

HIGH-YIELD PRINCIPLES IN

Psychiatry

“Words of comfort, skillfully administered, are the oldest therapy known to man.”

—Louis Nizer

“Psychiatry at its best is what all medicine needs more of—humanity, art, listening, and sympathy.”

—Susannah Cahalan

“It’s time to tell everyone who’s dealing with a mental health issue that they’re not alone, and that getting support and treatment isn’t a sign of weakness, it’s a sign of strength.”

—Michelle Obama

“I have schizophrenia. I am not schizophrenia. I am not my mental illness. My illness is a part of me.”

—Jonathan Harnisch

This chapter encompasses overlapping areas in psychiatry, psychology, sociology, and psychopharmacology. High-yield topics include schizophrenia, mood disorders, eating disorders, personality disorders, somatic symptom disorders, substance use disorders, and antipsychotics. Know the DSM-5 criteria for diagnosing common psychiatric disorders.

► Psychology 572

► Pathology 575

► Pharmacology 592

▶ PSYCHIATRY—PSYCHOLOGY

Classical conditioning	Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food).	Usually elicits involuntary responses. Pavlov's classical experiments with dogs—ringing the bell provoked salivation.									
Operant conditioning	Learning in which a particular action is elicited because it produces a punishment or reward. Usually elicits voluntary responses.										
Reinforcement	Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).	Skinner operant conditioning quadrants:									
Punishment	Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior.										
Extinction	Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.	<table border="1"> <thead> <tr> <th></th> <th>Increase behavior</th> <th>Decrease behavior</th> </tr> </thead> <tbody> <tr> <td>Add a stimulus</td> <td>Positive reinforcement</td> <td>Positive punishment</td> </tr> <tr> <td>Remove a stimulus</td> <td>Negative reinforcement</td> <td>Negative punishment</td> </tr> </tbody> </table>		Increase behavior	Decrease behavior	Add a stimulus	Positive reinforcement	Positive punishment	Remove a stimulus	Negative reinforcement	Negative punishment
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Transference and countertransference

Transference	Patient projects feelings about formative or other important persons onto physician (eg, psychiatrist is seen as parent).
Countertransference	Physician projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling).

Ego defenses	Thoughts and behaviors (voluntary or involuntary) used to resolve conflict and prevent undesirable feelings (eg, anxiety, depression).	
IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Acting out	Subconsciously coping with stressors or emotional conflict using actions rather than reflections or feelings.	A patient skips therapy appointments after deep discomfort from dealing with his past.
Denial	Avoiding the awareness of some painful reality.	A patient with cancer plans a full-time work schedule despite being warned of significant fatigue during chemotherapy.
Displacement	Redirection of emotions or impulses to a neutral person or object (vs projection).	After being reprimanded by her principal, a frustrated teacher returns home and criticizes her wife's cooking instead of confronting the principal directly.
Dissociation	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress. Patient has incomplete or no memory of traumatic event.	A survivor of sexual abuse sees the abuser and suddenly becomes numb and detached.

Ego defenses (continued)

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Fixation	Partially remaining at a more childish level of development (vs regression).	A college student studying for a stressful exam begins sucking her thumb.
Idealization	Expressing extremely positive thoughts of self and others while ignoring negative thoughts.	A patient boasts about his physician and his accomplishments while ignoring any flaws.
Identification	Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.	A resident starts putting her stethoscope in her pocket like her favorite attending, instead of wearing it around her neck like before.
Intellectualization	Using facts and logic to emotionally distance oneself from a stressful situation.	A patient diagnosed with cancer discusses the pathophysiology of the disease.
Isolation (of affect)	Separating feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Passive aggression	Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition.	A disgruntled employee is repeatedly late to work, but won't admit it is a way to get back at the manager.
Projection	Attributing an unacceptable internal impulse to an external source (vs displacement).	A man who wants to cheat on his wife accuses his wife of being unfaithful.
Rationalization	Asserting plausible explanations for events that actually occurred for other reasons, usually to avoid self-blame.	An employee who was recently fired claims that the job was not important anyway.
Reaction formation	Replacing a warded-off idea or feeling with an emphasis on its opposite (vs sublimation).	A stepfather treats a child he resents with excessive nurturing and overprotection.
Regression	Involuntarily turning back the maturational clock to behaviors previously demonstrated under stress (vs fixation).	A previously toilet-trained child begins bedwetting again following the birth of a sibling.
Repression	Involuntarily withholding an idea or feeling from conscious awareness (vs suppression).	A 20-year-old does not remember going to counseling during his parents' divorce 10 years earlier.
Splitting	Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Common in borderline personality disorder. Borders split countries.	A patient says that all the nurses are cold and insensitive, but the physicians are warm and friendly.
MATURE DEFENSES		
Sublimation	Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation).	A teenager's aggression toward her parents because of their high expectations is channeled into excelling in sports.
Altruism	Alleviating negative feelings via unsolicited generosity, which provides gratification (vs reaction formation).	A mafia boss makes a large donation to charity.
Suppression	Intentionally withholding an idea or feeling from conscious awareness (vs repression); temporary.	An athlete focuses on other tasks to prevent worrying about an important upcoming match.
Humor	Lightheartedly expressing uncomfortable feelings to shift the internal focus away from the distress.	A nervous medical student jokes about the boards.

Mature adults wear a **SASH**.

Grief

Natural feeling that occurs in response to the death of a loved one. Symptoms and trajectory vary for each individual, are specific to each loss, and do not follow a fixed series of stages. In addition to guilt, sadness, and yearning, patients may experience somatic symptoms, hallucinations of the deceased, and/or transient episodes of wishing they had died with or instead of their loved one. Typical acute grief is time limited (adaptations within 6 months) and is not a disorder.

Prolonged grief disorder—diagnosed if thoughts are persistent and prolonged, significantly impair functioning, and do not meet criteria for another disorder (eg, major depressive disorder [MDD]).

Normal infant and child development

Milestone dates are ranges that have been approximated and vary by source. Children not meeting milestones may need assessment for potential developmental delay.

AGE	MOTOR	SOCIAL	VERBAL/COGNITIVE
Infant	Parents	Start	Observing,
0–12 mo	Primitive reflexes disappear— Moro, rooting, palmar, Babinski (Mr. Peanut Butter) Posture —lifts head up prone (by 1 mo), rolls and sits (by 6 mo), crawls (by 8 mo), stands (by 10 mo), walks (by 12–18 mo) Picks —passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo) Points to objects (by 12 mo)	Social smile (by 2 mo) Stranger anxiety (by 6 mo) Separation anxiety (by 9 mo)	Orients —first to voice (by 4 mo), then to name and gestures (by 9 mo) Object permanence (by 9 mo) Oratory —says “mama” and “dada” (by 10 mo)
Toddler	Child	Rearing	Working,
12–36 mo	Cruises , takes first steps (by 12 mo) Climbs stairs (by 18 mo) Cubes stacked (number = age (yr) × 3) Cutlery —feeds self with fork and spoon (by 20 mo) Kicks ball (by 24 mo)	Recreation —parallel play (by 24–36 mo) Rapprochement —moves away from and returns to parent (by 24 mo) Realization —core gender identity formed (by 36 mo)	Words —uses 50–200 words (by 2 yr), uses 300+ words (by 3 yr)
Preschool	Don't	Forget, they're still	Learning!
3–5 yr	Drive —tricycle (3 wheels at 3 yr) Drawings —copies line or circle, stick figure (by 4 yr) Dexterity —hops on one foot by 4 yr (“4 on one foot”), uses buttons or zippers, grooms self (by 5 yr)	Freedom —comfortably spends part of day away from parent (by 3 yr) Friends —cooperative play, has imaginary friends (by 4 yr)	Language —understands 1000 (3 zeros) words (by 3 yr), uses complete sentences and prepositions (by 4 yr) Legends —can tell detailed stories (by 4 yr)

► PSYCHIATRY—PATHOLOGY

Child abuse

	Physical abuse	Sexual abuse	Emotional abuse
SIGNS	<p>Nonaccidental trauma (eg, fractures, bruises, burns). Injuries often in different stages of healing or in patterns resembling possible implements of injury.</p> <p>Includes abusive head trauma (shaken baby syndrome), characterized by subdural hematomas or retinal hemorrhages.</p> <p>Caregivers may delay seeking medical attention for the child or provide explanations inconsistent with the child's developmental stage or pattern of injury.</p>	<p>STIs, UTIs, and genital, anal, or oral trauma. Most often, there are no physical signs; sexual abuse should not be excluded from a differential diagnosis in the absence of physical trauma.</p> <p>Children often exhibit sexual knowledge or behavior incongruent with their age.</p>	<p>Babies or young children may lack a bond with the caregiver but are overly affectionate with less familiar adults.</p> <p>They may be aggressive toward children and animals or unusually anxious.</p> <p>Older children are often emotionally labile and prone to angry outbursts. They may distance themselves from caregivers and other children.</p> <p>They can experience vague somatic symptoms for which a medical cause cannot be found.</p>
EPIDEMIOLOGY	40% of deaths related to child abuse or neglect occur in children < 1 year old.	Peak incidence 9–12 years old.	~80% of young adult victims of child emotional abuse meet the criteria for ≥ 1 psychiatric illness by age 21.
Child neglect			
<p>Failure to provide a child with adequate food, shelter, supervision, education, and/or affection.</p> <p>Most common form of child maltreatment. Signs: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive.</p> <p>As with other types of child abuse, suspected child neglect must be reported to local child protective services.</p>			
Vulnerable child syndrome			
<p>Parents perceive the child as especially susceptible to illness or injury (vs factitious disorder imposed on another). Usually follows a serious illness or life-threatening event. Can result in missed school or overuse of medical services.</p>			

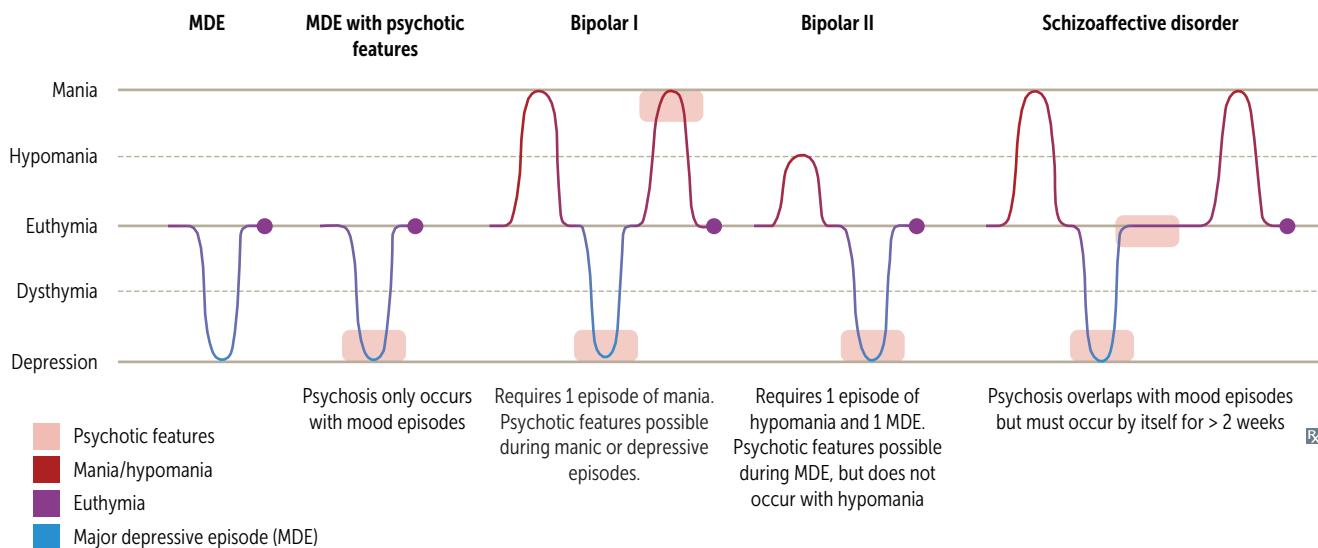
Childhood and early-onset disorders

Attention-deficit hyperactivity disorder	Onset before age 12, but diagnosis can only be established after age 4. Characterized by hyperactivity, impulsivity, and/or inattention in ≥ 2 settings (eg, school, home, places of worship). Normal intelligence, but commonly coexists with difficulties in school. Often persists into adulthood. Commonly coexists with other behavioral, cognitive, or developmental disorders. Treatment: stimulants (eg, methylphenidate) +/– behavioral therapy; alternatives include atomoxetine and α_2 -agonists (eg, clonidine, guanfacine).
Autism spectrum disorder	Onset in early childhood. Social and communication deficits, repetitive/ritualized behaviors, restricted interests. May be accompanied by intellectual disability and/or above average abilities in specific skills (eg, music). More common in males. Associated with ↑ head and/or brain size.
Conduct disorder	Repetitive, pervasive behavior violating societal norms or the basic rights of others (eg, aggression toward people and animals, destruction of property, theft). After age 18, often reclassified as antisocial personality disorder. Conduct = children, antisocial = adults. Treatment: psychotherapy (eg, cognitive behavioral therapy [CBT]).
Disruptive mood dysregulation disorder	Onset before age 10. Severe, recurrent temper outbursts out of proportion to situation. Child is constantly angry and irritable between outbursts. Treatment: CBT, stimulants, antipsychotics.
Intellectual disability	Global cognitive deficits (vs specific learning disorder) that affect reasoning, memory, abstract thinking, judgment, language, learning. Adaptive functioning is impaired, leading to major difficulties with education, employment, communication, socialization, independence. Treatment: psychotherapy, occupational therapy, special education.
Intermittent explosive disorder	Onset after age 6. Recurrent verbal or physical outbursts representing a failure to control aggressive impulses. Outbursts last < 30 minutes and are out of proportion to provocation and may lead to legal, financial, or social consequences. Episodes are not premeditated and may provide an immediate sense of relief, followed by remorse. Treatment: psychotherapy, SSRIs.
Oppositional defiant disorder	Pattern of anger and irritability with argumentative, vindictive, and defiant behavior toward authority figures lasting ≥ 6 months. Treatment: psychotherapy (eg, CBT).
Selective mutism	Onset before age 5. Anxiety disorder lasting ≥ 1 month involving refraining from speech in certain situations despite speaking in other, usually more comfortable situations. Development (eg, speech and language) not typically impaired. Interferes with social, academic, and occupational tasks. Commonly coexists with social anxiety disorder. Treatment: behavioral, family, and play therapy; SSRIs.
Separation anxiety disorder	Overwhelming fear of separation from home or attachment figure lasting ≥ 4 weeks. Can be normal behavior up to age 3–4. May lead to factitious physical complaints to avoid school. Treatment: CBT, play therapy, family therapy.
Specific learning disorder	Onset during school-age years. Inability to acquire or use information from a specific subject (eg, math, reading, writing) near age-expected proficiency for ≥ 6 months despite focused intervention. General functioning and intelligence are normal (vs intellectual disability). Treatment: academic support, counseling, extracurricular activities.
Tourette syndrome	Onset before age 18. Sudden, recurrent, nonrhythmic, stereotyped motor (eg, grimacing, shrugging) and vocal (eg, grunting, throat clearing) tics that persist for > 1 year. Coprolalia (involuntary obscene speech) found in some patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics: tetrabenazine, antipsychotics, α_2 -agonists.

PSYCHIATRY

Psychosis	Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with psychiatric illness or another medical condition, or secondary to substance or medication use.
Delusions	False, fixed, idiosyncratic beliefs that persist despite evidence to the contrary and are not typical of a patient's culture or religion (eg, a patient who believes that others are reading his thoughts). Types include erotomaniac, grandiose, jealous, persecutory, somatic, mixed, and unspecified.
Disorganized thought	Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations").
Hallucinations	Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present). Contrast with misperceptions (eg, illusions) of real external stimuli. Types include: <ul style="list-style-type: none"> ▪ Auditory—more commonly due to psychiatric illness (eg, schizophrenia) than neurologic disease. ▪ Visual—more commonly due to neurologic disease (eg, dementia), delirium, or drug intoxication than psychiatric illness. ▪ Tactile—common in alcohol withdrawal and stimulant use (eg, "cocaine crawlies," a type of delusional parasitosis). ▪ Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors. ▪ Gustatory—rare, but seen in epilepsy. ▪ Hypnagogic—occurs while going to sleep. Sometimes seen in narcolepsy. ▪ Hypnopompic—occurs while waking from sleep ("get pumped up in the morning"). Sometimes seen in narcolepsy. Contrast with illusions, which are misperceptions of real external stimuli (eg, mistaking a shadow for a black cat).

Mood disorder	Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive, bipolar, dysthymic, and cyclothymic disorders. Episodic superimposed psychotic features (delusions, hallucinations, disorganized speech/behavior) may be present at any time during mood episodes (other than hypomania).
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Schizophrenia spectrum disorders

Schizophrenia

Chronic illness causing profound functional impairment. Symptom categories include:

- Positive—excessive or distorted functioning (eg, hallucinations, delusions, unusual thought processes, disorganized speech, bizarre behavior)
- Negative—diminished functioning (eg, flat or blunted affect, apathy, anhedonia, alogia, social withdrawal)
- Cognitive—reduced ability to understand or make plans, diminished working memory, inattention

Diagnosis requires ≥ 2 of the following active symptoms, including ≥ 1 from symptoms #1–3:

1. Delusions
2. Hallucinations, often auditory
3. Disorganized speech
4. Disorganized or catatonic behavior
5. Negative symptoms

Symptom onset ≥ 6 months prior to diagnosis; requires ≥ 1 month of active symptoms over the past 6 months.

Associated with altered dopaminergic activity, ↑ serotonergic activity, and ↓ dendritic branching. Ventriculomegaly on brain imaging. Lifetime prevalence—1.5% (males > females). Presents earlier in males (late teens to early 20s) than in females (late 20s to early 30s). ↑ suicide risk.

Heavy cannabis use in adolescence is associated with ↑ incidence and worsened course of psychotic, mood, and anxiety disorders.

Hypomanic episode	Similar to a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. Abnormally ↑ activity or energy usually present. No psychotic features. Lasts ≥ 4 consecutive days.
Bipolar disorder	<p>Bipolar I (requires 1 type of episode)—≥ 1 manic episode +/- a hypomanic or depressive episode (may be separated by any length of time).</p> <p>Bipolar II (requires 2 types of episodes)—a hypomanic and a depressive episode (no history of manic episodes).</p> <p>Patient's mood and functioning usually normalize between episodes. Use of antidepressants can destabilize mood. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproate, carbamazepine, lamotrigine), atypical antipsychotics.</p> <p>Cyclothymic disorder—milder form of bipolar disorder fluctuating between mild depressive and hypomanic symptoms. Must last ≥ 2 years with symptoms present at least half of the time, with any remission lasting ≤ 2 months.</p>
Major depressive disorder	<p>Recurrent episodes lasting ≥ 2 weeks characterized by ≥ 5 of 9 diagnostic symptoms including depressed mood or anhedonia (or irritability in children). SIG: E CAPS:</p> <ul style="list-style-type: none"> ▪ Sleep disturbances ▪ ↓ Interest in pleasurable activities (anhedonia) ▪ Guilt or feelings of worthlessness ▪ ↓ Energy ▪ ↓ Concentration ▪ Appetite/weight changes ▪ Psychomotor retardation or agitation ▪ Suicidal ideation <p>Screen for previous manic or hypomanic episodes to rule out bipolar disorder.</p> <p>Treatment: CBT and SSRIs are first line; alternatives include SNRIs, mirtazapine, bupropion, electroconvulsive therapy (ECT), ketamine.</p> <p>Responses to a significant loss (eg, bereavement, natural disaster, disability) may resemble a depressive episode. Diagnosis of MDD is made if criteria are met.</p>
MDD with psychotic features	MDD + hallucinations or delusions. Psychotic features are typically mood congruent (eg, depressive themes of inadequacy, guilt, punishment, nihilism, disease, or death) and occur only in the context of major depressive episode (vs schizoaffective disorder). Treatment: antidepressant with atypical antipsychotic, ECT.
Persistent depressive disorder	Also called dysthymia. Often milder than MDD; ≥ 2 depressive symptoms lasting ≥ 2 years (≥ 1 year in children), with any remission lasting ≤ 2 months.
MDD with seasonal pattern	Formerly called seasonal affective disorder. Major depressive episodes occurring only during a particular season (usually winter) in ≥ 2 consecutive years and in most years across a lifetime. Atypical symptoms common. Treatment: standard MDD therapies + light therapy.
Depression with atypical features	Characterized by mood reactivity (transient improvement in response to a positive event), hypersomnia, hyperphagia, leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors are effective but not first line because of their risk profile.

Peripartum mood disturbances	Onset during pregnancy or within 4 weeks of delivery. ↑ risk with history of mood disorders.
Postpartum blues	50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 2 weeks. Treatment: supportive. Follow up to assess for possible MDD with peripartum onset.
MDD with peripartum onset	10–15% incidence rate. Formerly called postpartum depression. Meets MDD criteria with onset either during pregnancy or within 4 weeks after delivery. Treatment: CBT and SSRIs are first line.
Postpartum psychosis	0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include first pregnancy, family history, bipolar disorder, psychotic disorder, recent medication change. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.
Electroconvulsive therapy	Rapid-acting method to treat refractory depression, depression with psychotic symptoms, catatonia,

Panic disorder

Recurrent panic attacks involving intense fear and discomfort +/- a known trigger. Attacks typically peak in 10 minutes with ≥ 4 of the following: palpitations, paresthesias, depersonalization or derealization, abdominal distress or nausea, intense fear of dying, intense fear of losing control, lightheadedness, chest pain, chills, choking, sweating, shaking, shortness of breath. Strong genetic component. ↑ risk of suicide.

Diagnosis requires attack followed by ≥ 1 month of ≥ 1 of the following:

- Persistent concern of additional attacks
- Worrying about consequences of attack
- Behavioral change related to attacks

Symptoms are systemic manifestations of fear.

Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.

Phobias

Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Treatment: CBT with exposure therapy.

Social anxiety disorder—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For performance type (eg, anxiety restricted to public speaking), use β -blockers or benzodiazepines as needed.

Agoraphobia—irrational fear, anxiety, and/or avoidance while facing or anticipating ≥ 2 specific situations (eg, public transportation, open/closed spaces, lines/crowds, being outside of home alone). Symptoms stem from the concern that help or escape may be unavailable. Associated with panic disorder. Treatment: CBT, SSRIs.

Generalized anxiety disorder

Excessive anxiety and worry about different aspects of daily life (eg, work, school, children) for most days of ≥ 6 months. Associated with ≥ 3 of the following for adults (≥ 1 for kids): difficulty Concentrating, Restlessness, Irritability, Muscle tension, fatigue (low Energy), Sleep disturbance (anxiety over CRIMES). Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.

Obsessive-compulsive disorders

Obsessions (recurring intrusive thoughts or sensations) that can cause severe distress), and/or compulsions (repetitive, often time-consuming actions that may relieve distress). Associated with tic disorders. Poor insight into beliefs/actions linked to worse outcomes. Treatment: CBT and SSRIs; clomipramine and venlafaxine are second line.

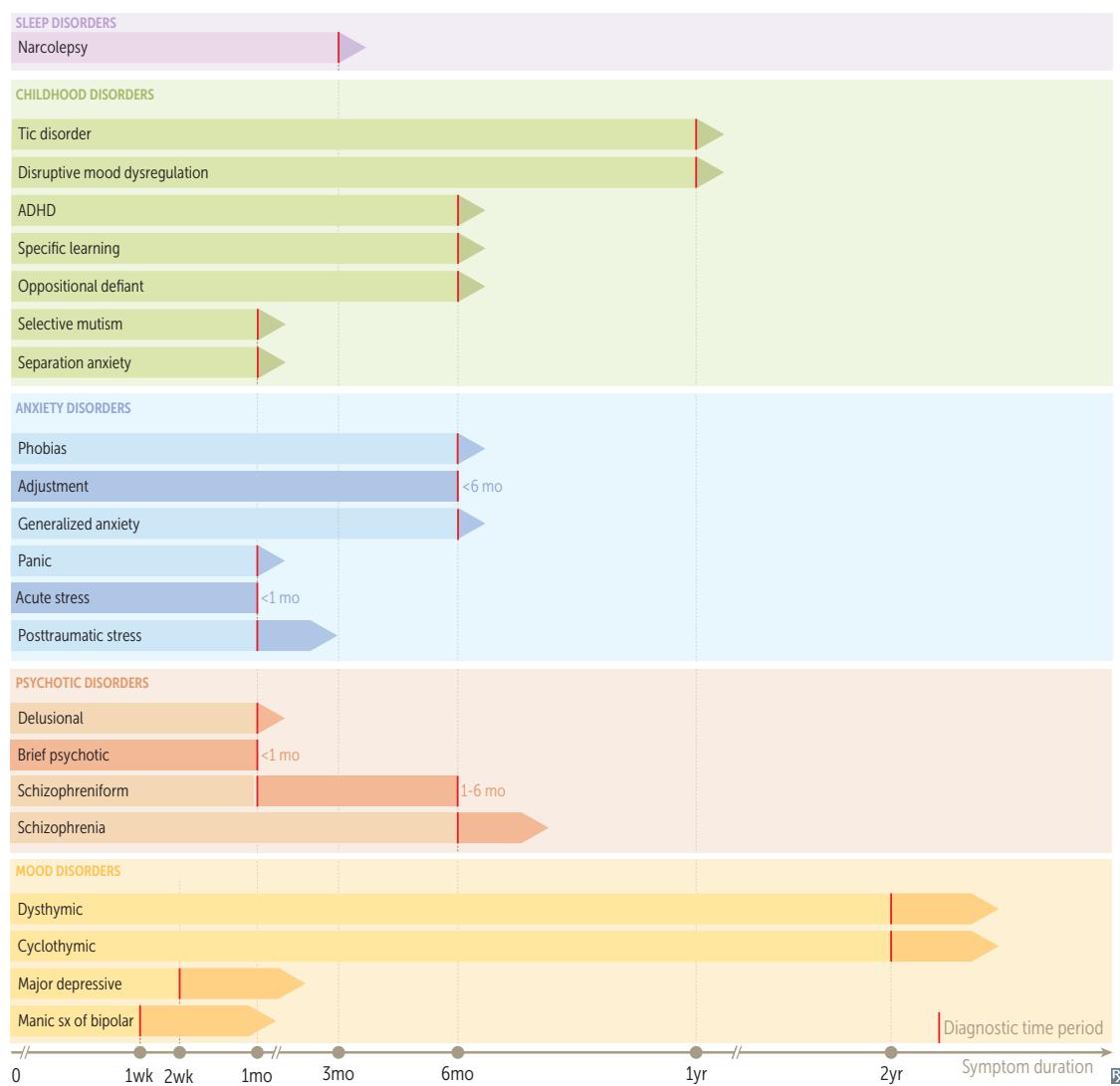
Body dysmorphic disorder—preoccupation with minor or imagined defects in appearance. Causes significant emotional distress and repetitive appearance-related behaviors (eg, mirror checking, excessive grooming). Common in eating disorders. Treatment: CBT.

Trichotillomania—compulsively pulling out one's hair. Causes significant distress and persists despite attempts to stop. Presents with areas of thinning hair or baldness on any area of the body, most commonly the scalp **A**. Remaining hair shafts are of different lengths (vs alopecia). Incidence highest in childhood but spans all ages. Treatment: psychotherapy.

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, witnessing, or discovering that a loved one has experienced a life-threatening situation (eg, serious injury, sexual assault) → persistent Hyperarousal, Avoidance of associated stimuli, intrusive Re-experiencing of the event (eg, nightmares, flashbacks), changes in cognition or mood (eg, fear, horror, Distress) (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



Personality disorders Inflexible, maladaptive, and rigidly pervasive patterns of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem (egosyntonic). Usually present by early adulthood. Contrast with **personality traits**—nonpathologic enduring patterns of perception and behavior.

Three clusters:

- Cluster A—odd or eccentric (remember as “weird”); inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.
- Cluster B—dramatic, emotional, or erratic (remember as “wild”); genetic association with mood disorders and substance use.
- Cluster C—anxious or fearful (remember as “worried”); genetic association with anxiety disorders.

Cluster A

Paranoid	Pervasive distrust (accusatory), suspiciousness, hypervigilance, and a profoundly cynical view of the world.
Schizoid	Prefers social withdrawal and solitary activities (vs avoidant), limited emotional expression, indifferent to others’ opinions (aloof).
Schizotypal	Eccentric appearance, odd beliefs or magical thinking, interpersonal awkwardness . Included on the schizophrenia spectrum. Pronounce “schizo- type -al” for odd-type thoughts.

Cluster B

Antisocial	Disregard for the rights of others with lack of remorse (bad). Involves criminality, impulsivity, hostility, and manipulation (sociopath). Males > females. Must be ≥ 18 years old with evidence of conduct disorder onset before age 15. If patient is < 18, diagnosis is conduct disorder.
Borderline	Unstable mood and interpersonal relationships, fear of abandonment, impulsivity, self-mutilation, suicidality, sense of emotional emptiness (borderline). Females > males. Splitting is a major defense mechanism. Treatment: dialectical behavior therapy.
Histrionic	Attention-seeking, dramatic speech and emotional expression, shallow and labile emotions, sexually provocative. May use physical appearance to draw attention (flamboyant).
Narcissistic	Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the “best” and reacts to criticism with rage and/or defensiveness (must be the best). Fragile self-esteem. Often envious of others.

Cluster C

Avoidant	Hypersensitive to rejection and criticism, socially inhibited, timid (cowardly), feelings of inadequacy, desires relationships with others (vs schizoid).
Obsessive-compulsive	Preoccupation with order, perfectionism, and control (obsessive-compulsive); egosyntonic: behavior consistent with one’s own beliefs and attitudes (vs OCD).
Dependent	Excessive need for support (clingy), submissive, low self-confidence. Patients often get stuck in abusive relationships.

Malingering

Symptoms are intentional, motivation is intentional. Patient consciously fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific 2° (external) gain (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).

Factitious disorders

Symptoms are intentional, motivation is unconscious. Patient consciously creates physical and/or psychological symptoms in order to assume “sick role” and to get medical attention and sympathy (1° [internal] gain).

Factitious disorder imposed on self

Formerly called Munchausen syndrome. Chronic factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures. More common in females and healthcare workers.

Factitious disorder imposed on another

Formerly called Munchausen syndrome by proxy. Illness in an individual being cared for (most often a child, also seen in disabled or older adults) is directly caused (eg, physically harming a child) or fabricated (eg, lying about a child’s symptoms) by the caregiver. Form of child/elder abuse.

Somatic symptom and related disorders

Symptoms are unconscious, motivation is unconscious. Category of disorders characterized by physical symptoms causing significant distress and impairment. Symptoms not intentionally produced or feigned.

Somatic symptom disorder

≥ 1 bodily complaints (eg, abdominal pain, fatigue) lasting months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness. Treatment: regular office visits with the same physician in combination with psychotherapy.

Conversion disorder

Also called functional neurologic symptom disorder. Unexplained loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient may be aware of but indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.

Illness anxiety disorder

Preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal to no somatic symptoms.

Malingering vs factitious disorder vs somatic symptom disorders

	Malingering	Factitious disorder	Somatic symptom disorders
SYMPTOMS	Intentional	Intentional	Unconscious
MOTIVATION	Intentional	Unconscious	Unconscious

Eating disorders	
Anorexia nervosa	Most common in young women. Intense fear of weight gain, overvaluation of thinness, and body image distortion leading to calorie restriction and severe weight loss resulting in inappropriately low body weight ($BMI < 18.5 \text{ kg/m}^2$ for adults). Physiological disturbances may present as bradycardia, hypotension, hypothermia, hypothyroidism, osteoporosis, lanugo, amenorrhea (low calorie intake $\rightarrow \downarrow \text{leptin} \rightarrow \downarrow \text{GnRH} \rightarrow \downarrow \text{LH}, \text{FSH} \rightarrow \downarrow \text{estrogen} \rightarrow \text{amenorrhea}$). Binge-eating/purging type —recurring purging behaviors (eg, laxative or diuretic abuse, self-induced vomiting) or binge eating over the last 3 months. Associated with hypokalemia. Restricting type —primary disordered behaviors include dieting, fasting, and/or over-exercising. No recurring purging behaviors or binge eating over the last 3 months. Refeeding syndrome —often occurs in significantly malnourished patients with sudden \uparrow calorie intake $\rightarrow \uparrow \text{insulin} \rightarrow \downarrow \text{PO}_4^{3-}, \downarrow \text{K}^+, \downarrow \text{Mg}^{2+} \rightarrow$ cardiac complications, rhabdomyolysis, seizures. Treatment: nutritional rehabilitation, psychotherapy, olanzapine.
Bulimia nervosa	Recurring episodes of binge eating with compensatory purging behaviors at least weekly over the last 3 months. BMI often normal or slightly overweight (vs anorexia). Associated with parotid gland hypertrophy (may see \uparrow serum amylase), enamel erosion, Mallory-Weiss syndrome, electrolyte disturbances (eg, $\downarrow \text{K}^+, \downarrow \text{Cl}^-$), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs). Bupropion is contraindicated due to seizure risk.
Binge-eating disorder	Recurring episodes of binge eating without purging behaviors at least weekly over the last 3 months. \uparrow diabetes risk. Most common eating disorder in adults. Treatment: psychotherapy (first line); SSRIs; lisdexamfetamine.
Pica	Recurring episodes of eating non-food substances (eg, ice, dirt, hair, paint chips) over ≥ 1 month that are not culturally or developmentally recognized as normal. May provide temporary emotional relief. Common in children and during pregnancy. Associated with malnutrition, iron deficiency anemia, developmental disabilities, emotional trauma. Treatment: psychotherapy and nutritional rehabilitation (first line); SSRIs (second line).
Gender dysphoria	Significant incongruence between one's gender identity and one's gender assigned at birth, lasting > 6 months and leading to persistent distress. Individuals experience marked discomfort with their assigned gender, which interferes with social, academic, and other areas of function. Individuals may pursue multiple domains of gender affirmation, including social, legal, and medical. Transgender —any individual who transiently or persistently experiences incongruence between their gender identity and their gender assigned at birth. Some individuals who are transgender will experience gender dysphoria. Nonconformity to one's assigned gender itself is not a mental disorder.
Sexual dysfunction	Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (genito-pelvic pain/penetration disorder). Differential diagnosis includes (PENIS): <ul style="list-style-type: none">▪ Psychological (if nighttime erections still occur)▪ Endocrine (eg, diabetes, low testosterone)▪ Neurogenic (eg, postoperative, spinal cord injury)▪ Insufficient blood flow (eg, atherosclerosis)▪ Substances (eg, antihypertensives, antidepressants, ethanol)

Sleep terror disorder

Periods of inconsolable terror with screaming in the middle of the night. Most common in children. Occurs during slow-wave/deep (stage N3) non-REM sleep with no memory of the arousal episode, as opposed to nightmares that occur during **REM** sleep (remembering a scary dream). Triggers include emotional stress, fever, and lack of sleep. Usually self limited.

Enuresis

Nighttime urinary incontinence ≥ 2 times/week for ≥ 3 months in person > 5 years old. First-line treatment: behavioral modification (eg, scheduled voids, nighttime fluid restriction) and positive reinforcement. For refractory cases: bedwetting alarm, oral desmopressin (ADH analog; preferred over imipramine due to fewer adverse effects).

Narcolepsy

Excessive daytime sleepiness (despite awakening well-rested) with recurrent episodes of rapid-onset, overwhelming sleepiness ≥ 3 times/week for the last 3 months. Due to \downarrow orexin (hypocretin) production in lateral hypothalamus and dysregulated sleep-wake cycles. Associated with:

- Hypnagogic (just before going to sleep) or hypnopompic (just before awakening; get **pomped** up in the morning) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter).

Treatment: good sleep hygiene (scheduled naps, regular sleep schedule), daytime stimulants (eg, amphetamines, modafinil) and/or nighttime sodium oxybate (GHB).

Substance use disorder

Maladaptive pattern of substance use involving ≥ 2 of the following in the past year:

- Tolerance
- Withdrawal
- Intense, distracting cravings
- Using more, or longer, than intended
- Persistent desire but inability to cut down
- Time-consuming substance acquisition, use, or recovery
- Impaired functioning at work, school, or home
- Social or interpersonal conflicts
- Reduced recreational activities
- > 1 episode of use involving danger (eg, unsafe sex, driving while impaired)
- Continued use despite awareness of harm

In the case of appropriate medical treatment with prescribed medications (eg, opioid analgesics, sedatives, stimulants), symptoms of tolerance and withdrawal do not indicate a substance use disorder.

Gambling disorder

Persistent, recurrent, problematic gambling that cannot be better explained as a manic episode. Diagnosis made if patient meets ≥ 4 of the following criteria:

- Is preoccupied with gambling
- Requires more gambling to reach desired level of excitement
- Has failed efforts to limit, cut back, or stop gambling
- Becomes restless or irritable when limiting or attempting to stop gambling
- Gambles to escape or relieve feelings of helplessness, guilt, anxiety, or depression
- After losing money gambling, continues gambling in an attempt to recover losses
- Lies to conceal the extent of gambling
- Puts at risk or has lost significant relationship, career, or academic pursuits because of gambling
- Relies on money from others to fix financial collapse due to gambling

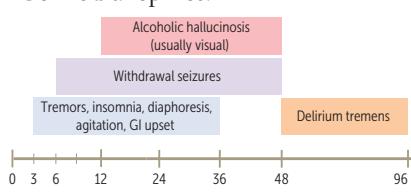
Transtheoretical model of change

STAGE	FEATURES	MOTIVATIONAL STRATEGIES
Precontemplation	Denies problem and its consequences.	Encourage introspection. Use patient's personal priorities in explaining risks. Affirm your availability to the patient.
Contemplation	Acknowledges problem but is ambivalent or unwilling to change.	Discuss pros of changing and cons of maintaining current behavior. Suggest means to support behavior changes.
Preparation/ determination	Committed to and planning for behavior change.	Employ motivational interviewing. Encourage initial changes, promote expectations for positive results, provide resources to assist in planning.
Action/willpower	Executes a plan and demonstrates a change in behavior.	Assist with strategies for self-efficacy, contingency management, and coping with situations that trigger old behaviors.
Maintenance	New behaviors become sustained, integrate into personal identity and lifestyle.	Reinforce developing habits. Evaluate and mitigate relapse risk. Praise progress.
Relapse	Regression to prior behavior (does not always occur).	Varies based on degree of regression. Encourage return to changes. Provide reassurance that change remains possible.

Psychiatric emergencies

	CAUSE	MANIFESTATION	TREATMENT
Serotonin syndrome	Any drug that ↑ 5-HT. Psychiatric drugs: MAO inhibitors, SSRIs, SNRIs, TCAs, vilazodone, vortioxetine, buspirone Nonpsychiatric drugs: tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan, meperidine, St. John's wort	3 A's: ↑ activity (neuromuscular; eg, clonus, hyperreflexia, hypertonia, tremor, seizure), autonomic instability (eg, hyperthermia, diaphoresis, diarrhea), altered mental status	Benzodiazepines and supportive care; cyproheptadine (5-HT ₂ receptor antagonist) if no improvement Prevention: avoid simultaneous serotonergic drugs, and allow a washout period between them
Hypertensive crisis	Eating tyramine-rich foods (eg, aged cheeses, cured meats, wine, chocolate) while taking MAO inhibitors, insufficient washout period when switching antidepressants to or from MAO inhibitors	Hypertensive crisis (tyramine displaces other neurotransmitters [eg, NE] in the synaptic cleft → ↑ sympathetic stimulation)	Phentolamine
Neuroleptic malignant syndrome	Antipsychotics (typical > atypical) + genetic predisposition	Malignant FEVER: Myoglobinuria, Fever, Encephalopathy, Vitals unstable, ↑ Enzymes (eg, CK), muscle Rigidity ("lead pipe")	Dantrolene, dopaminergics (eg, bromocriptine, amantadine), benzodiazepines; discontinue causative agent
Delirium tremens	Alcohol withdrawal; occurs 2–4 days after last drink Classically seen in hospital setting when inpatient cannot drink	Altered mental status, hallucinations, autonomic hyperactivity, anxiety, seizures, tremors, psychomotor agitation, insomnia, nausea	Longer-acting benzodiazepines
Acute dystonia	Typical antipsychotics, anticonvulsants (eg, carbamazepine), metoclopramide	Sudden onset of muscle spasms, stiffness, and/or oculogyric crisis occurring hours to days after medication use; can lead to laryngospasm requiring intubation	Benztropine or diphenhydramine
Lithium toxicity	↑ lithium dosage, ↓ renal elimination (eg, acute kidney injury), medications affecting clearance (eg, ACE inhibitors, thiazide diuretics, NSAIDs) Narrow therapeutic window	Nausea, vomiting, slurred speech, hyperreflexia, seizures, ataxia, nephrogenic diabetes insipidus	Discontinue lithium, hydrate aggressively with isotonic sodium chloride, consider hemodialysis
Tricyclic antidepressant toxicity	TCA overdose	Respiratory depression, hyperpyrexia, prolonged QT Tricyclic's: convulsions, coma, cardiotoxicity (arrhythmia due to Na ⁺ channel inhibition)	Supportive treatment, monitor ECG, NaHCO ₃ (prevents arrhythmia), activated charcoal

Psychoactive drug intoxication and withdrawal

DRUG	MECHANISM	INTOXICATION	WITHDRAWAL
Depressants			
		Nonspecific: mood elevation, ↓ anxiety, sedation, behavioral disinhibition, respiratory depression.	Nonspecific: anxiety, tremor, seizures, insomnia.
Alcohol	GABA-A receptor positive allosteric modulator.	Emotional lability, slurred speech, ataxia, coma, blackouts. AST value is $2 \times$ ALT value (“ToAST 2 ALcohol”). Treatment: supportive (eg, fluids, antiemetics).	Treatment: longer-acting benzodiazepines.  Alcoholic hallucinosis (usually visual) Withdrawal seizures Tremors, insomnia, diaphoresis, agitation, GI upset Delirium tremens Time from last drink (hours)
Barbiturates	GABA-A receptor positive allosteric modulator.	Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, ↑ BP).	Delirium, life-threatening cardiovascular collapse.
Benzodiazepines	GABA-A receptor positive allosteric modulator.	Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist).	Seizures, sleep disturbance, depression.
Opioids	Opioid receptor modulator.	Activation of μ receptors causes the prototypic effects of pupillary constriction (pinpoint pupils), ↓ GI motility, respiratory and CNS depression, euphoria, ↓ gag reflex, seizures. Most common cause of drug overdose death. Overdose treatment: naloxone.	Dilated pupils, diarrhea, flulike symptoms, rhinorrhea, yawning, nausea, sweating, piloerection (“cold turkey”), lacrimation. Treatment: symptom management, methadone, buprenorphine.
Inhalants	Enhanced GABA signaling.	Disinhibition, euphoria, slurred speech, ataxia, disorientation, drowsiness. Effects often have rapid onset and resolution. Perinasal/perioral rash.	Irritability, dysphoria, sleep disturbance, headache.
Stimulants			
		Nonspecific: mood elevation, ↓ appetite, psychomotor agitation, insomnia, cardiac arrhythmias, tachycardia, anxiety.	Nonspecific: post-use “crash,” including depression, lethargy, ↑ appetite, sleep disturbance, vivid nightmares.
Amphetamines	Induces reversal of monoamine transporters (VMAT, DAT, SERT, NET), ↑ neurotransmitter release.	Euphoria, grandiosity, mydriasis, prolonged wakefulness, hyperalertness, hypertension, paranoia, fever. Skin excoriations with methamphetamine use. Severe: cardiac arrest, seizures. Treatment: benzodiazepines for agitation and seizures.	Meth mites

Psychoactive drug intoxication and withdrawal (continued)

DRUG	MECHANISM	INTOXICATION	WITHDRAWAL
Caffeine	Adenosine receptor antagonist.	Palpitation, agitation, tremor, insomnia.	Headache, difficulty concentrating, flu-like symptoms.
Cocaine	Blocks reuptake of dopamine (DAT), serotonin (SERT), and norepinephrine (NET) transporters.	Impaired judgment, pupillary dilation, diaphoresis, hallucinations (including formication), paranoia, angina, sudden cardiac death. Chronic use may lead to perforated nasal septum due to vasoconstriction and resulting ischemic necrosis. Treatment: benzodiazepines.	Restlessness, hunger, severe depression, sleep disturbance.
Nicotine	Stimulates central nicotinic acetylcholine receptors.	Restlessness.	Irritability, anxiety, restlessness, ↓ concentration, ↑ appetite/weight. Treatment: nicotine replacement therapy (eg, patch, gum, lozenge); bupropion/varenicline.
Hallucinogens			
Lysergic acid diethylamide	5-HT _{2A} receptor agonist.	Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, flashbacks (usually nondisturbing), mydriasis.	
Cannabis/cannabinoids	CB1 receptor agonist.	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations.	Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite.
MDMA	Induces reversal of transporters for monoamines (SERT > DAT, NET), increasing their neurotransmitter release.	Also called ecstasy. Euphoria, hallucinations, disinhibition, hyperactivity, ↑ thirst, bruxism, distorted sensory and time perception, mydriasis. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.	Depression, fatigue, change in appetite, difficulty concentrating, anxiety.
Phencyclidine	NMDA receptor antagonist.	Violence, nystagmus, impulsivity, psychomotor agitation, tachycardia, hypertension, analgesia, psychosis, delirium, seizures.	

Alcohol use disorder	Diagnosed using criteria for substance use disorder. Complications: vitamin B ₁ (thiamine) deficiency, alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy. Treatment: naltrexone (reduces cravings; avoid in liver failure), acamprosate (contraindicated in renal failure), disulfiram (to condition the patient to abstain from alcohol use). Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.
Wernicke-Korsakoff syndrome	Results from vitamin B ₁ deficiency. Symptoms can be precipitated by administering dextrose before vitamin B ₁ . Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome). Treatment: IV vitamin B ₁ (before dextrose).

► PSYCHIATRY—PHARMACOLOGY

Psychotherapy

Behavioral therapy	Teaches patients how to identify and change maladaptive behaviors or reactions to stimuli (eg, systematic desensitization for specific phobia).
Cognitive behavioral therapy	Teaches patients to recognize distortions in their thought processes, develop constructive coping skills, and ↓ maladaptive coping behaviors → greater emotional control and tolerance of distress (eg, recognizing triggers for alcohol consumption).
Dialectical behavioral therapy	Designed for use in borderline personality disorder, but can be used in other psychiatric conditions as well (eg, depression).
Interpersonal therapy	Focused on improving interpersonal relationships and communication skills.
Motivational interviewing	Enhances intrinsic motivation to change by exploring and resolving ambivalence. Used in substance use disorder and weight loss.
Supportive therapy	Utilizes empathy to help individuals during a time of hardship to maintain optimism or hope.

Preferred medications for selected psychiatric conditions

PSYCHIATRIC CONDITION	PREFERRED DRUGS
ADHD	Stimulants
Alcohol withdrawal	Benzodiazepines
Bipolar disorder	Carbamazepine, atypical antipsychotics, lithium, lamotrigine, valproate. Character a little less variable
Bulimia nervosa	SSRIs
Depression	SSRIs
Generalized anxiety disorder	SSRIs, SNRIs
Obsessive-compulsive disorder	SSRIs, venlafaxine, clomipramine
Panic disorder	SSRIs, venlafaxine, benzodiazepines
PTSD	SSRIs, venlafaxine, prazosin (for nightmares)
Schizophrenia	Atypical antipsychotics
Social anxiety disorder	SSRIs, venlafaxine
Tourette syndrome	Performance only: β-blockers, benzodiazepines Antipsychotics

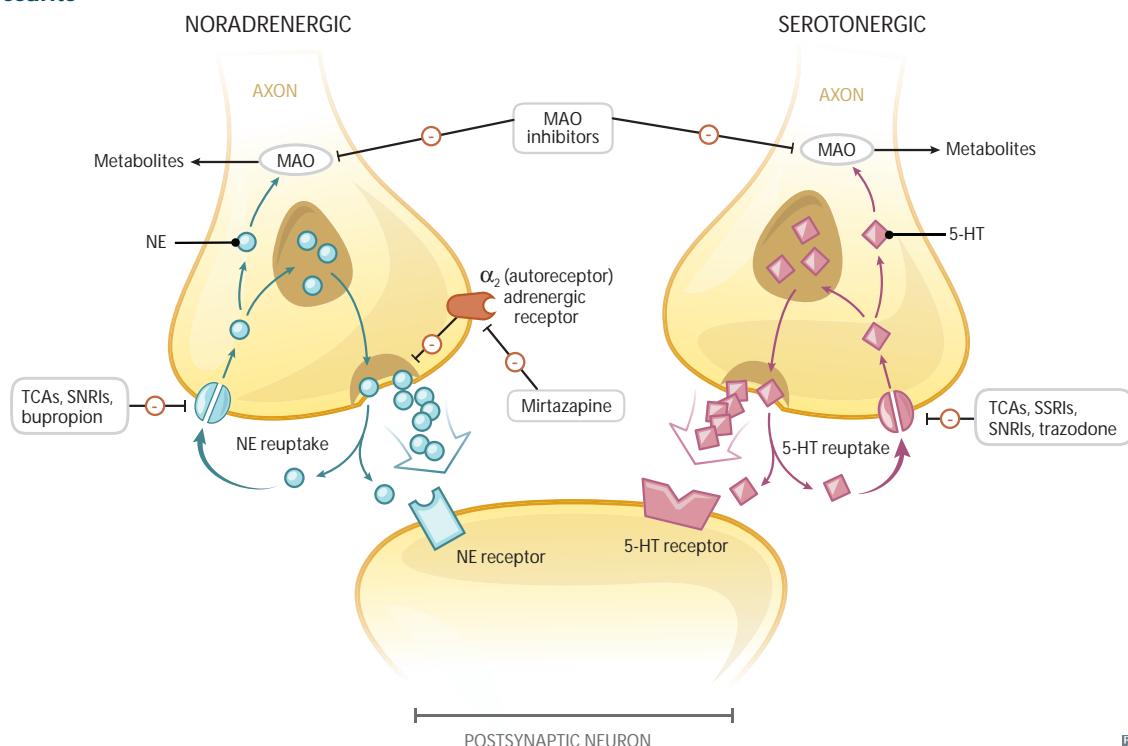
Central nervous system Methylphenidate
stimulants

Lithium

MECHANISM	Affects neurotransmission (\downarrow excitatory, \uparrow inhibitory) and second messenger systems (eg, G proteins).	LiTHIUM: Low Thyroid (hypothyroidism) Heart (Ebstein anomaly) Insipidus (nephrogenic diabetes insipidus) Unwanted Movements (tremor)
CLINICAL USE	Mood stabilizer for bipolar disorder; treats acute manic episodes and prevents relapse.	
ADVERSE EFFECTS	Tremor, hypothyroidism, hyperthyroidism, mild hypercalcemia, polyuria (causes nephrogenic diabetes insipidus), teratogenesis (causes Ebstein anomaly). Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT via Na^+ channels. Thiazides, ACE inhibitors, NSAIDs, and other drugs affecting clearance are implicated in lithium toxicity.	

Buspirone

MECHANISM	Partial 5-HT _{1A} receptor agonist.	I get anxious if the bus doesn't arrive at one , so I take buspirone .
CLINICAL USE	Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Begins to take effect after 1–2 weeks. Does not interact with alcohol (vs barbiturates, benzodiazepines).	

Antidepressants

Selective serotonin reuptake inhibitors	Fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram.	
MECHANISM	Inhibit 5-HT reuptake.	It normally takes 4–8 weeks for antidepressants to show appreciable effect.
CLINICAL USE	Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, binge-eating disorder, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.	
ADVERSE EFFECTS	Fewer than TCAs. Serotonin syndrome, GI distress, SIADH, sexual dysfunction (anorgasmia, erectile dysfunction, ↓ libido), mania precipitation if underlying bipolar disorder.	
Serotonin-norepinephrine reuptake inhibitors	Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.	
MECHANISM	Inhibit 5-HT and NE reuptake.	
CLINICAL USE	Depression, generalized anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine and milnacipran are also indicated for fibromyalgia.	
ADVERSE EFFECTS	↑ BP, stimulant effects, sedation, sexual dysfunction, nausea.	
Tricyclic antidepressants	Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine.	
MECHANISM	TCAs inhibit 5-HT and NE reuptake.	
CLINICAL USE	MDD, peripheral neuropathy, chronic neuropathic pain, migraine prophylaxis, OCD (clomipramine), nocturnal enuresis (imipramine).	
ADVERSE EFFECTS	Sedation, α_1 -blocking effects including postural hypotension, and atropine-like (anticholinergic) adverse effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval. Tri-CyClic's: Convulsions, Coma, Cardiotoxicity (arrhythmia due to Na^+ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations are more common in older adults due to anticholinergic adverse effects (2° amines [eg, nortriptyline] better tolerated). Treatment: NaHCO_3 to prevent arrhythmia.	
Monoamine oxidase inhibitors	Tranylcypromine, phenelzine, isocarboxazid, selegiline (selective MAO-B inhibitor). (MAO takes pride in Shanghai).	
MECHANISM	Nonselective MAO inhibition → ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).	
CLINICAL USE	Atypical depression, anxiety. Parkinson disease (selegiline).	
ADVERSE EFFECTS	CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan, pseudoephedrine, linezolid (to avoid precipitating serotonin syndrome). Wait 2 weeks after stopping MAO inhibitors before starting serotonergic drugs or stopping dietary restrictions.	

Atypical antidepressants

Bupropion	Inhibits NE and DA reuptake. Also used for smoking cessation. Adverse effects: stimulant effects (tachycardia, insomnia), headache, seizures in patients with bulimia and anorexia nervosa. ↓ risk of sexual adverse effects and weight gain compared to other antidepressants.
Mirtazapine	α_2 -antagonist (↑ release of NE and 5-HT), potent 5-HT ₂ and 5-HT ₃ receptor antagonist, and H ₁ antagonist. Adverse effects: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in underweight patients), dry mouth.
Trazodone	Primarily blocks 5-HT ₂ , α ₁ -adrenergic, and H ₁ receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Adverse effects: sedation, nausea, priapism, postural hypotension. Think traZZZobone due to sedative and male-specific adverse effects.
Vilazodone	Inhibits 5-HT reuptake; 5-HT _{1A} receptor partial agonist. Used for MDD. Adverse effects: headache, diarrhea, nausea, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.
Vortioxetine	Inhibits 5-HT reuptake; 5-HT _{1A} receptor agonist and 5-HT ₃ receptor antagonist. Used for MDD. Adverse effects: nausea, sexual dysfunction, sleep disturbances, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.

Pharmacotherapies for smoking cessation

Nicotine replacement therapy	Binds to nicotinic ACh receptors. Aim to relieve withdrawal symptoms upon stopping smoking. Long-acting patch and short-acting products (ie, gum, lozenge) can be used in combination. Adverse effects: headache, oral irritation.
Varenicline	Nicotinic ACh receptor partial agonist. Diminishes effect on reward system, but also reduces withdrawal. Adverse effects: GI discomfort, sleep disturbance. Varenicline helps nicotine cravings decline.
Medically supervised opioid withdrawal and relapse prevention	Injection drug use ↑ risk for HBV, HCV, HIV, skin and soft tissue infections, bacteremia, right-sided infective endocarditis.
Methadone	Long-acting oral opioid used for medically supervised opioid (eg, heroin) withdrawal or long-term maintenance therapy.
Buprenorphine	Partial opioid agonist. Sublingual form (film) used to suppress withdrawal and for maintenance therapy. Partial agonists can precipitate withdrawal symptoms in opioid-dependent individuals or when administered shortly after use of a full agonist.
Naloxone	Short-acting opioid antagonist given IM, IV, or as a nasal spray to treat acute opioid overdose, particularly to reverse respiratory and CNS depression.
Naltrexone	Long-acting oral opioid antagonist used after detoxification to prevent relapse. May help alcohol and nicotine cessation, weight loss. Use naltrexone for the long trex back to sobriety.

Renal

“But I know all about love already. I know precious little still about kidneys.”

—Aldous Huxley, *Antic Hay*

“This too shall pass. Just like a kidney stone.”

—Hunter Madsen

“Playing dead is difficult with a full bladder.”

—Diane Lane

► Embryology	598
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Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), acute and chronic kidney disease, urine casts, diuretics, ACE inhibitors, and AT II receptor blockers. Renal anomalies associated with various congenital defects are also high-yield associations to think about when evaluating pediatric vignettes.

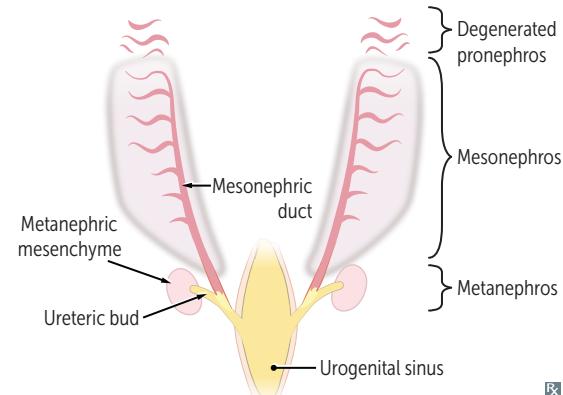
▶ RENAL—EMBRYOLOGY

Kidney embryology

Pronephros—week 4 of development; then degenerates.
 Mesonephros—week 4 of development; functions as interim kidney for 1st trimester; persists in the male genital system as Wolffian duct, forming ductus deferens and epididymis.
 Metanephros—permanent; first appears in week 5 of development; nephrogenesis is normally completed by week 36 of gestation.

- Ureteric bud (metanephric diverticulum)—derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by week 10 of development
- Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
- Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)

Ureteropelvic junction—last to canalize
 → congenital obstruction. Can be unilateral or bilateral. Most common pathologic cause of prenatal hydronephrosis. Detected by prenatal ultrasound.



Rx

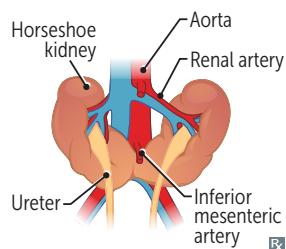
Potter sequence

Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (eg, low-set ears and retrognathia, flattened nose A), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).
 Caused by chronic placental insufficiency or reduced renal output, including ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis.

Babies who can't "Pee" in utero develop Potter sequence.

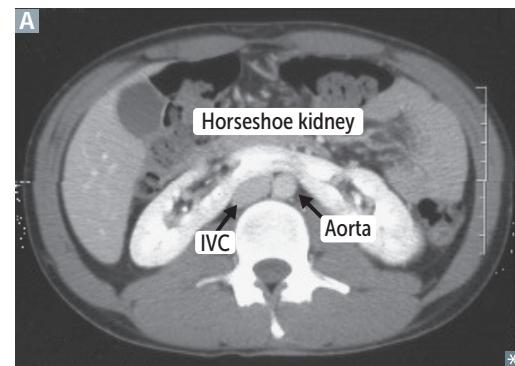
POTTER sequence associated with:

- Pulmonary hypoplasia
- Oligohydramnios (trigger)
- Twisted face
- Twisted skin
- Extremity defects
- Renal failure (in utero)

Horseshoe kidney

Inferior poles of both kidneys fuse abnormally **A**. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys can function normally, but associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, ↑ risk of renal cancer.

Higher incidence in chromosomal aneuploidy (eg, Turner syndrome, trisomies 13, 18, 21).

**Congenital solitary functioning kidney**

Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound.

Unilateral renal agenesis

Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.

Multicystic dysplastic kidney

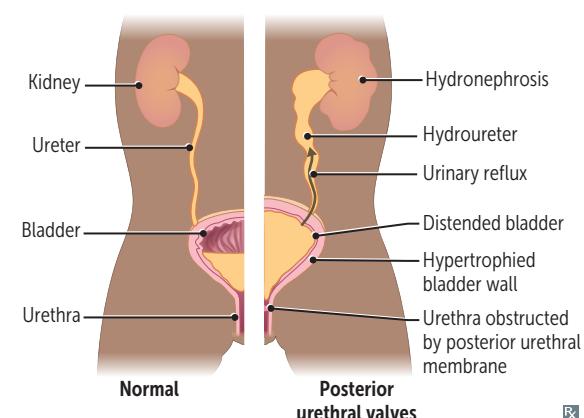
Ureteric bud develops, but fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Predominantly nonhereditary and usually unilateral; bilateral leads to Potter sequence.

Duplex collecting system

Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs. Frequently presents with hydronephrosis.

Posterior urethral valves

Membrane remnant in posterior (prostatic) urethra in males; its persistence can lead to urethral obstruction. Diagnosed prenatally by bilateral hydronephrosis and dilated or thick-walled bladder on ultrasound. Severe obstruction in fetus associated with oligohydramnios. Most common cause of bladder outlet obstruction in male infants.

**Vesicoureteral reflux**

Retrograde flow of urine from bladder toward upper urinary tract. Can be 1° due to abnormal/insufficient insertion of the ureter within the vesicular wall (ureterovesical junction [UVJ]) or 2° due to abnormally high bladder pressure resulting in retrograde flow via the UVJ. ↑ risk of recurrent UTIs.

Renal clearance

$C_x = (U_x V) / P_x$ = volume of plasma from which the substance is completely cleared in the urine per unit time.

If $C_x < \text{GFR}$: net tubular reabsorption and/or not freely filtered.

If $C_x > \text{GFR}$: net tubular secretion of X.

If $C_x = \text{GFR}$: no net secretion or reabsorption.

C_x = clearance of X (mL/min).

U_x = urine concentration of X (eg, mg/mL).

P_x = plasma concentration of X (eg, mg/mL).

V = urine flow rate (mL/min).

Glomerular filtration rate

Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

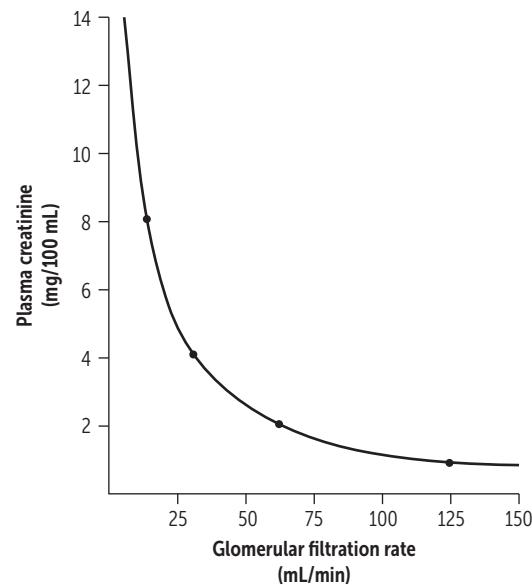
$$C_{\text{inulin}} = \text{GFR} = U_{\text{inulin}} \times V / P_{\text{inulin}}$$

$$= K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})]$$

(P_{GC} = glomerular capillary hydrostatic pressure; P_{BS} = Bowman space hydrostatic pressure; π_{GC} = glomerular capillary oncotic pressure; π_{BS} = Bowman space oncotic pressure; π_{BS} normally equals zero; K_f = filtration coefficient).

Normal GFR ≈ 100 mL/min.

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.

**Renal blood flow autoregulation**

Autoregulatory mechanisms help maintain a constant RBF and GFR to protect the kidney from rapid increases or decreases in renal perfusion pressure that could cause renal injury or decrease glomerular filtration. Mechanisms:

Myogenic: \uparrow arterial pressure \rightarrow stretch of afferent arteriole \rightarrow mechanical activation of vascular smooth muscle \rightarrow vasoconstriction of afferent arteriole \rightarrow \downarrow RBF.

Tubuloglomerular: \uparrow NaCl or tonicity of the filtrate sensed by macula densa cells \rightarrow paracrine-driven vasoconstriction of afferent arteriole \rightarrow \downarrow RBF.

Effective renal plasma flow

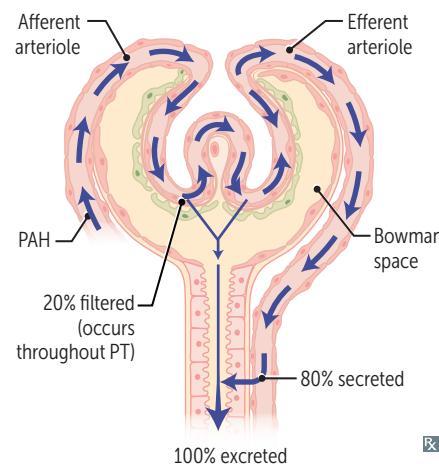
Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly complete excretion of all PAH that enters the kidney.

$$\text{eRPF} = U_{\text{PAH}} \times V / P_{\text{PAH}} = C_{\text{PAH}}$$

Renal blood flow (RBF) = RPF/(1 - Hct).

Usually 20–25% of cardiac output.

eRPF underestimates true renal plasma flow (RPF) slightly.



Filtration

Filtration fraction (FF) = GFR/RPF.

Normal FF = 20%.

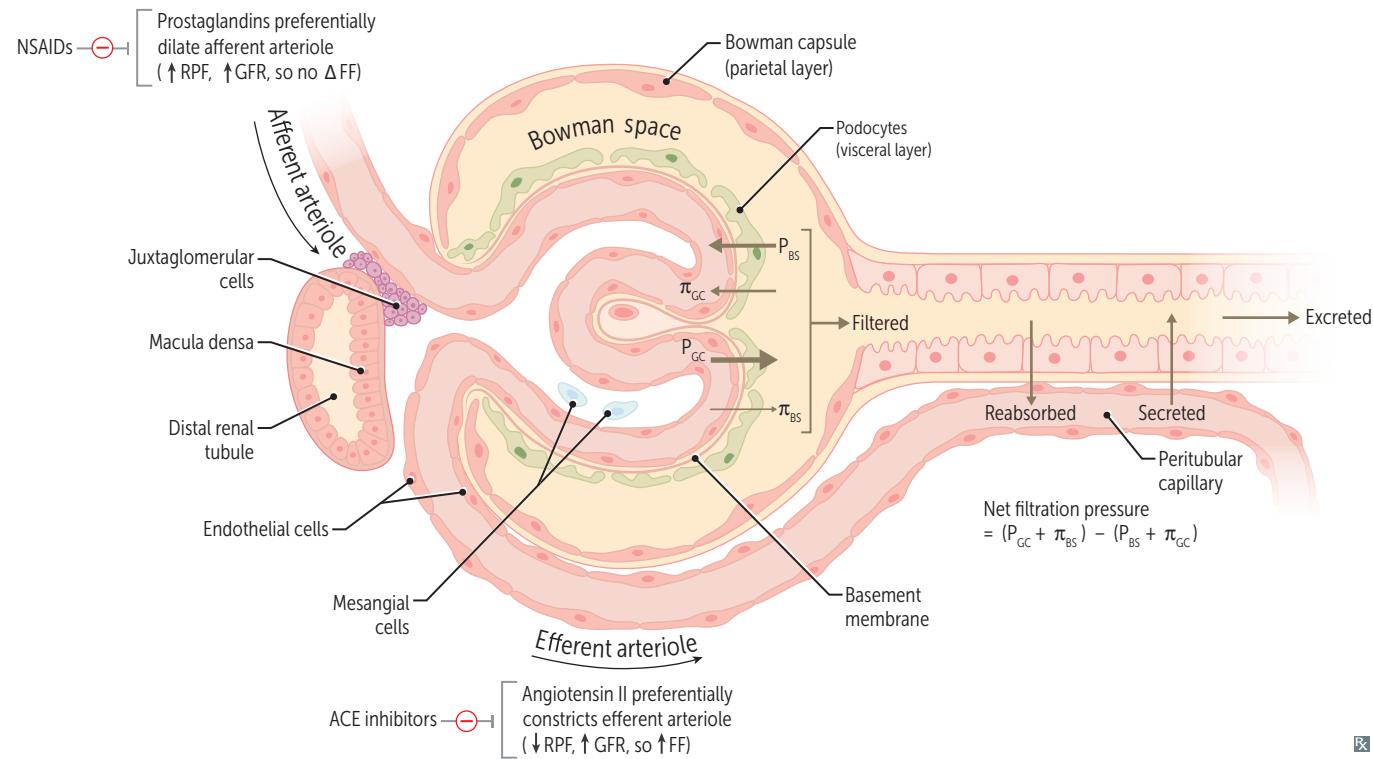
Filtered load (mg/min) = GFR (mL/min)
× plasma concentration (mg/mL).

GFR can be estimated with creatinine clearance.

RPF is best estimated with PAH clearance.

Prostaglandins Dilate Afferent arteriole (PDA).

Angiotensin II Constricts Efferent arteriole (ACE).

**Changes in glomerular dynamics**

	GFR	RPF	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	—
Efferent arteriole constriction	↑	↓	↑
↑ plasma protein concentration	↓	—	↓
↓ plasma protein concentration	↑	—	↑
Constriction of ureter	↓	—	↓
Dehydration	↓	↓↓	↑

Calculation of reabsorption and secretion rate

Filtered load = GFR × P_x .

Excretion rate = $V \times U_x$.

Reabsorption rate = filtered – excreted.

Secretion rate = excreted – filtered.

$F_{e_{Na}}$ = fractional excretion of sodium.

$$F_{e_{Na}} = \frac{\text{Na}^+ \text{ excreted}}{\text{Na}^+ \text{ filtered}} = \frac{V \times U_{Na}}{\text{GFR} \times P_{Na}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}} \text{ where GFR} = \frac{U_{Cr} \times V}{P_{Cr}}$$

Glucose clearance

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na^+ /glucose cotransport.

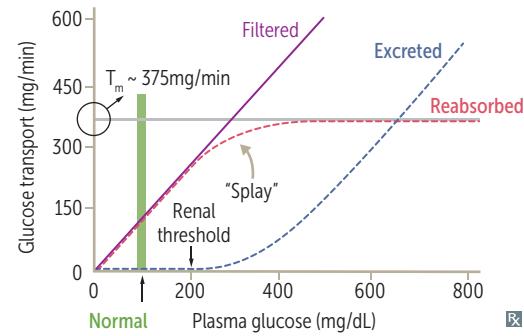
In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (T_m).

Normal pregnancy is associated with ↑ GFR. With ↑ filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations → glucosuria at normal plasma glucose levels.

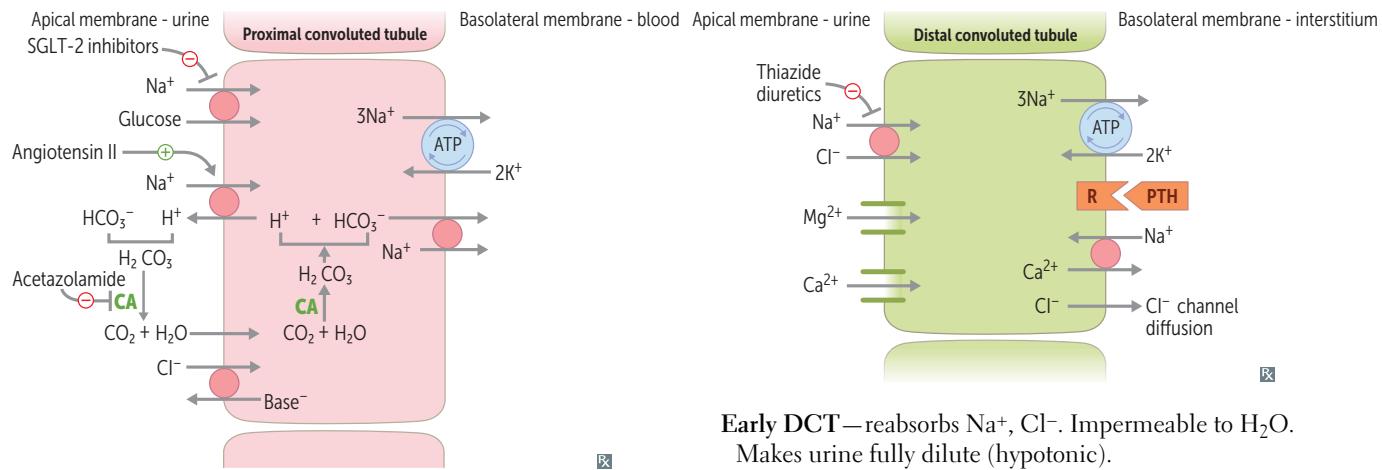
Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -floxin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay phenomenon— T_m for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different T_m points); represented by the portion of the titration curve between threshold and T_m .



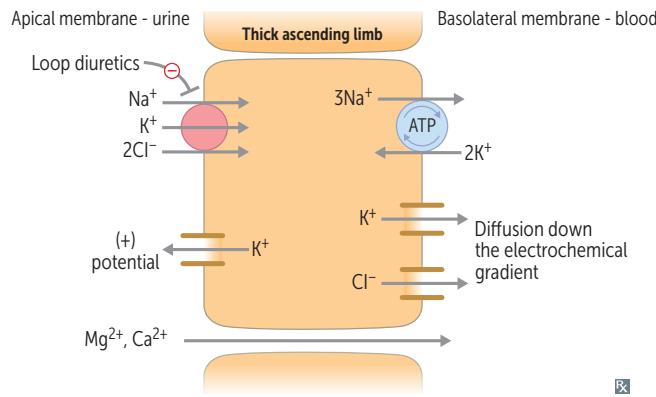
Nephron transport physiology



Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO₃⁻, Na⁺, Cl⁻, PO₄³⁻, K⁺, H₂O, and uric acid. Isotonic absorption. Generates and secretes NH₃, which enables the kidney to secrete more H⁺.

PTH—inhibits Na⁺/PO₄³⁻ cotransport PO₄³⁻ excretion.
AT II—stimulates Na⁺/H⁺ exchange Na⁺, H₂O, and HCO₃⁻ reabsorption (permitting contraction alkalosis).
65–80% Na⁺ and H₂O reabsorbed.

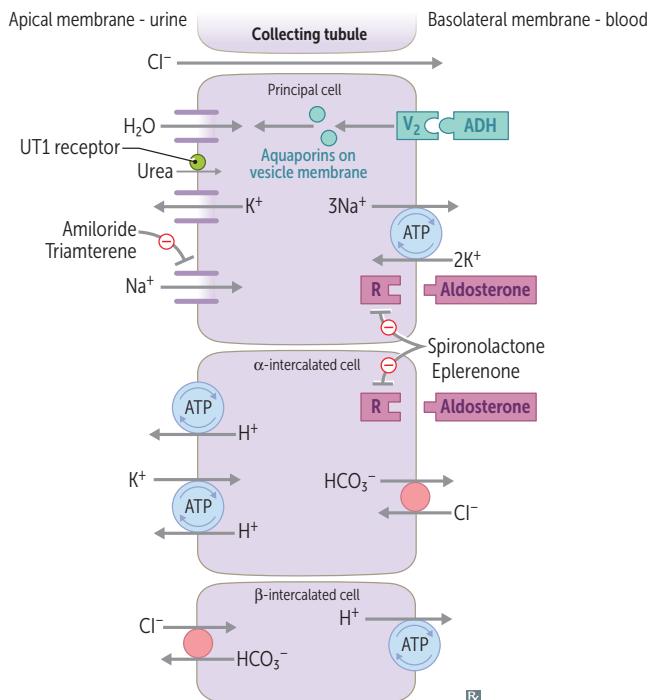
Thin descending loop of Henle—passively reabsorbs H₂O via medullary hypertonicity (impermeable to Na⁺). Concentrating segment. Makes urine hypertonic.



Thick ascending loop of Henle—reabsorbs Na⁺, K⁺, and Cl⁻. Indirectly induces paracellular reabsorption of Mg²⁺ and Ca²⁺ through + lumen potential generated by K⁺ backleak. Impermeable to H₂O. Makes urine less concentrated as it ascends.
10–20% Na⁺ reabsorbed.

Early DCT—reabsorbs Na⁺, Cl⁻. Impermeable to H₂O. Makes urine fully dilute (hypotonic).

PTH—Ca²⁺/Na⁺ exchange Ca²⁺ reabsorption.
5–10% Na⁺ reabsorbed.

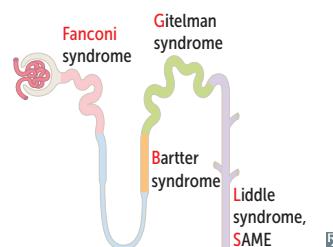


Collecting tubule—reabsorbs Na⁺ in exchange for secreting K⁺ and H⁺ (regulated by aldosterone).

Aldosterone—acts on mineralocorticoid receptor mRNA protein synthesis. In principal cells: apical K⁺ conductance, Na⁺/K⁺ pump, epithelial Na⁺ channel (ENaC) activity lumen negativity K⁺ secretion. In α-intercalated cells: lumen negativity H⁺ ATPase activity H⁺ secretion HCO₃⁻/Cl⁻ exchanger activity.

ADH—acts at V₂ receptor insertion of aquaporin H₂O channels on apical side.
3–5% Na⁺ reabsorbed.

Renal tubular defects Order: Fanconi's BaGeLS



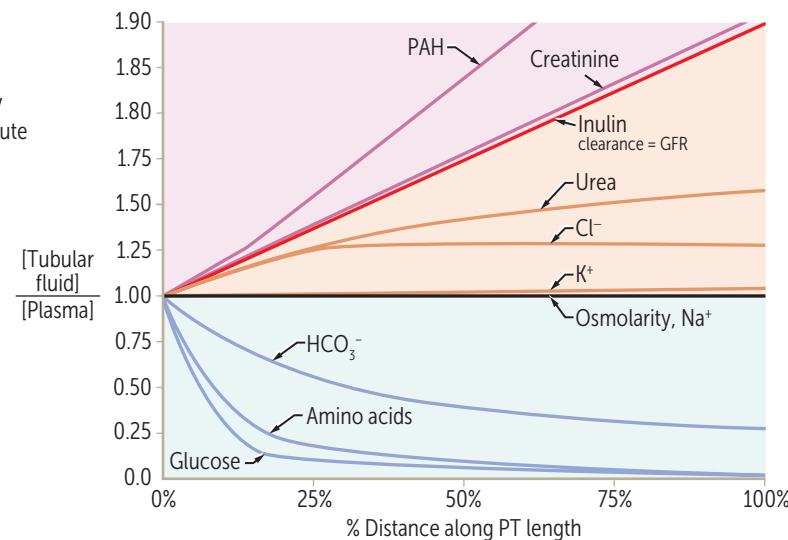
	DEFECTS	EFFECTS	CAUSES	NOTES
Fanconi syndrome	Generalized reabsorption defect in PCT → ↑ excretion of amino acids, glucose, HCO_3^- , and PO_4^{3-} , and all substances reabsorbed by the PCT	Metabolic acidosis (proximal RTA), hypophosphatemia, hypokalemia	Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, drugs (eg, ifosfamide, cisplatin, tenofovir, lead poisoning)	Growth retardation and rickets/osteopenia common due to hypophosphatemia Volume depletion also common
Bartter syndrome	Reabsorption defect in thick ascending loop of Henle (affects $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ cotransporter)	Metabolic alkalosis, hypokalemia, hypercalciuria	Autosomal recessive	Presents similarly to chronic loop diuretic use
Gitelman syndrome	Reabsorption defect of NaCl in DCT	Metabolic alkalosis, hypomagnesemia, hypokalemia, hypocalciuria	Autosomal recessive	Presents similarly to chronic thiazide diuretic use Less severe than Bartter syndrome
Liddle syndrome	Gain of function mutation → ↓ Na^+ channel degradation → ↑ Na^+ reabsorption in collecting tubules	Metabolic alkalosis, hypokalemia, hypertension, ↓ aldosterone	Autosomal dominant	Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable Treatment: amiloride
Syndrome of Apparent Mineralocorticoid Excess	Cortisol activates mineralocorticoid receptors; 11β -HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11β -HSD deficiency → ↑ cortisol → ↑ mineralocorticoid receptor activity	Metabolic alkalosis, hypokalemia, hypertension ↓ serum aldosterone level; cortisol tries to be the SAME as aldosterone	Autosomal recessive Can acquire disorder from glycyrrhetic acid (present in licorice), which blocks activity of 11β -hydroxysteroid dehydrogenase	Treatment: K^+ -sparing diuretics (↓ mineralocorticoid effects) or corticosteroids (exogenous corticosteroid ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation)

Relative concentrations along proximal tubule

$[TF/P] > 1$
when solute is
reabsorbed less quickly
than water or when solute
is secreted

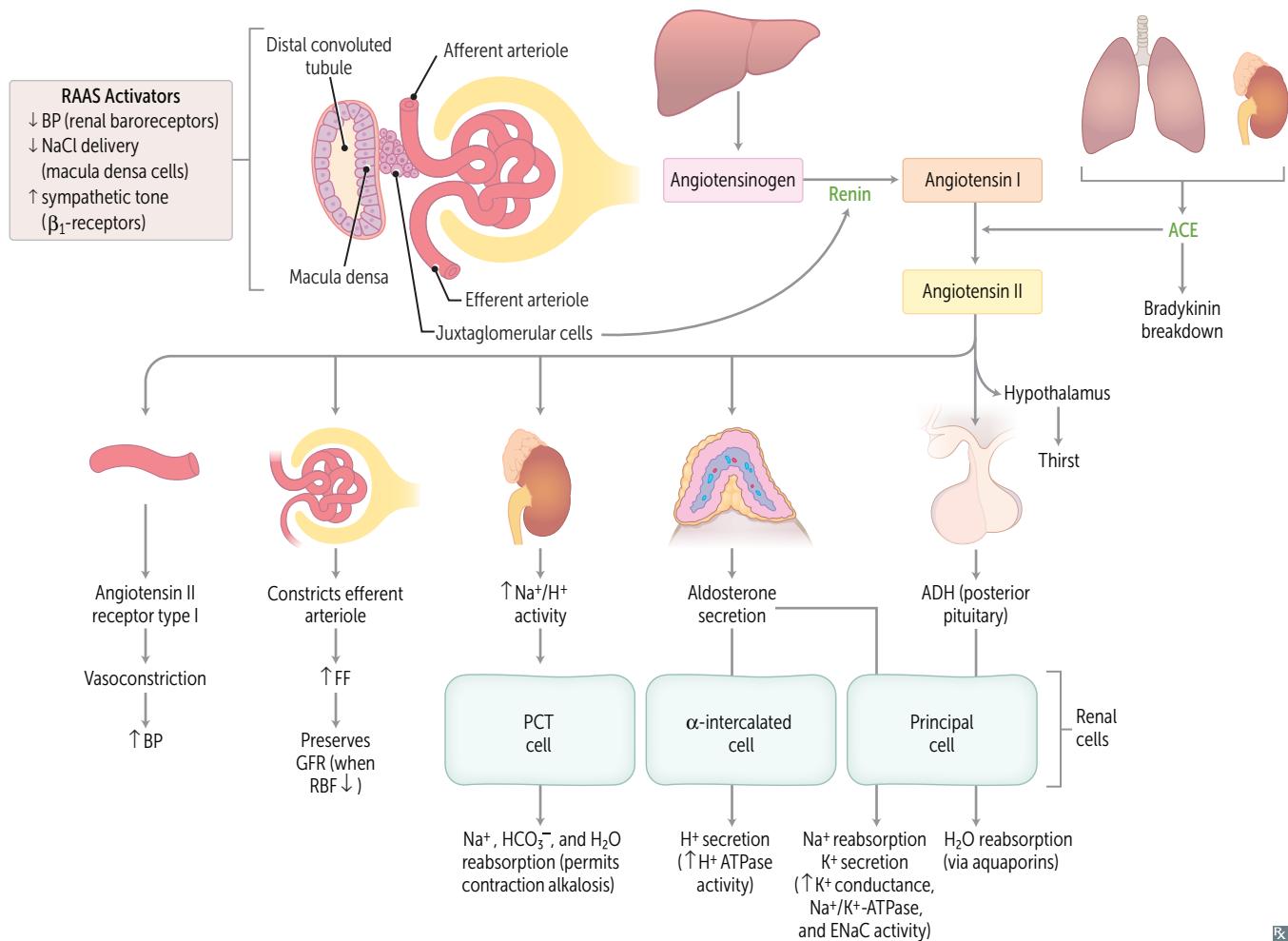
$[TF/P] = 1$
when solute
and water are
reabsorbed at the
same rate

$[TF/P] < 1$
when solute
is reabsorbed more
quickly than water



Tubular inulin ↑ in concentration (but not amount) along the PT as a result of water reabsorption. Cl^- reabsorption occurs at a slower rate than Na^+ in early PCT and then matches the rate of Na^+ reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.

Renin-angiotensin-aldosterone system



Renin	Secreted by JG cells in response to ↓ renal perfusion pressure (detected in afferent arteriole), ↑ renal sympathetic discharge (β_1 effect), and ↓ NaCl delivery to macula densa cells.
ACE	Catalyzes conversion of angiotensin I to angiotensin II. Located in many tissues but conversion occurs most extensively in the lung. Produced by vascular endothelial cells in the lung.
AT II	Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.
ANP, BNP	Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; inhibits renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin. Dilates afferent arteriole, promotes natriuresis.
ADH (vasopressin)	Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient.
Aldosterone	Primarily regulates ECF volume and Na^+ content; ↑ release in hypovolemic states. Responds to hyperkalemia by ↑ K^+ excretion.

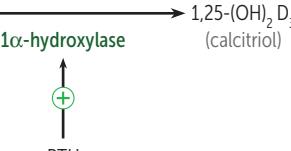
Juxtaglomerular apparatus

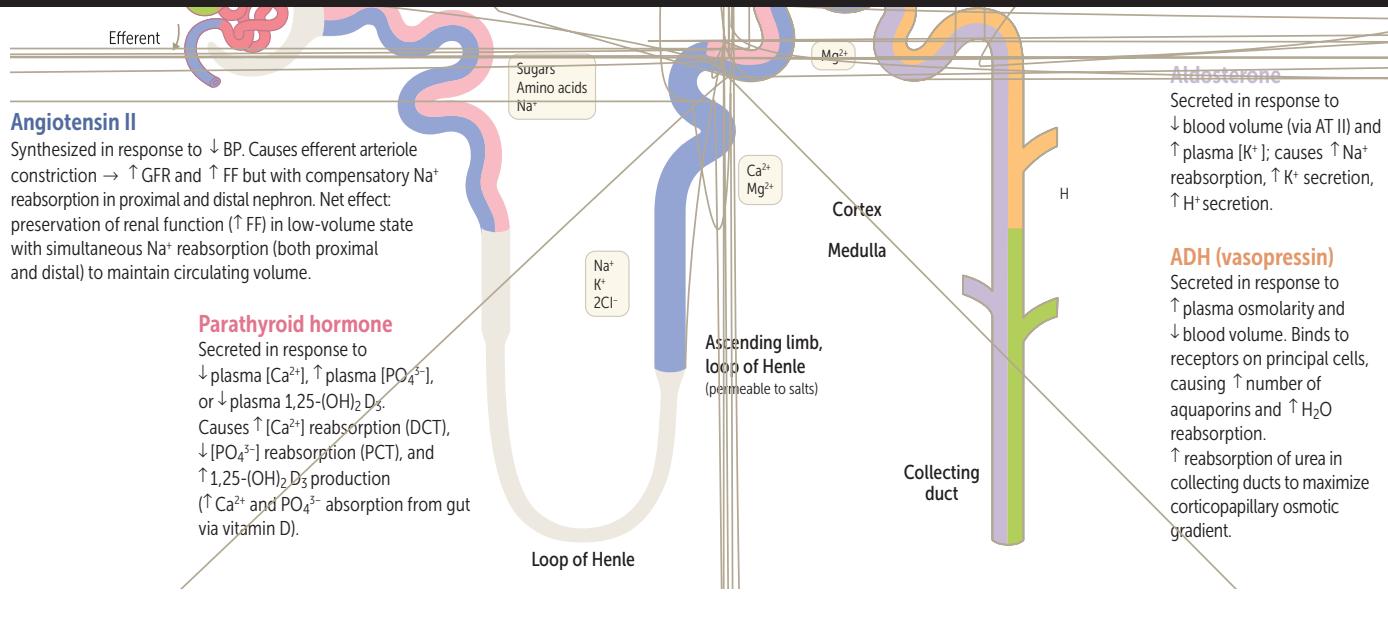
Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole), and the macula densa (NaCl sensor located at the DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone (β_1). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR.

JGA maintains GFR via renin-angiotensin-aldosterone system.

β -blockers ↓ BP by ↓ CO and inhibiting β_1 -receptors of the JGA → ↓ renin release.

Kidney hormone functions

Erythropoietin	Released by interstitial cells in peritubular capillary bed in response to hypoxia.	Stimulates RBC proliferation in bone marrow. Administered for anemia secondary to chronic kidney disease. ↑ risk of HTN.
Calciferol (vitamin D)	PCT cells convert 25-OH vitamin D ₃ to 1,25-(OH) ₂ vitamin D ₃ (calcitriol, active form). Increases calcium absorption in small bowel.	$\text{25-OH D}_3 \xrightarrow{\text{1}\alpha\text{-hydroxylase}} \text{1},25\text{-(OH)}_2 \text{D}_3$ 
Prostaglandins	Paracrine secretion vasodilates afferent arterioles to ↑ RBF.	NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute kidney injury in low renal blood flow states.
Dopamine	Secreted by PT cells, promotes natriuresis. At low doses; dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses; acts as vasoconstrictor.	



Electrolyte disturbances

ELECTROLYTE	LOW SERUM CONCENTRATION	HIGH SERUM CONCENTRATION
Sodium	Nausea, malaise, stupor, coma, seizures	Irritability, stupor, coma
Potassium	U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness	Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness
Calcium	Tetany, seizures, QT prolongation, twitching (eg, Chvostek sign), spasm (eg, Trousseau sign)	Stones (renal), bones (pain), groans (abdominal pain), thrones (↑ urinary frequency), psychiatric overtones (anxiety, altered mental status)
Magnesium	Tetany, torsades de pointes, hypokalemia, hypocalcemia (when $[Mg^{2+}] < 1.0 \text{ mEq/L}$)	↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia
Phosphate	Bone loss, osteomalacia (adults), rickets (children)	Renal stones, metastatic calcifications, hypocalcemia

Features of renal disorders

CONDITION	BLOOD PRESSURE	PLASMA RENIN	ALDOSTERONE	SERUM Mg^{2+}	URINE Ca^{2+}
SIADH	—/↑	↓	↓	—	—
Primary hyperaldosteronism	↑	↓	↑	—	—
Renin-secreting tumor	↑	↑	↑	—	—
Bartter syndrome	—	↑	↑	—	↑
Gitelman syndrome	—	↑	↑	↓	↓
Liddle syndrome, syndrome of apparent mineralocorticoid excess	↑	↓	↓	—	—

↑ ↓ = important differentiating feature.

Acid-base physiology Metabolic acid-base disorders cause HCO_3^- alterations. Respiratory acid-base disorders cause PCO_2 alterations.

	pH	PCO_2	$[\text{HCO}_3^-]$	COMPENSATORY RESPONSE
Metabolic acidosis	↓	↓	↓	Hyperventilation (immediate)
Metabolic alkalosis	↑	↑	↑	Hypoventilation (immediate)
Respiratory acidosis	↓	↑	↑	↑ renal $[\text{HCO}_3^-]$ reabsorption (delayed)
Respiratory alkalosis	↑	↓	↓	↓ renal $[\text{HCO}_3^-]$ reabsorption (delayed)

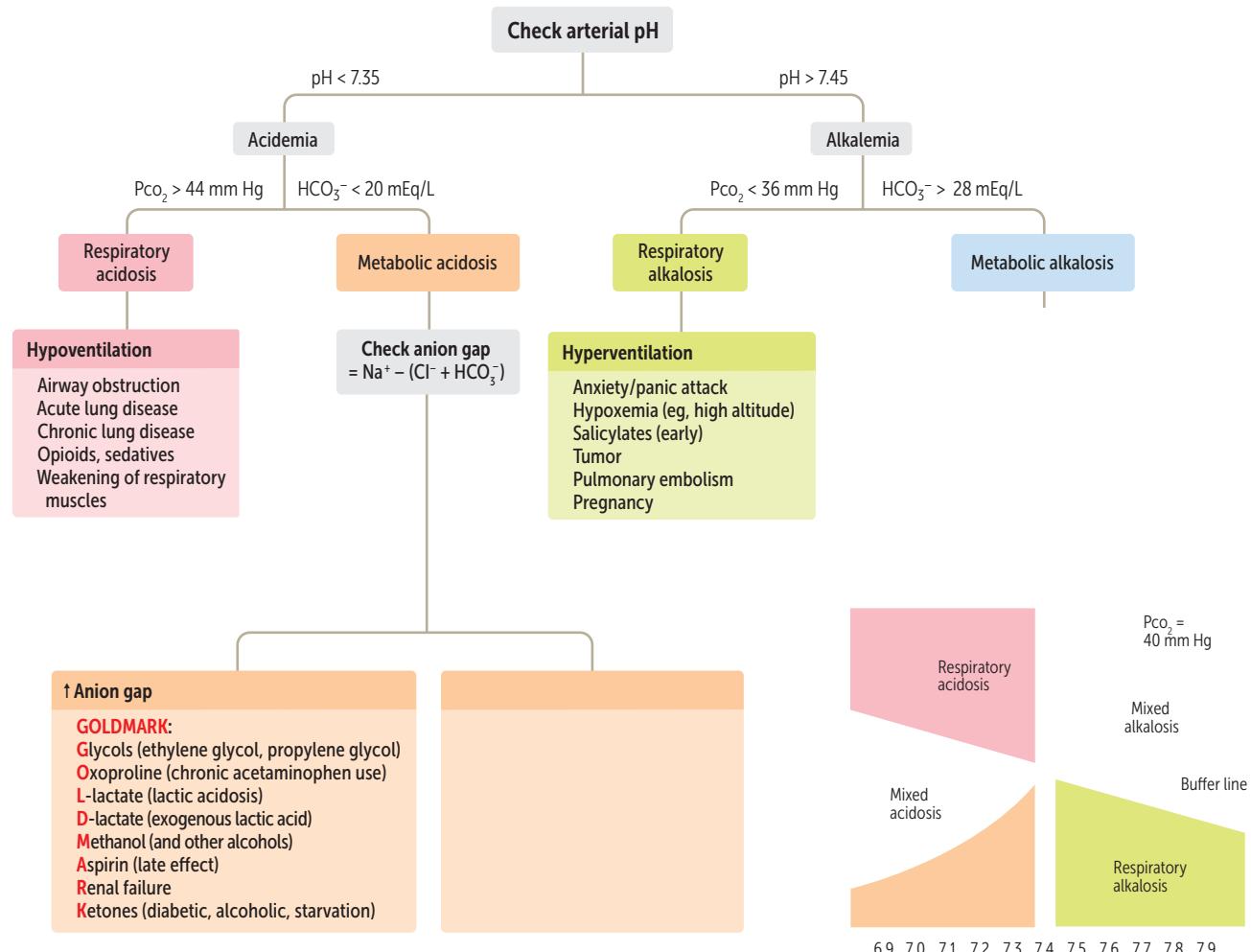
Key: ↓ ↑ = compensatory response.

$$\text{Henderson-Hasselbalch equation: } \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ PCO}_2}$$

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured $\text{PCO}_2 >$ predicted $\text{PCO}_2 \rightarrow$ concomitant respiratory acidosis; if measured $\text{PCO}_2 <$ predicted $\text{PCO}_2 \rightarrow$ concomitant respiratory alkalosis:

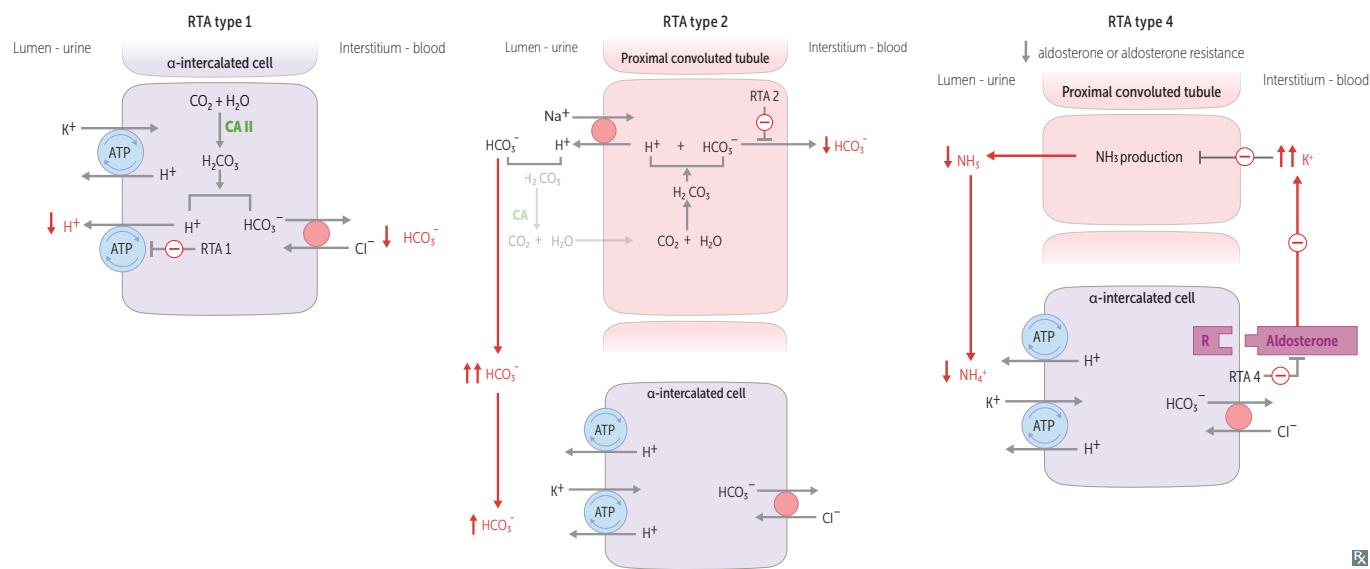
$$\text{PCO}_2 = 1.5 [\text{HCO}_3^-] + 8 \pm 2$$

Acidosis and alkalosis



Renal tubular acidosis

	Distal renal tubular acidosis (RTA type 1)	Proximal renal tubular acidosis (RTA type 2)	Hyperkalemic tubular acidosis (RTA type 4)
DEFECT	Inability of α -intercalated cells to secrete H^+ → no new HCO_3^- is generated → metabolic acidosis	Defect in PCT HCO_3^- reabsorption → ↑ excretion of HCO_3^- in urine → metabolic acidosis Urine can be acidified by α -intercalated cells in collecting duct, but not enough to overcome ↑ HCO_3^- excretion	Hypoaldosteronism or aldosterone resistance; hyperkalemia → ↓ NH_3 synthesis in PCT → ↓ NH_4^+ excretion
URINE pH	> 5.5	< 5.5 when plasma HCO_3^- below reduced resorption threshold > 5.5 when filtered HCO_3^- exceeds resptive threshold	< 5.5 (or variable)
SERUM K^+	↓	↓	↑
CAUSES	Amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract, autoimmune diseases (eg, SLE)	Fanconi syndrome, multiple myeloma, carbonic anhydrase inhibitors	↓ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARB, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K^+ -sparing diuretics, nephropathy due to obstruction, TMP-SMX)
ASSOCIATIONS	↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover related to buffering)	↑ risk for hypophosphatemic rickets (in Fanconi syndrome)	



▶ RENAL—PATHOLOGY

Casts in urine

Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin.
 Bladder cancer, kidney stones → hematuria, no casts.
 Acute cystitis → pyuria, no casts.
 All casts contain a matrix composed primarily of Tamm-Horsfall mucoprotein (uromodulin), secreted by renal tubular cells to prevent UTIs.

RBC casts A

Glomerulonephritis, hypertensive emergency.

WBC casts B

Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.

Granular casts C

Acute tubular necrosis (ATN). Can be “muddy brown” in appearance.

Fatty casts (“oval fat bodies”)

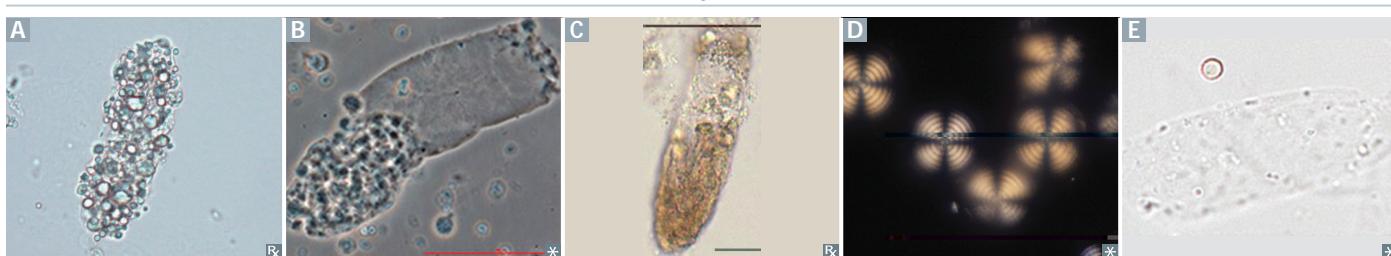
Nephrotic syndrome. Associated with “Maltese cross” sign D.

Waxy casts

End-stage renal disease/chronic kidney disease.

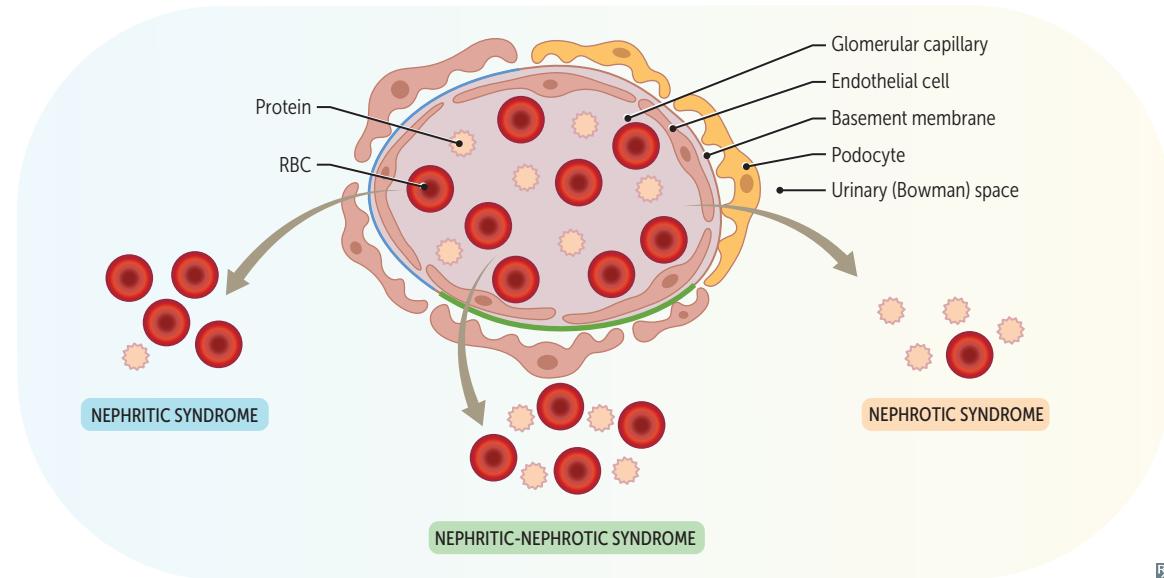
Hyaline casts E

Nonspecific, can be a normal finding with dehydration, exercise, or diuretic therapy.

**Nomenclature of glomerular disorders**

TYPE	CHARACTERISTICS	EXAMPLE
Focal	< 50% of glomeruli are involved	Focal segmental glomerulosclerosis
Diffuse	> 50% of glomeruli are involved	Diffuse proliferative glomerulonephritis
Proliferative	Hypercellular glomeruli	Membranoproliferative glomerulonephritis
Membranous	Thickening of glomerular basement membrane (GBM)	Membranous nephropathy
Primary glomerular disease	1° disease of the kidney specifically impacting the glomeruli	Minimal change disease
Secondary glomerular disease	Systemic disease or disease of another organ system that also impacts the glomeruli	SLE, diabetic nephropathy

Glomerular diseases



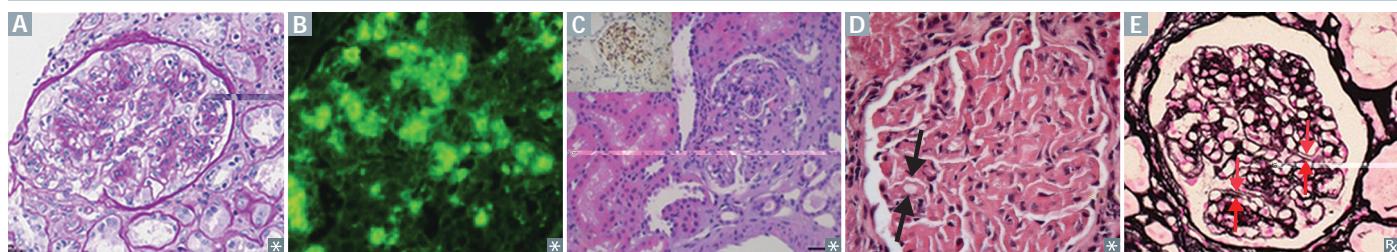
TYPE	ETIOLOGY	CLINICAL PRESENTATION	EXAMPLES
Nephritic syndrome	Glomerular inflammation → GBM damage → loss of RBCs into urine → dysmorphic RBCs, hematuria	Hematuria, RBC casts in urine ↓ GFR → oliguria, azotemia ↑ renin release, HTN Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range	<ul style="list-style-type: none"> Infection-associated glomerulonephritis Goodpasture syndrome IgA nephropathy (Berger disease) Alport syndrome Membranoproliferative glomerulonephritis
Nephrotic syndrome	Podocyte damage → impaired charge barrier → proteinuria	Massive proteinuria (> 3.5 g/day) with edema, hypoalbuminemia → ↑ hepatic lipogenesis → hypercholesterolemia Frothy urine with fatty casts Associated with hypercoagulable state due to antithrombin III loss in urine and ↑ risk of infection (loss of IgGs in urine and soft tissue compromise by edema)	May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process): <ul style="list-style-type: none"> Focal segmental glomerulosclerosis (1° or 2°) Minimal change disease (1° or 2°) Membranous nephropathy (1° or 2°) Amyloidosis (2°) Diabetic glomerulonephropathy (2°)
Nephritic-nephrotic syndrome	Severe GBM damage → loss of RBCs into urine + impaired charge barrier → hematuria + proteinuria	Nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephritic syndrome	Can occur with any form of nephritic syndrome, but is most common with: <ul style="list-style-type: none"> Diffuse proliferative glomerulonephritis Membranoproliferative glomerulonephritis

Nephritic syndrome

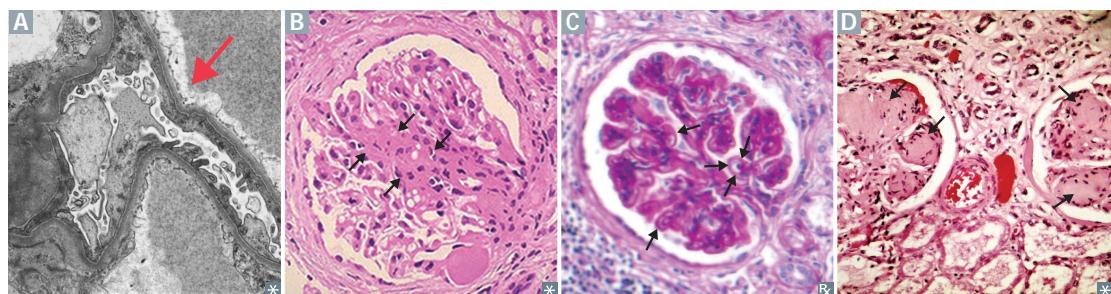
	MECHANISM	LIGHT MICROSCOPY	IMMUNOFLUORESCENCE	ELECTRON MICROSCOPY
Infection-related glomerulonephritis	Type III hypersensitivity reaction with consumptive hypocomplimentemia Children: seen ~2–4 weeks after group A streptococcal pharyngitis or skin infection Adults: <i>Staphylococcus</i> is additional causative agent	Enlarged and hypercellular glomeruli A	Granular (“starry sky”) appearance (“lumpy-bumpy”) B due to IgG, IgM, and C3 deposition along GBM and mesangium	Subepithelial IC humps
IgA nephropathy (Berger disease)	Occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings) Renal pathology of IgA vasculitis	Mesangial proliferation	IgA-based IC deposits in mesangium	Mesangial IC deposition
Rapidly progressive (crescentic) glomerulonephritis	Poor prognosis Multiple causes: Type II HSR in Goodpasture syndrome	Crescent moon shape C ; crescents consist of fibrin and plasma proteins (eg, C3b) with glomerular parietal cells, monocytes, macrophages	Linear IF due to antibodies to GBM and alveolar basement membrane: Goodpasture syndrome—hematuria/hemoptysis; type II hypersensitivity reaction Negative IF/Pauci-immune (no IgC3 deposition): granulomatosis with polyangiitis—PR3-ANCA/c-ANCA, eosinophilic granulomatosis with polyangiitis, or Microscopic polyangiitis—MPO-ANCA/p-ANCA Granular IF—PSGN or DPGN	Goodpasture syndrome: breaks in GMB, necrosis and crescent formation with no deposits Pauci-immune: usually no deposits; if IC deposits, more severe presentation PSGN: dome-shaped subendothelial and subepithelial electron-dense deposits (humps)

Nephritic syndrome (continued)

Disease proliferative glomerulonephritis	Often due to SLE (think “wire lupus”); DPGN and MPGN often present as nephritic and nephrotic syndromes concurrently	“Wire looping” of capillaries D	Granular	Subendothelial, sometimes subepithelial or intramembranous IgG-based ICs often with C3 deposition
Alport syndrome	Type IV collagen mutation → glomerular basement membrane alterations; X-linked dominant. Eye problems (eg, retinopathy, anterior lenticonus), glomerulonephritis, SNHL (can't see, can't pee, can't hear a bee)	Irregular thinning and thickening and splitting of glomerular basement membrane	Initially negative; Irregular deposits of IgG, IgM, and/or C3 may be observed later.	“Basket-weave” appearance due to irregular thickening and longitudinal splitting of GBM
Membrano-proliferative glomerulonephritis	Type I may be 2° to HBV or HCV infection; type II associated with C3 nephritic factor (IgG autoantibody that stabilizes C3 convertase → persistent complement activation → ↓ C3)	Mesangial ingrowth → GBM splitting → “tram-track” on H&E and PAS E stains	Granular	Type I—Subendothelial IC deposits Type II—Intramembranous deposits, also called dense deposit disease



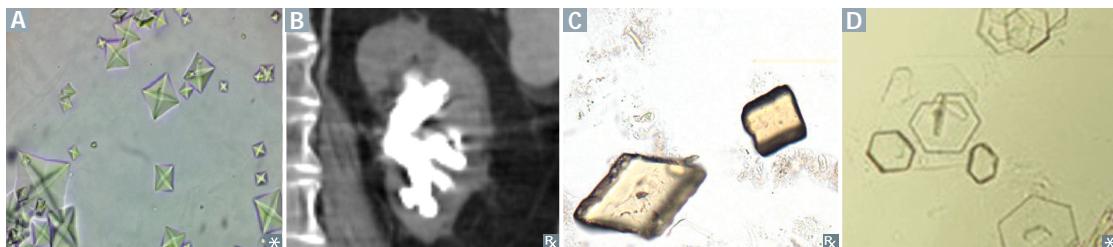
Nephrotic syndrome	Massive proteinuria (>3.5 g/day)	MECHANISM	LIGHT MICROSCOPY	IMMUNOFLUORESCENCE	ELECTRON MICROSCOPY
Minimal change disease	Also called lipid nephrosis. Often 1° (idiopathic), triggered by recent infection, immunization, immune stimulus (4 Is); rarely 2° to lymphoma (eg, cytokine-mediated damage). Loss of antithrombin III → renal vein thrombosis.	Normal glomeruli (lipid may be seen in PT cells)	⊕	Effacement of podocyte foot processes A	
Focal segmental glomerulosclerosis	Can be 1° (idiopathic) or 2° (eg, HIV infection, sickle cell disease, heroin use, obesity, INF treatment, or congenital malformations); may progress to CKD. More common in Black people.	Segmental sclerosis and hyalinosis B	Often ⊕ but may be ⊕ for nonspecific focal deposits of IgM, C3, Cl	Effacement of podocyte foot processes	
Membranous nephropathy	Also called membranous glomerulonephritis. Can be 1° (eg, antibodies to phospholipase A ₂ receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors. ↑ risk of thromboembolism (eg, DVT, renal vein thrombosis).	Diffuse capillary and GBM thickening C	Granular due to immune complex (IC) deposition	“Spike and dome” appearance of subepithelial deposits	
Amyloidosis	Kidney most commonly involved organ. Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid, prolonged dialysis).	Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium	AL amyloidosis: may be positive for lambda and kappa light chains AA amyloidosis: positive for AA protein	Mesangial expansion by amyloid fibrils	
Diabetic glomerulonephropathy	Most common cause of ESRD in United States. Hyperglycemia → nonenzymatic glycation of tissue proteins → mesangial expansion → GBM thickening and ↑ permeability. Hyperfiltration (glomerular HTN and ↑ GFR) → glomerular hypertrophy and glomerular scarring (glomerulosclerosis) → further progression of nephropathy. Look for albuminuria with ↑ urine albumin-to-creatinine ratio. ACEIs and ARBs are renoprotective.	Mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions D)	Non-specific staining. Usually negative.	Prominent thickening of GBM with expanded mesangium, predominantly due to increased mesangial matrix, segmental podocyte effacement	



Kidney stones

Can lead to severe complications such as hydronephrosis, pyelonephritis, and acute kidney injury. Obstructed stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake. Radiolucent stones: I can't **c** (see) **u** (you) (**cystine** and **uric acid**).

CONTENT	PRECIPITATES WITH	X-RAY FINDINGS	CT FINDINGS	URINE CRYSTAL	NOTES
Calcium	Calcium oxalate: hypocitraturia	Radiopaque	Hyperdense	Shaped like envelope A or dumbbell	Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones. Can result from ethylene glycol (antifreeze) ingestion, vitamin C overuse, hypocitraturia (usually associated with ↓ urine pH), malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet.
	Calcium phosphate: ↑ pH	Radiopaque	Hyperdense	Wedge-shaped prism	Treatment: low-sodium diet, thiazides.
Ammonium magnesium phosphate (struvite)	↑ pH	Radiopaque	Hyperdense	Coffin lid ("sarcophagus")	Account for 15% of stones. Caused by infection with urease \oplus bugs (eg, <i>Proteus mirabilis</i> , <i>Staphylococcus saprophyticus</i> , <i>Klebsiella</i>) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi B . Treatment: eradication of underlying infection, surgical removal of stone.
Uric acid	↓ pH	Radiolucent	Visible	Rhomboid C or rosettes	About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover (eg, leukemia). Treatment: alkalinization of urine, allopurinol.
Cystine	↓ pH	Faintly radiopaque	Moderately radiodense	Hexagonal D	Hereditary (autosomal recessive) condition in which Cystine -reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine , Lysine , Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test \oplus . "Sixtine" stones have six sides. Treatment: low sodium diet, alkalinization of urine, chelating agents (eg, tiopronin, penicillamine) if refractory.



Acute cystitis

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent.

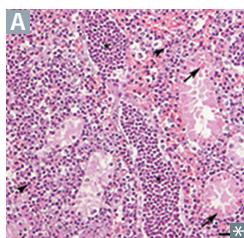
Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying.

Causes:

- *E coli* (most common)
- *Staphylococcus saprophyticus*—seen in sexually active young women (*E coli* is still more common in this group)
- *Klebsiella*
- *Proteus mirabilis*—urine has ammonia scent

Labs: + leukocyte esterase. + nitrites (indicates presence of Enterobacteriaceae). Sterile pyuria (pyuria with - urine cultures) could suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

Pyelonephritis**Acute pyelonephritis**

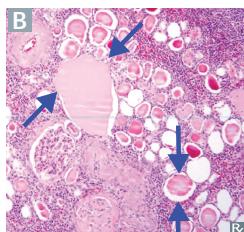
Neutrophils infiltrate renal interstitium **A**. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills.

Causes include ascending UTI (*E coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/- WBC casts. CT would show striated parenchymal enhancement.

Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy (progesterone-mediated ↓ in uterine tone and compression by gravid uterus).

Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess (with possible posterior spread to adjacent psoas muscle), urosepsis.

Treatment: antibiotics.

Chronic pyelonephritis

The result of recurrent or inadequately treated episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones. Coarse, asymmetric corticomedullary scarring, blunted calyces. Tubules can contain eosinophilic casts resembling thyroid tissue **B** (thyroidization of kidney).

Xanthogranulomatous pyelonephritis—rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages. Associated with *Proteus* infection.

Acute kidney injury

	Prerenal azotemia	Intrinsic renal failure	Postrenal azotemia
ETIOLOGY	Hypovolemia ↓ cardiac output ↓ effective circulating volume (eg, HF, liver failure)	Tubules and interstitium: ■ Acute tubular necrosis (ischemia, nephrotoxins) ■ Acute interstitial nephritis Glomerulus: ■ Acute glomerulonephritis Vascular: ■ Vasculitis ■ Hypertensive emergency ■ TTP-HUS	Stones BPH Neoplasm Congenital anomalies
PATHOPHYSIOLOGY	↓ RBF → ↓ GFR → ↑ reabsorption of Na ⁺ /H ₂ O and urea	In ATN, patchy necrosis → debris obstructing tubules and fluid backflow → ↓ GFR	Outflow obstruction (bilateral)
URINE OSMOLALITY (mOsm/kg)	>500	<350	Varies
URINE Na ⁺ (mEq/L)	<20	>40	Varies
FE _{Na}	<1%	>2%	Varies
SERUM BUN/Cr	>20	<15	Varies

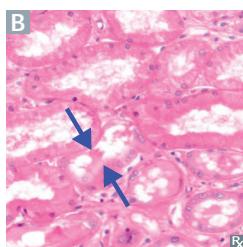
Acute interstitial nephritis

Also called tubulointerstitial nephritis. Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, NSAIDs, penicillin derivatives, proton pump inhibitors, rifampin, quinolones, sulfonamides). Less commonly may be 2° to other processes such as systemic infections (eg, *Mycoplasma*) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

Associated with fever, rash, pyuria, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember these **5 P'S**:

- Pee (diuretics)
- Pain-free (NSAIDs)
- Penicillins and cephalosporins
- Proton pump inhibitors
- RifamPin
- Sulfa drugs

Acute tubular necrosis

Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. ↑ FE_{Na}.

Key finding: granular casts (often muddy brown in appearance) **A**.

3 stages:

1. Inciting event
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals

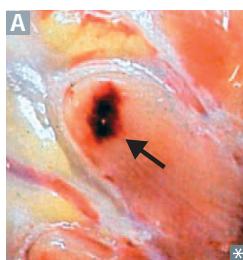
Can be caused by ischemic or nephrotoxic injury:

- Ischemic—2° to ↓ renal blood flow (eg, prerenal azotemia). Results in death of tubular cells that may slough into tubular lumen **B** (PT and thick ascending limb are highly susceptible to injury).
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol), myoglobinuria (rhabdomyolysis), hemoglobinuria. PTs are particularly susceptible to injury.

Diseuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.

Associated with obstetric catastrophes (eg, placental abruption), septic shock.

Renal papillary necrosis

Sloughing of necrotic renal papillae **A** → gross hematuria. May be triggered by recent infection or immune stimulus.

Associated with:

- Sickle cell disease or trait
- Acute pyelonephritis
- Analgesics (eg, NSAIDs)
- Diabetes mellitus

SAAD papa with papillary necrosis.

Consequences of renal failure

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (**MAD HUNGER**):

- Metabolic Acidosis
- Dyslipidemia (especially ↑ triglycerides)
- High potassium
- Uremia
- Na⁺/H₂O retention (HF, pulmonary edema, hypertension)
- Growth retardation and developmental delay
- Erythropoietin deficiency (anemia)
- Renal osteodystrophy

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

Incremental reductions in GFR define the stages of chronic kidney disease.

Normal phosphate levels are maintained during early stages of CKD due to ↑ levels of fibroblast growth factor 23 (FGF23), which promotes renal excretion of phosphate. “**FGF23 fights f(ph)osphate.**”

Uremia—syndrome resulting from high serum urea. Can present with **Pericarditis, Encephalopathy** (seen with asterixis), **Anorexia, Nausea** (pronounce “**Ure-PEAN**” [European]).

Renal osteodystrophy

Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic kidney disease → 2° hyperparathyroidism → 3° hyperparathyroidism (if 2° poorly managed). High serum phosphate can bind with Ca^{2+} → tissue deposits → ↓ serum Ca^{2+} . ↓ 1,25-(OH)₂D₃ → ↓ intestinal Ca^{2+} absorption. Causes subperiosteal thinning of bones.

Renal cyst disorders**Autosomal dominant polycystic kidney disease**

Numerous cysts in cortex and medulla **A** causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with combinations of flank pain, hematuria, hypertension, urinary infection, progressive renal failure in ~ 50% of individuals.

Mutation in genes encoding polycystin protein: PKD1 (85% of cases, chromosome 16) or PKD2 (15% of cases, chromosome 4). Complications include chronic kidney disease and hypertension (caused by ↑ renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis.

Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.

Autosomal recessive polycystic kidney disease

Mutation in PKHD1 encoding fibrocystin. Cystic dilation of collecting ducts **B**. Often presents in infancy, and may be seen on prenatal ultrasound. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.

Autosomal dominant tubulointerstitial kidney disease

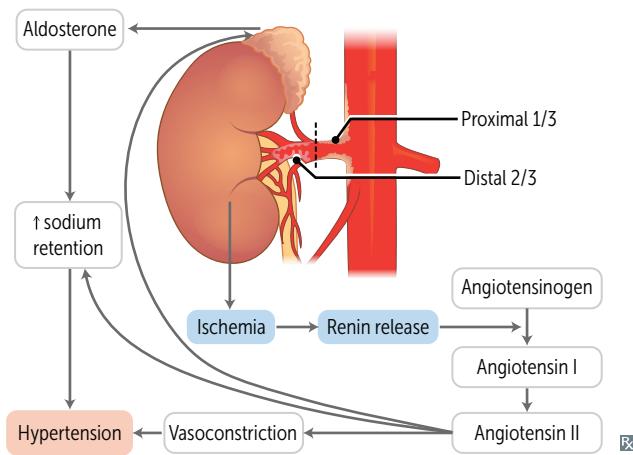
Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.

Simple vs complex renal cysts

Simple cysts are filled with ultrafiltrate (anechoic on ultrasound). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic.

Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to possibility of renal cell carcinoma.

Renovascular disease



Unilateral or bilateral renal artery stenosis (RAS) → ↓ renal perfusion → ↑ renin → ↑ angiotensin → HTN. Most common cause of 2° HTN in adults.

Main causes of RAS:

- Atherosclerotic plaques: proximal 1/3 of renal artery, usually in older males, smokers.
- Fibromuscular dysplasia: distal 2/3 of renal artery or segmental branches, usually young or middle-aged females

For unilateral RAS, affected kidney can atrophy → asymmetric kidney size. Renal venous sampling will show ↑ renin in affected kidney, ↓ renin in unaffected kidney.

For bilateral RAS, patients can have a sudden rise in creatinine after starting an ACE inhibitor, ARB, or renin inhibitor, due to their interference on RAAS-mediated renal perfusion.

Can present with severe/refractory HTN, flash pulmonary edema, epigastric/flank bruit.

Patients with RAS may also have stenosis in other large vessels.

Renal cell carcinoma

Polygonal clear cells **A** filled with accumulated lipids and carbohydrate. Often golden-yellow **B** due to ↑ lipid content.

Originates from PCT → invades renal vein (may develop varicocele if left sided) → IVC → hematogenous spread → metastasis to lung and bone.

Manifests with flank pain, palpable mass, hematuria (classic triad) as well as anemia, 2° polycythemia (less common), fever, weight loss.

Treatment: surgery/ablation for localized disease. Immunotherapy (eg, ipilimumab) or targeted therapy for metastatic disease, rarely curative. Resistant to radiation and chemotherapy.

Most common 1° renal malignancy **C**.

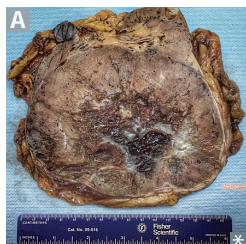
Most common in males 50–70 years old, ↑ incidence with tobacco smoking and obesity.

Associated with paraneoplastic syndromes, eg, PTHrP, Ectopic EPO, ACTH, Renin (“PEAR”-aneoplastic).

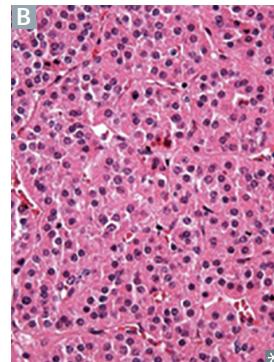
Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).

RCC = 3 letters = chromosome 3 = associated with **VHL** (also 3 letters).



Renal oncocytoma

Benign epithelial cell tumor arising from collecting ducts (arrows in **A** point to well-circumscribed mass with central scar). Large eosinophilic cells with abundant mitochondria without perinuclear clearing (**B**) (vs chromophobe renal cell carcinoma). Presents with painless hematuria, flank pain, abdominal mass. Often resected to exclude malignancy (eg, renal cell carcinoma).

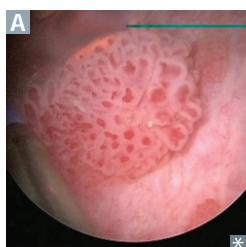
**Nephroblastoma**

Also called Wilms tumor. Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Most often present with large, palpable, unilateral flank mass **A** and/or hematuria and possible HTN.

Can be associated with loss-of-function mutations of tumor suppressor genes **WT1** or **WT2** on chromosome **11** (W11ms tumor).

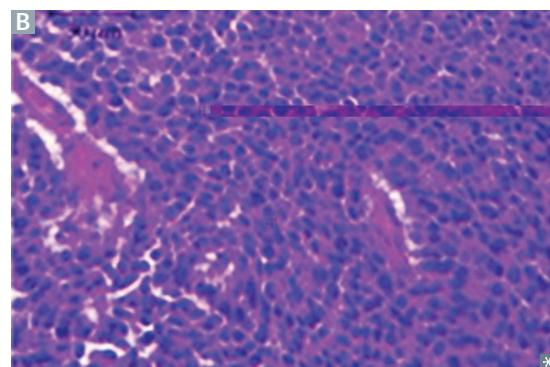
May be a part of several syndromes:

- **WAGR complex**—Wilms tumor, **A**niridia (absence of iris), **G**enitourinary malformations, **R**ange of developmental delays (**WT1** deletion)
- **Denys-Drash syndrome**—Wilms tumor, **D**iffuse mesangial sclerosis (early-onset nephrotic syndrome), **D**ysgenesis of gonads (male pseudohermaphroditism), **WT1** mutation
- **Beckwith-Wiedemann syndrome**—Wilms tumor, macroglossia, organomegaly, hemihyperplasia (imprinting defect causing genetic overexpression, associated with **WT2** mutation), omphalocele

Urothelial carcinoma of the bladder

Also called transitional cell carcinoma. Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) **A** **B**. Can be suggested by painless hematuria (no casts).

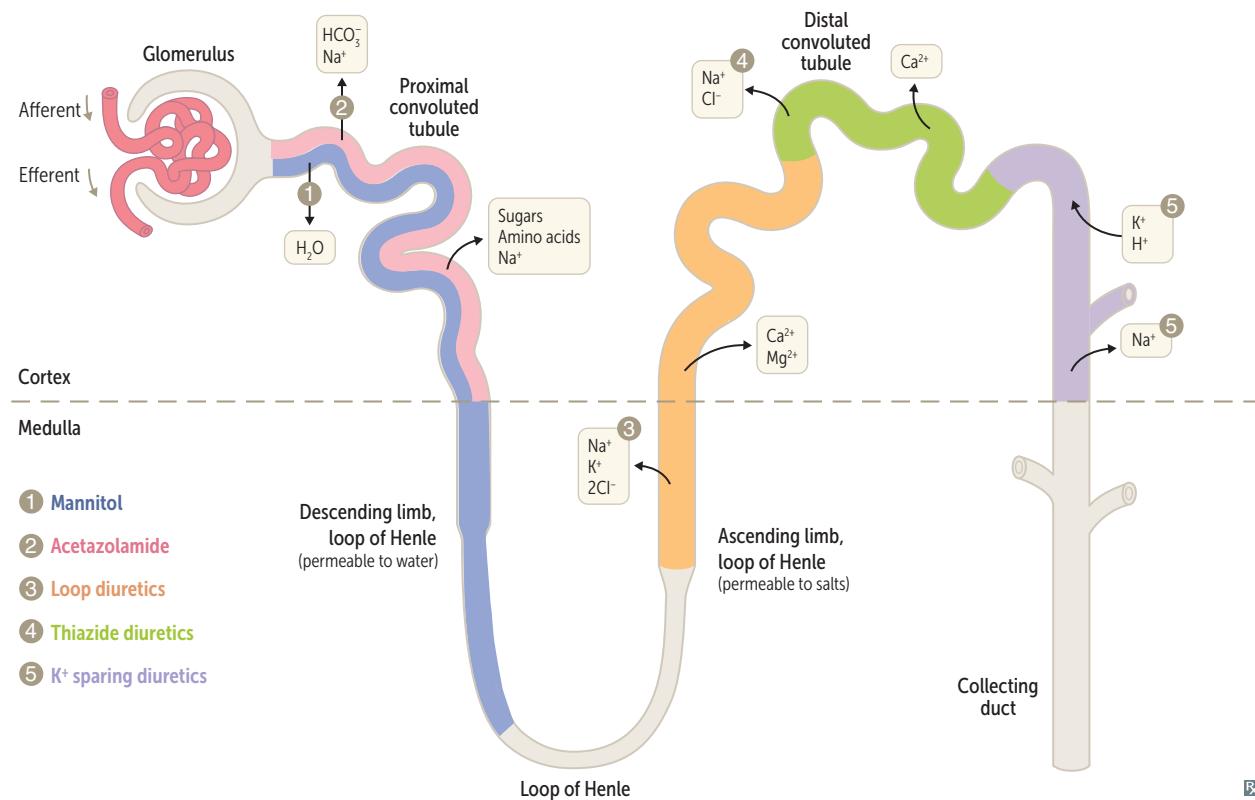
Associated with problems in your Pee SAC:
Phenacetin, **t**obacco **S**moking, **A**romatic amines (found in dyes), **C**yclophosphamide.

**Squamous cell carcinoma of the bladder**

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.
Risk factors include **4 S's**: **S**chistosoma **h**aematobium infection (Middle East), chronic cystitis (“**s**ystitis”), **s**moking, chronic nephrolithiasis (**s**tones). Presents with painless hematuria (no casts).

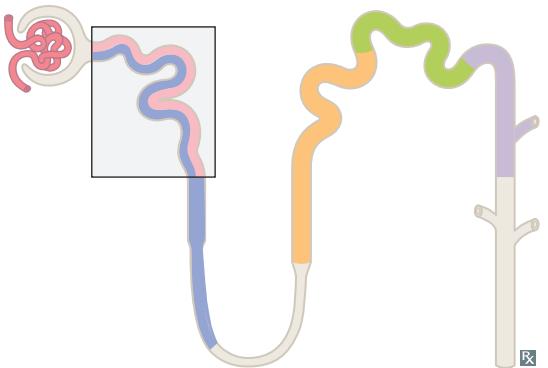
► RENAL—PHARMACOLOGY

Diuretics site of action

**Mannitol**

MECHANISM	Osmotic diuretic. ↑ serum osmolality → fluid shift from interstitium to intravascular space → ↑ urine flow, ↓ intracranial/intraocular pressure.
CLINICAL USE	Drug overdose, elevated intracranial/intraocular pressure.
ADVERSE EFFECTS	Dehydration, hypo- or hypernatremia, pulmonary edema. Contraindicated in anuria, HF.

Acetazolamide

MECHANISM	Carbonic anhydrase inhibitor. Causes self-limited NaHCO_3 diuresis and \downarrow total body HCO_3^- stores. Alkalizes urine.	
CLINICAL USE	Glaucoma, metabolic alkalosis, altitude sickness (by offsetting respiratory alkalosis), idiopathic intracranial hypertension.	
ADVERSE EFFECTS	Proximal renal tubular acidosis (type 2 RTA), paresthesias, NH_3 toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stone formation (insoluble at high pH).	" Acid " azolamide causes acidosis .

Loop diuretics

Furosemide, bumetanide, torsemide

MECHANISM	Sulfonamide loop diuretics. Inhibit cotransport system ($\text{Na}^+/\text{K}^+/2\text{Cl}^-$) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Associated with \uparrow PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. $\uparrow \text{Ca}^{2+}$ excretion. Loops lose Ca^{2+} .
CLINICAL USE	Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.
ADVERSE EFFECTS	Ototoxicity, Hypokalemia, Hypomagnesemia, Dehydration, Allergy (sulfa), metabolic Alkalosis, Nephritis (interstitial), Gout.

OH DAANG!

Ethacrynic acid

MECHANISM	Nonsulfonamide inhibitor of cotransport system ($\text{Na}^+\text{-aANG}$
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Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, metolazone.
MECHANISM	Inhibit NaCl reabsorption in early DCT → ↓ diluting capacity of nephron. ↓ Ca ²⁺ excretion.
CLINICAL USE	Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.
ADVERSE EFFECTS	Hypokalemic metabolic alkalosis, hyponatremia, hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia. Sulfa allergy.

Hypergluc.

Potassium-sparing diuretics	Spironolactone, Eplerenone, Amiloride, Triamterene.	Keep your SEAT.
MECHANISM	Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride block Na ⁺ channels at the same part of the tubule.	
CLINICAL USE	Hyperaldosteronism, K ⁺ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen (spironolactone).	
ADVERSE EFFECTS	Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects), metabolic acidosis.	

Diuretics: electrolyte changes

Urine NaCl	↑ with all diuretics (concentration varies based on potency of diuretic effect). Serum NaCl may decrease as a result.
Urine K⁺	↑ especially with loop and thiazide diuretics, excluding K ⁺ -sparing diuretics.
Blood pH	↓ (acidemia): carbonic anhydrase inhibitors: ↓ HCO ₃ ⁻ reabsorption. K ⁺ sparing: aldosterone blockade prevents K ⁺ secretion and H ⁺ secretion. Additionally, hyperkalemia leads to K ⁺ entering all cells (via H ⁺ /K ⁺ exchanger) in exchange for H ⁺ exiting cells. ↑ (alkalemia): loop diuretics and thiazides cause alkalemia through several mechanisms: <ul style="list-style-type: none">▪ Volume contraction → ↑ AT II → ↑ Na⁺/H⁺ exchange in PCT → ↑ HCO₃⁻ reabsorption (“contraction alkalosis”)▪ K⁺ loss leads to K⁺ exiting all cells (via H⁺/K⁺ exchanger) in exchange for H⁺ entering cells▪ In low K⁺ state, H⁺ (rather than K⁺) is exchanged for Na⁺ in cortical collecting tubule → alklosis and “paradoxical aciduria”
Urine Ca²⁺	↑ with loop diuretics: ↓ paracellular Ca ²⁺ reabsorption → hypocalcemia. ↓ with thiazides: enhanced Ca ²⁺ reabsorption.

Angiotensin-converting enzyme inhibitors

Captopril, enalapril, lisinopril, ramipril.

MECHANISM	Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator.
CLINICAL USE	Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.
ADVERSE EFFECTS	Cough, Angioedema (both due to ↑ bradykinin; contraindicated in Cl esterase inhibitor deficiency), Teratogen (fetal renal malformations), ↑ Creatinine (↓ GFR), Hyperkalemia , and Hypotension . Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR → renal failure.

In chronic kidney disease (eg, diabetic nephropathy), ↓ intraglomerular pressure, slowing GBM thickening.

Captopril's **CATCHH**.

Angiotensin II receptor blockers

Losartan, candesartan, valsartan.

MECHANISM	Selectively block binding of angiotensin II to AT ₁ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin.
CLINICAL USE	Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema).
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension; teratogen.

Aliskiren

MECHANISM	Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. Aliskiren kills renin.
CLINICAL USE	Hypertension.
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs and contraindicated in pregnancy.