a patient who speaks little English should utilize a professionally trained medical interpreter unless the physician is also fluent in the patient's preferred language. Interpretation services may be provided in person, by telephone, or by video call. If the patient prefers to utilize a family member, this should be recorded in the chart. Do not assume that a patient is a poor English speaker because of name, skin tone, or accent. Ask the patient what language is preferred. The physician should make eye contact with the patient and speak to them normally, without use of third-person statements such as "tell him." Allow extra time for the interview, and ask one question at a time. For in-person spoken language interpretation, the interpreter should ideally be next to or slightly behind the patient. For sign language interpretation, the interpreter should be next to or slightly behind the physician.

**Challenging patient and ethical scenarios**

The most appropriate response is usually one that is open ended, empathetic, and patient centered. It often honors one or more of the principles of autonomy, beneficence, nonmaleficence, and justice. Appropriate responses are respectful of patients and other members of the healthcare team.

SITUATION	APPROPRIATE RESPONSE
Patient is not adherent.	Determine whether there are financial, logistical, or other obstacles preventing the patient's adherence. Do not coerce the patient into adhering or refer the patient to another physician.
Patient desires an unnecessary procedure.	Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient or refer to another physician. Avoid performing unnecessary procedures.
Patient has difficulty taking medications.	Determine what factors are involved in the patient's difficulties. If comprehension or memory are issues, use techniques such as providing written instructions, using the teach-back method, or simplifying treatment regimens.
Family members ask for information about patient's prognosis.	Avoid discussing issues with relatives without the patient's permission.
A patient's family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be "unable to handle it."	Explore why the family member believes this would be detrimental, including possible cultural factors. Explain that if the patient would like to know information concerning care, it will not be withheld. However, if you believe the patient might seriously harm self or others if informed, you may invoke therapeutic privilege and withhold the information.
A 17-year-old is pregnant and requests an abortion.	Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient's decision for, or against, an elective abortion (regardless of patient's age or fetal condition). Discuss options for terminating the pregnancy and refer to abortion care, if needed.
A 15-year-old is pregnant and wants to raise the child. Her parents want you to tell her to give the child up for adoption.	The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical aspects of caring for a baby. Discuss options for terminating the pregnancy, if requested. Encourage discussion between the teenager and her parents to reach the best decision.
A terminally ill patient requests physician-assisted dying.	The overwhelming majority of states prohibit most forms of physician-assisted dying. Physicians may, however, prescribe medically appropriate analgesics even if they potentially shorten the patient's life.
Patient is suicidal.	Assess the seriousness of the threat. If patient is actively suicidal with a plan, suggest remaining in the hospital voluntarily; patient may be hospitalized involuntarily if needed.
Patient states that you are attractive and asks if you would go on a date.	Use a chaperone if necessary. Romantic relationships with patients are never appropriate. It may be necessary to transition care to another physician.
A woman who had a mastectomy says she now feels "ugly."	Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, "You still look good").
Patient is angry about the long time spent in the waiting room.	Acknowledge the patient's anger, but do not take a patient's anger personally. Thank the patient for being patient and apologize for any inconvenience. Stay away from efforts to explain the delay.
Patient is upset with treatment received from another physician.	Suggest that the patient speak directly to that physician regarding the concern. If the problem is with a member of the office staff, tell the patient you will speak to that person.
An invasive test is performed on the wrong patient.	Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made.

**Challenging patient and ethical scenarios (continued)**

SITUATION	APPROPRIATE RESPONSE
A patient requires a treatment not covered by insurance.	Discuss all treatment options with patients, even if some are not covered by their insurance companies. <u>Inform patient of financial assistance programs.</u>
A 7-year-old boy loses a sister to cancer and now feels responsible.	At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister's death. Avoid clichés and euphemisms. Reassure the boy that he is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).
Patient is victim of intimate partner violence.	<u>Ask if patient is safe and help devise an emergency plan if there isn't one. Educate patient on intimate partner violence resources.</u> Do not necessarily pressure patient to leave a partner or disclose the incident to the authorities (unless required by state law).
Patient wants to try alternative or holistic medicine.	Explore any underlying reasons with the patient in a supportive, nonjudgmental manner. Advise the patient of known benefits and risks of treatment, including adverse effects, contraindications, and medication interactions.
Physician colleague presents to work impaired.	<u>This presents a potential risk to patient safety. You have an ethical and usually a legal obligation to report impaired colleagues so they can cease patient care and receive appropriate assistance in a timely manner. Seek guidance in reporting as procedures and applicable law vary by institution and state.</u>
Patient is officially determined to suffer brain death. Patient's family insists on maintaining life support indefinitely because patient is still moving when touched.	Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support.
A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug.	Reject this offer. Generally, decline gifts and sponsorships to avoid any conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors.
Patient requests a nonemergent procedure that is against your personal or religious beliefs.	Provide accurate and unbiased information so patients can make an informed decision. <u>In a neutral, nonjudgmental manner, explain</u> to the patient that you do not perform the procedure but offer to refer to another physician.
Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah's Witnesses.	Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor based solely on faith.
<u>A dependent patient presents with injuries inconsistent with caretaker's story.</u>	<u>Document detailed history and physical. If possible and appropriate, interview the patient alone. Provide any necessary medical care. If suspicion remains, contact the appropriate agencies or authorities (eg, child or adult protective services) for an evaluation. Inform the caretaker of your obligation to report. Physicians are required by law to report any reasonable suspicion of abuse, neglect, or endangerment.</u>
<u>A pediatrician recommends standard vaccinations for a patient, but the child's parent refuses.</u>	<u>Address any concerns the parent has. Explain the risks and benefits of vaccinations and why they are recommended. Do not administer routine vaccinations without the parent's consent.</u>

**Pancreatic islet cell tumors****Insulinoma**

Tumor of pancreatic  $\beta$  cells  $\rightarrow$  overproduction of insulin  $\rightarrow$  hypoglycemia.  
May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have  $\downarrow$  blood glucose and  $\uparrow$  C-peptide levels (vs exogenous insulin use).  $\sim 10\%$  of cases associated with MEN 1 syndrome.

Treatment: surgical resection.

**Glucagonoma**

Tumor of pancreatic  $\alpha$  cells  $\rightarrow$  overproduction of glucagon.

Presents with **6 D's**: **d**ermatitis (necrolytic migratory erythema), **d**iabetes (hyperglycemia), **D**VT, **d**eclining weight, **d**epression, **d**iarrhea.

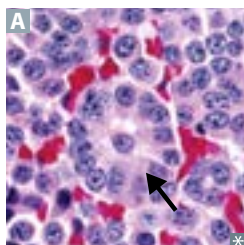
Treatment: octreotide, surgical resection.

**Somatostatinoma**

Tumor of pancreatic  $\delta$  cells  $\rightarrow$  overproduction of somatostatin  $\rightarrow \downarrow$  secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP).

May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria.

Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

**Carcinoid tumors**

Carcinoid tumors arise from neuroendocrine cells, most commonly in the intestine or lung.

Neuroendocrine cells secrete 5-HT, which undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in the lung. If 5-HT reaches the systemic circulation (eg, after liver metastasis), carcinoid tumor may present with **carcinoid syndrome**—episodic flushing, diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), niacin deficiency (pellagra).

Histology: prominent rosettes (arrow in **A**), chromogranin A  $\oplus$ , synaptophysin  $\oplus$

Treatment: surgical resection, somatostatin analog (eg, octreotide) or tryptophan hydroxylase inhibitor (eg, telotristat) for symptom control.

**Rule of thirds:**

- $1/3$  metastasize
- $1/3$  present with 2nd malignancy
- $1/3$  are multiple

**Zollinger-Ellison syndrome**

Gastrin-secreting tumor (gastrinoma) of duodenum or pancreas. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test:  $\uparrow$  gastrin levels after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.



**Antimetabolites**

All are S-phase specific except cladribine, which is cell cycle nonspecific.

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Thiopurines</b> <u>Azathioprine,</u> <u>6-mercaptopurine</u>	Purine (thiol) analogs → ↓ de novo purine synthesis AZA is converted to 6-MP, which is then activated by HGPRT	Rheumatoid arthritis, IBD, <u>SLE, ALL; steroid-refractory</u> <u>disease</u> <u>Prevention of organ rejection</u> <u>Weaning from steroids</u>	Myelosuppression; GI, liver toxicity 6-MP is inactivated by xanthine oxidase (↑ toxicity with allopurinol or febuxostat)
<b>Cladribine,</b> <b>pentostatin</b>	Purine analogs → multiple mechanisms (eg, inhibition of ADA, DNA strand breaks)	Hairy cell leukemia	Myelosuppression
<b>Cytarabine</b> <u>(arabinofuranosyl</u> <u>cytidine)</u>	Pyrimidine analog → DNA chain termination Inhibits DNA polymerase	Leukemias (AML), lymphomas	Myelosuppression
<b>5-Fluorouracil</b>	Pyrimidine analog bioactivated to 5-FdUMP → thymidylate synthase inhibition → ↓ dTMP → ↓ DNA synthesis Capecitabine is a prodrug	Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical) Effects enhanced with the addition of leucovorin	Myelosuppression, palmar- plantar erythrodysesthesia (hand-foot syndrome)
<b>Hydroxyurea</b>	Inhibits ribonucleotide reductase → ↓ DNA synthesis	Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell disease (↑ HbF)	Severe myelosuppression, megaloblastic anemia
<b>Methotrexate</b>	Folic acid analog that competitively inhibits dihydrofolate reductase → ↓ dTMP → ↓ DNA synthesis	Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas <u>Nonneoplastic</u> : ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis	Myelosuppression (reversible with leucovorin “rescue”), hepatotoxicity, mucositis (eg, mouth ulcers), pulmonary fibrosis, folate deficiency (teratogenic), nephrotoxicity

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<b>Alkylating agents</b>		<u>All are cell cycle nonspecific.</u>	
DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Busulfan</b>	Cross-links DNA	Used to ablate patient's bone marrow before bone marrow transplantation	Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation
<b>Nitrogen mustards</b> <u>Cyclophosphamide, ifosfamide</u>	Cross-link DNA Require bioactivation by liver	Solid tumors, leukemia, lymphomas, rheumatic disease (eg, SLE, granulomatosis with polyangiitis)	<u>Myelosuppression, SIADH, Fanconi syndrome (ifosfamide), hemorrhagic cystitis and bladder cancer (prevent with mesna)</u>
<b>Nitrosoureas</b> <u>Carmustine, lomustine</u>	Cross-link DNA Require bioactivation Cross blood-brain barrier → CNS entry	Brain tumors (including <u>glioblastoma multiforme</u> ) Put <b>nitro</b> in your <b>Mustang</b> and travel the <b>globe</b>	CNS toxicity (convulsions, dizziness, ataxia)
<b>Procarbazine</b>	Mechanism unknown Weak MAO inhibitor	Hodgkin lymphoma, brain tumors	Bone marrow suppression, pulmonary toxicity, leukemia, disulfiram-like reaction

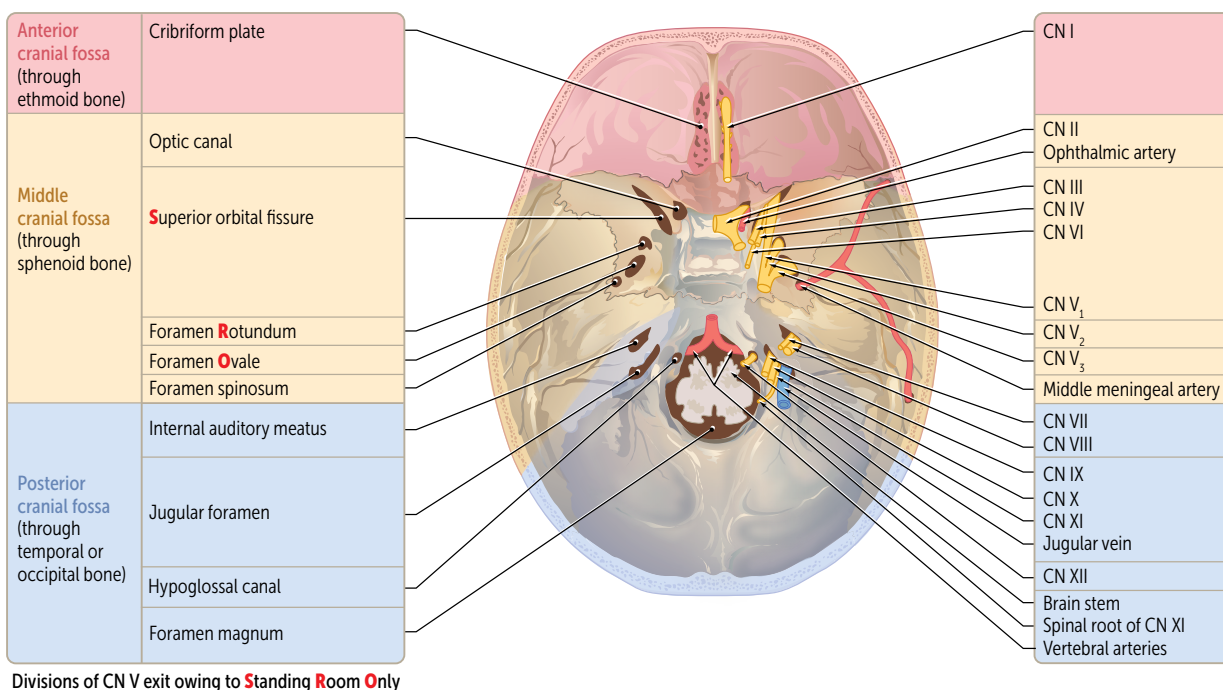
<b>Platinum compounds</b>	Cisplatin, carboplatin, oxaliplatin.		
MECHANISM	Cross-link DNA. Cell cycle nonspecific.		
CLINICAL USE	Solid tumors (eg, testicular, bladder, ovarian, GI, lung), lymphomas.		
ADVERSE EFFECTS	Nephrotoxicity (eg, Fanconi syndrome; prevent with amifostine), peripheral neuropathy, ototoxicity.		

<b>Microtubule inhibitors</b>	<u>All are M-phase specific.</u>		
DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Taxanes</b> <u>Docetaxel, paclitaxel</u>	Hyper <b>stabilize</b> polymerized microtubules → prevent mitotic spindle breakdown	<u>Various tumors (eg, ovarian and breast carcinomas)</u>	Myelosuppression, neuropathy, hypersensitivity <b>Taxes stabilize</b> society
<b>Vinca alkaloids</b> <u>Vincristine, vinblastine</u>	Bind $\beta$ -tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation	Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas	<u>Vincristine (crisps the nerves): neurotoxicity (axonal neuropathy), constipation (including ileus)</u> <u>Vinblastine (blasts the marrow): myelosuppression</u>

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### Cranial nerves and vessel pathways

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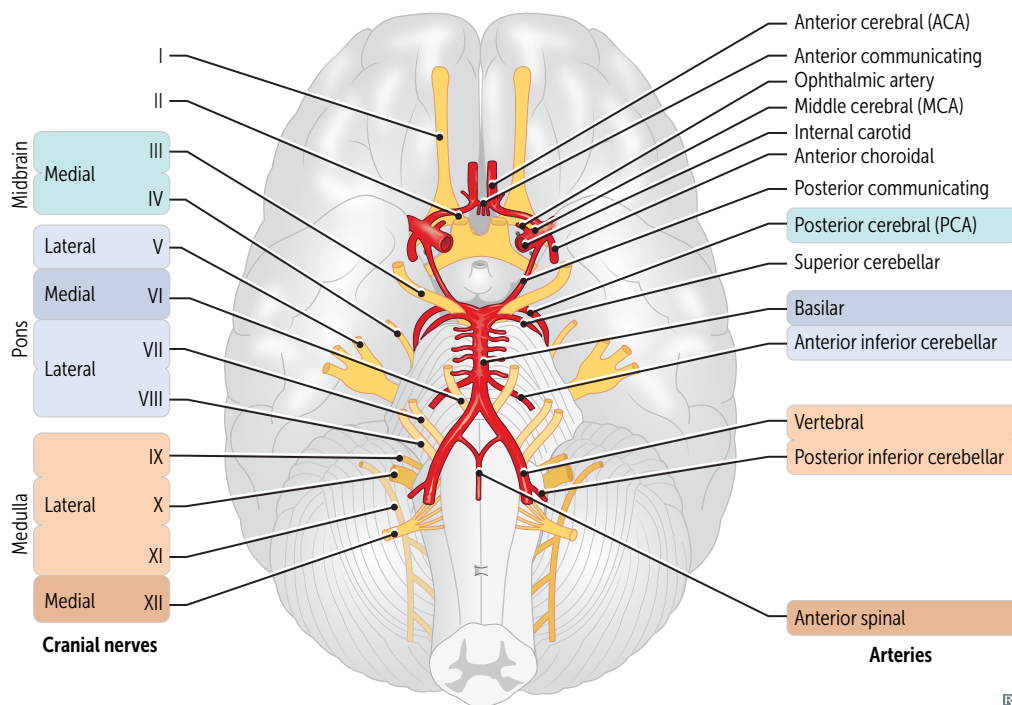


### Cranial nerves and arteries

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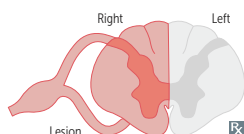
**Poliomyelitis**

Caused by poliovirus (fecal-oral transmission). Replicates in lymphoid tissue of oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).

Signs of LMN lesion: asymmetric weakness (vs symmetric weakness in spinal muscular atrophy), hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc. CSF shows ↑ WBCs (lymphocytic pleocytosis) and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

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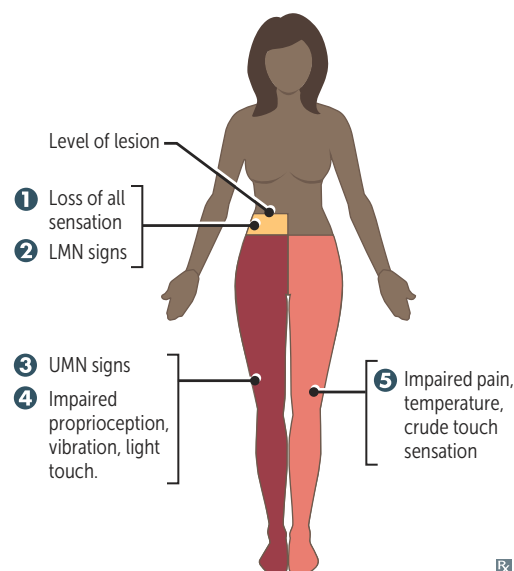
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**Brown-Séquard syndrome**

Hemisection of spinal cord. Findings:

- ① Ipsilateral loss of all sensation **at** level of lesion
- ② Ipsilateral LMN signs (eg, flaccid paralysis) **at** level of lesion
- ③ Ipsilateral UMN signs **below** level of lesion (due to corticospinal tract damage)
- ④ Ipsilateral loss of proprioception, vibration, and light touch (2-point discrimination) **below** level of lesion (due to dorsal column damage)
- ⑤ Contralateral loss of pain, temperature, and crude (non-discriminative) touch **below** level of lesion (due to spinothalamic tract damage)

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.



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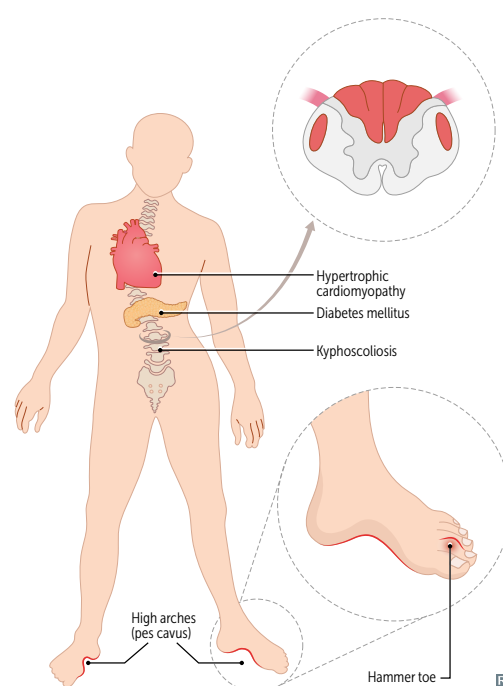
**Friedreich ataxia**

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Autosomal recessive trinucleotide repeat disorder ( $GAA$ )<sub>n</sub> on chromosome 9 in gene that encodes frataxin (iron-binding protein). Leads to impairment in mitochondrial functioning. Degeneration of lateral corticospinal tract (spastic paralysis), spinocerebellar tract (ataxia), dorsal columns (↓ vibratory sense, proprioception), and dorsal root ganglia (loss of DTRs). **Staggering** gait, frequent **falling**, nystagmus, dysarthria, pes cavus, hammer toes, **diabetes** mellitus, **hypertrophic cardiomyopathy** (cause of death). Presents in childhood with kyphoscoliosis.

Friedreich is **fr**atastic (**frataxin**): he's your favorite **frat** brother, always **staggering** and **falling** but has a **sweet, big heart**. Ataxic **GAA**it!



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## Trauma and stress-related disorders

### Adjustment disorder

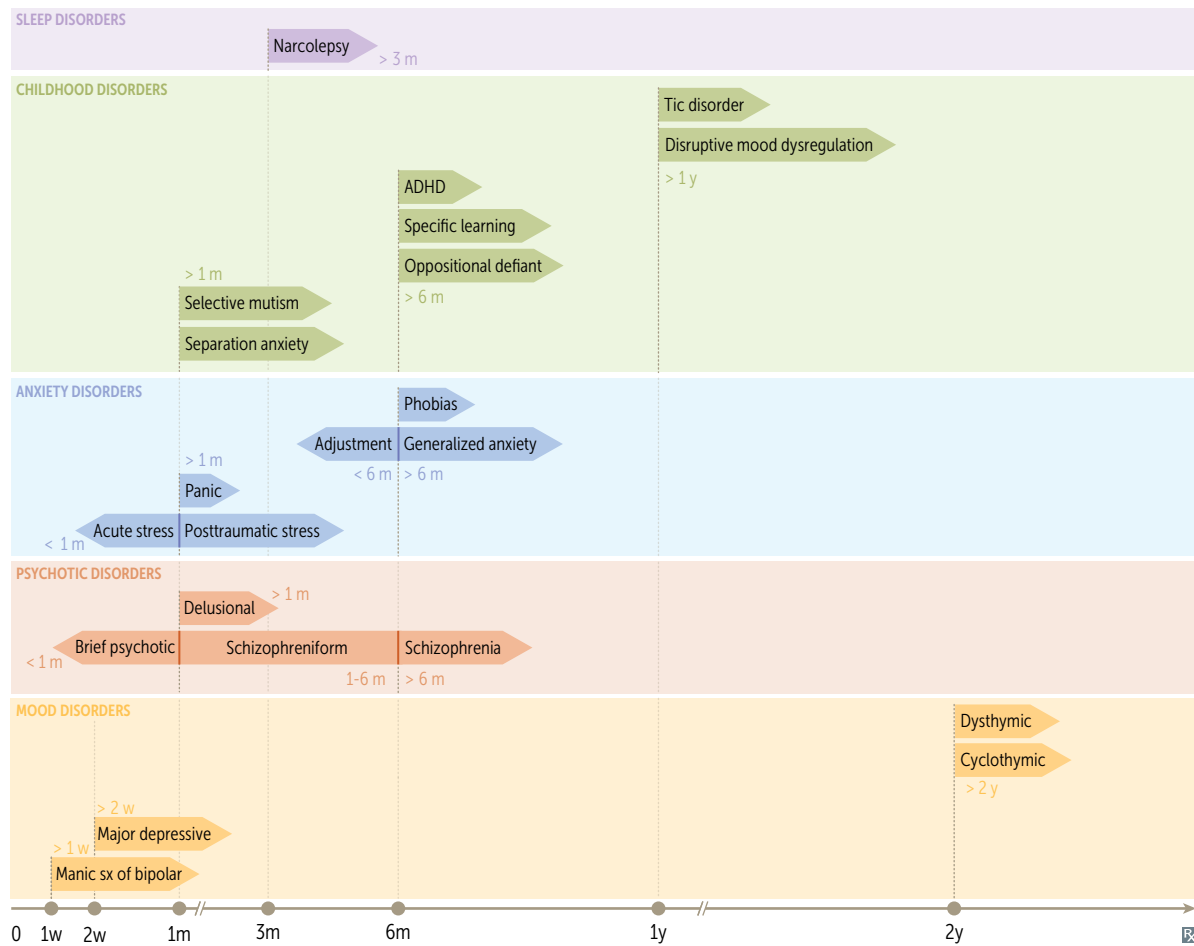
Emotional or behavioral symptoms (eg, anxiety, outbursts) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) lasting < 6 months once the stressor has ended. Symptoms do not meet criteria for another psychiatric illness. If symptoms persist > 6 months after stressor ends, reevaluate for other explanations (eg, MDD, GAD). Treatment: CBT is first line; antidepressants and anxiolytics may be considered.

### Post-traumatic stress disorder

Experiencing, or discovering that a loved one has experienced, a life-threatening situation (eg, serious injury, rape, witnessing death) → persistent **H**yperarousal, **A**voidance of associated stimuli, intrusive **R**e-experiencing of the event (eg, nightmares, flashbacks), changes in cognition or mood (eg, fear, horror, **D**istress) (having PTSD is **HARD**). Disturbance lasts > 1 month with significant distress or impaired functioning. Treatment: CBT, SSRIs, and venlafaxine are first line. Prazosin can reduce nightmares.

**Acute stress disorder**—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated.

## Diagnostic criteria by symptom duration



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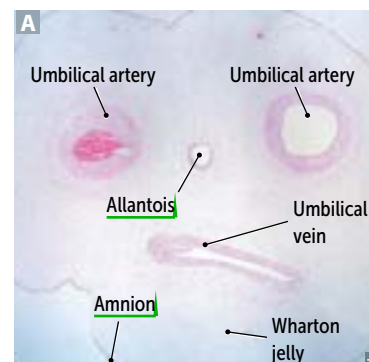
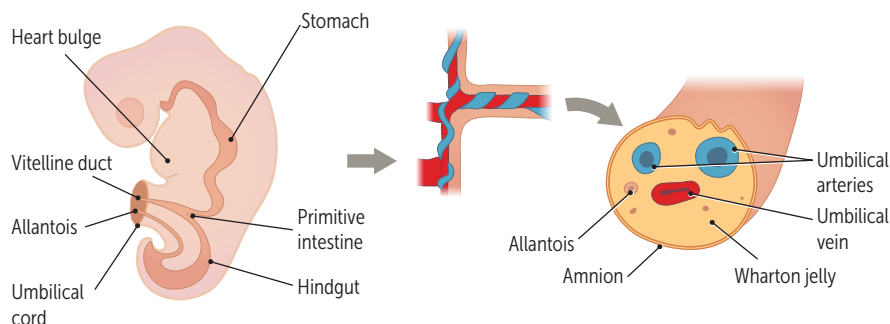
**Umbilical cord**

Two umbilical arteries return deoxygenated blood from fetal internal iliac arteries to placenta **A**.

One umbilical vein supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus.

Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies.

Umbilical arteries and vein are derived from allantois.



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**Urachus**

Allantois forms from hindgut and extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus. Failure of urachus to involute can lead to anomalies that may increase risk of infection and/or malignancy (eg, adenocarcinoma) if not treated. Obliterated urachus is represented by the median umbilical ligament after birth, which is covered by median umbilical fold of the peritoneum.

**Patent urachus**

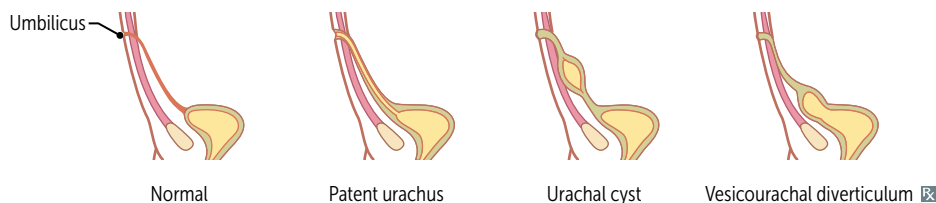
Total failure of urachus to obliterate → urine discharge from umbilicus.

**Urachal cyst**

Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Cyst can become infected and present as painful mass below umbilicus.

**Vesicourachal diverticulum**

Slight failure of urachus to obliterate → outpouching of bladder.



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**Vitelline duct**

Also called omphalomesenteric duct. Connects yolk sac to midgut lumen. Obliterates during week 7 of development.

**Patent vitelline duct**

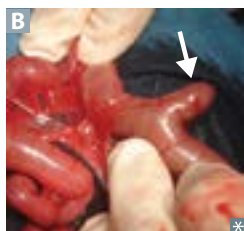
Total failure of vitelline duct to obliterate → meconium discharge from umbilicus.

**Vitelline duct cyst**

Partial failure of vitelline duct to obliterate. ↑ risk for volvulus.

**Meckel diverticulum**

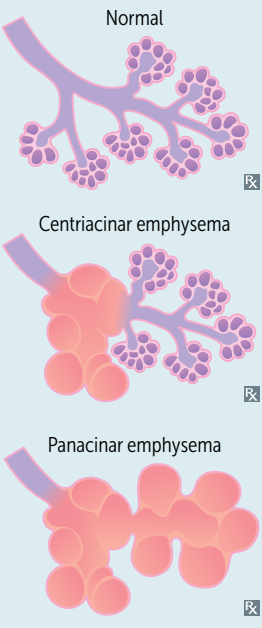







Slight failure of vitelline duct to obliterate → outpouching of ileum (true diverticulum, arrow in **B**). Usually asymptomatic. May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.



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**Obstructive lung diseases**

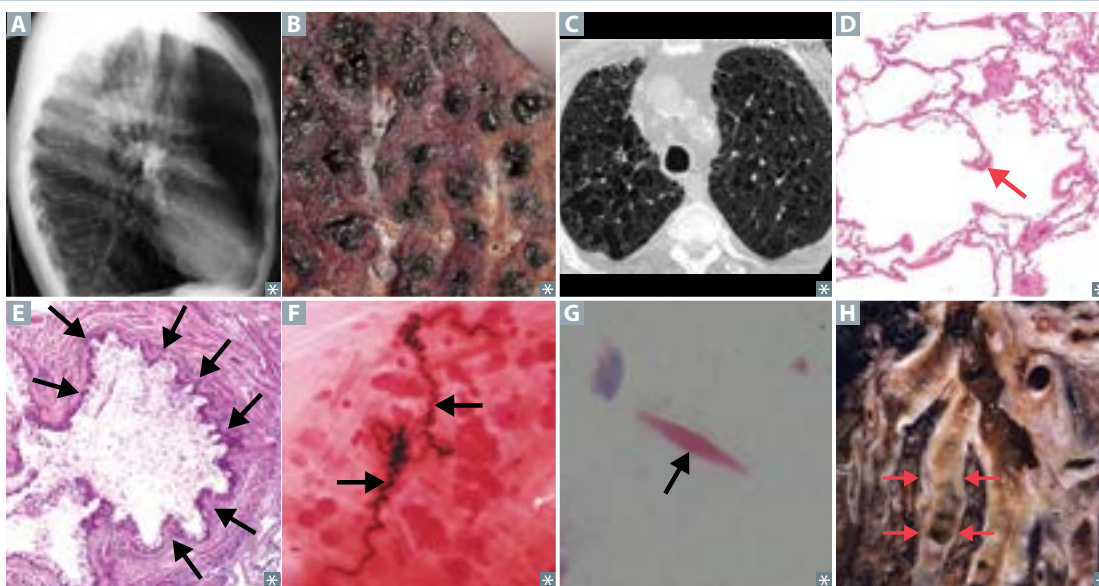
Obstruction of air flow ( $\uparrow$  FRC,  $\uparrow$  RV,  $\uparrow$  TLC)  $\rightarrow$  air trapping in lungs with premature airway closure at high lung volumes ( $\downarrow$  FEV<sub>1</sub>,  $\downarrow$  FVC  $\downarrow$  FEV<sub>1</sub>/FVC ratio). Leads to  $\dot{V}/\dot{Q}$  mismatch.

TYPE	PRESENTATION	PATHOLOGY	OTHER
<b>Chronic bronchitis</b>	Wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO <sub>2</sub> retention, 2° polycythemia.	Hypertrophy and hyperplasia of mucus-secreting glands in bronchi $\rightarrow$ Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) $> 50\%$ . DLCO may be normal.	Diagnostic criteria: productive cough for $\geq 3$ months in a year for $> 2$ consecutive years.
<b>Emphysema</b> 	Barrel-shaped chest  , expiration is prolonged and/or through pursed lips (increases airway pressure and prevents airway collapse).	Centriacinar—affects respiratory bronchioles while sparing distal alveoli, associated with tobacco smoking   . Frequently in upper lobes (smoke rises up). Panacinar—affects respiratory bronchioles and alveoli, associated with $\alpha_1$ -antitrypsin deficiency. Frequently in lower lobes. Enlargement of air spaces $\downarrow$ recoil, $\uparrow$ compliance, $\downarrow$ DLCO from destruction of alveolar walls (arrow in  ) and $\downarrow$ blood volume in pulmonary capillaries. Imbalance of proteases and antiproteases $\rightarrow$ $\uparrow$ elastase activity $\rightarrow$ $\uparrow$ loss of elastic fibers $\rightarrow$ $\uparrow$ lung compliance.	CXR: $\uparrow$ AP diameter, flattened diaphragm, $\uparrow$ lung field lucency. Chronic inflammation is mediated by CD8 <sup>+</sup> T cells, neutrophils, and macrophages.
<b>Asthma</b>	Asymptomatic baseline with intermittent episodes of coughing, wheezing, tachypnea, dyspnea, hypoxemia, $\downarrow$ inspiratory/expiratory ratio, mucus plugging  . Severe attacks may lead to pulsus paradoxus. Triggers: viral URIs, allergens, stress.	Hyperresponsive bronchi $\rightarrow$ reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Curschmann spirals  (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals  (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). DLCO normal or $\uparrow$ .	Type I hypersensitivity reaction. Diagnosis supported by spirometry $\pm$ methacholine challenge. NSAID-exacerbated respiratory disease is a combination of COX inhibition (leukotriene overproduction $\rightarrow$ airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms.



**Obstructive lung diseases (continued)**

TYPE	PRESENTATION	PATHOLOGY	OTHER
<b>Bronchiectasis</b>	Daily <u>purulent sputum</u> , recurrent infections (most often <i>P aeruginosa</i> ), hemoptysis, digital clubbing.	Chronic necrotizing infection of bronchi or obstruction → permanently dilated airways.	Associated with bronchial obstruction, poor ciliary motility (eg, <u>tobacco</u> smoking, Kartagener syndrome), cystic fibrosis (arrows in <b>H</b> show dilated airway with mucus plug), allergic bronchopulmonary aspergillosis.



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**Restrictive lung diseases**

May lead to ↓ lung volumes (↓ FVC and TLC). PFTs: normal or ↑ FEV<sub>1</sub>/FVC ratio. Patient presents with short, shallow breaths.

Types:

- Altered respiratory mechanics (extrapulmonary, normal D<sub>LCO</sub>, normal A-a gradient):
  - Respiratory muscle weakness—polio, myasthenia gravis, Guillain-Barré syndrome, ALS
  - Chest wall abnormalities—scoliosis, severe obesity
- Diffuse parenchymal lung diseases, also known as interstitial lung diseases (pulmonary, ↓ D<sub>LCO</sub>, ↑ A-a gradient):
  - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granulomas; ↑ ACE and Ca<sup>2+</sup>
  - Idiopathic pulmonary fibrosis
  - Granulomatosis with polyangiitis
  - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate)
  - Acute respiratory distress syndrome
  - Radiation-induced lung injury—Associated with proinflammatory cytokine release (eg, TNF-α, IL-1, IL-6). May be asymptomatic but most common symptoms are dry cough and dyspnea ± low-grade fever. Acute radiation pneumonitis develops within 3–12 weeks (exudative phase); radiation fibrosis may develop after 6–12 months.