Cilia structure

Motile cilia consist of 9 doublet + 2 singlet arrangement of microtubules (axoneme). Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets with no central microtubules.

Nonmotile (primary) cilia work as chemical signal sensors and have a role in signal transduction and cell growth control. Dysgenesis may lead to polycystic kidney disease, mitral valve prolapse, or retinal degeneration.

Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.

Gap junctions enable coordinated ciliary movement.

Primary ciliary dyskinesia

Also called Kartagener syndrome. Autosomal recessive. Dynein arm defect → immotile cilia → dysfunctional ciliated epithelia.

Developmental abnormalities due to impaired migration and orientation (eg, situs inversus, hearing loss due to dysfunctional eustachian tube cilia); recurrent infections (eg, sinusitis, ear infections, bronchiectasis due to impaired ciliary clearance of debris/pathogens); infertility (↑ risk of ectopic pregnancy due to dysfunctional fallopian tube cilia, immotile spermatozoa).

Lab findings: ↓ nasal nitric oxide (used as screening test).

Sodium-potassium pump

Na⁺/K⁺/ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, 2 K⁺ go in to the cell (pump dephosphorylated) and 3 Na⁺ go out of the cell (pump phosphorylated).

2 strikes? K⁺, you're still in. 3 strikes? Nah, you're out!

Cardiac glycosides (digoxin and digitoxin) directly inhibit Na⁺/K⁺/ATPase → indirect inhibition of Na⁺/Ca²⁺ exchange → ↑ [Ca²⁺], → ↑ cardiac contractility.
**Phenylketonuria**

Caused by ↓ phenylalanine hydroxylase (PAH). Tyrosine becomes essential. ↑ phenylalanine → ↑ phenyl ketones in urine.

**Tetrahydrobiopterin (BH₄) deficiency**—BH₄ essential cofactor for PAH. BH₄ deficiency → ↓ phenylalanine. Varying degrees of clinical severity. Untreated patients typically die in infancy.

**Phenylalanine embryopathy**—↓ phenylalanine levels in pregnant patients with untreated PKU can cause fetal growth restriction, microcephaly, intellectual disability, congenital heart defects. Can be prevented with dietary measures.

**Maple syrup urine disease**

Blocked degradation of branched amino acids (Isoleucine, leucine, valine) due to ↓ branched-chain α-ketoacid dehydrogenase (B₃). Causes ↑ α-ketoacids in the blood, especially those of leucine.

Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

**Alkaptonuria**

Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid builds up in tissue. Autosomal recessive. Usually benign.

Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).
**Vaccination**

Induces an active immune response (humoral and/or cellular) to specific pathogens.

<table>
<thead>
<tr>
<th>VACCINE TYPE</th>
<th>DESCRIPTION</th>
<th>PROS/CONS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live attenuated vaccine.</strong></td>
<td>Microorganism rendered nonpathogenic but retains capacity for transient growth within inoculated host. MMR and varicella vaccines can be given to people living with HIV without evidence of immunity if CD4+ cell count $\geq 200$ cells/mm³.</td>
<td>Pros: induces cellular and humoral responses. Cons: may revert to virulent form. Contraindicated in pregnancy and patients with immunodeficiency.</td>
<td>Adenovirus (nonattenuated, given to military recruits), typhoid (Ty21a, oral), polio (Sabin), varicella (chickenpox), smallpox, BCG, yellow fever, influenza (intranasal), MMR, rotavirus. “Attention teachers! Please vaccinate small, Beautiful young infants with MMR regularly!”</td>
</tr>
<tr>
<td><strong>Killed or inactivated vaccine.</strong></td>
<td>Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response.</td>
<td>Pros: safer than live vaccines. Cons: weaker cell-mediated immune response; booster shots usually needed.</td>
<td>Hepatitis A, Typhoid (Vi polysaccharide, intramuscular), Rabies, Influenza (intramuscular), Polio (SalK). A TRIP could Kill you.</td>
</tr>
<tr>
<td><strong>Subunit, recombinant, polysaccharide, and conjugate</strong></td>
<td>All use specific antigens that best stimulate the immune system.</td>
<td>Pros: targets specific epitopes of antigen; lower chance of adverse reactions. Cons: expensive; weaker immune response.</td>
<td>HBV (antigen = HBsAg), HPV, acellular pertussis (aP), Neisseria meningitidis (various strains), Strepococcus pneumoniae (PPSV23, polysaccharide primarily T-cell–independent response; PCV13 conjugated polysaccharide produces T-cell–dependent response), Haemophilus influenzae type b, herpes zoster.</td>
</tr>
<tr>
<td><strong>Toxoid</strong></td>
<td>Denatured bacterial toxin with an intact receptor binding site. Stimulates immune system to make antibodies without potential for causing disease.</td>
<td>Pros: protects against the bacterial toxins. Cons: antitoxin levels decrease with time, thus booster shots may be needed.</td>
<td>Clostridium tetani, Corynebacterium diphtheriae.</td>
</tr>
<tr>
<td><strong>mRNA</strong></td>
<td>A lipid nanoparticle delivers mRNA, causing cells to synthesize foreign protein (e.g., spike protein of SARS-CoV-2). Induces cellular and humoral immunity.</td>
<td>Pros: high efficacy, safe in pregnancy. Cons: local and transient systemic (fatigue, headache, myalgia) reactions are common. Rare myocarditis, pericarditis particularly in young males.</td>
<td>SARS-CoV-2</td>
</tr>
</tbody>
</table>
Bacterial genetics

**Transformation**
Competent bacteria can bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially *S. pneumoniae*, *H. influenzae* type b, and *Neisseria* (SHiN). Adding deoxyribonuclease degrades naked DNA, preventing transformation.

![Image of transformation process]

**Conjugation**

**F+ × F−**
F+ plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed F−. Sex pilus on F+ bacterium contacts F− bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge (“mating bridge”). No transfer of chromosomal DNA.

![Image of conjugation process]

**Hfr × F−**
F+ plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. Recipient cell remains F− but now may have new bacterial genes.

![Image of Hfr process]

**Transduction**

**Generalized**
A “packaging” error. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.

![Image of transduction process]

**Specialized**
An “excision” event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium. Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (ABCD’S): Group A strep erythrogenic toxin, Botulinum toxin, Cholera toxin, Diphtheria toxin, Shiga toxin.

![Image of specialized transduction process]
Opportunistic fungal infections

Candida albicans

alba = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C \textit{A}, germ tubes at 37°C \textit{B}.

Systemic or superficial fungal infection. Causes oral \textit{C} and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, infective endocarditis (people who inject drugs), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis.

Treatment: oral fluconazole/topical azoles for vaginal; nystatin, azoles, or, rarely, echinocandins for oral; fluconazole, echinocandins, or amphotericin B for esophageal or systemic disease.

Aspergillus fumigatus

Septate hyphae that branch at 45° \textit{Acute Angle \textit{D}}. Causes invasive aspergillosis in immunocompromised patients, especially those with neutrophil dysfunction (eg, chronic granulomatous disease) because \textit{Aspergillus} is catalase \textit{⊕}.

Can cause aspergillomas \textit{E} in pre-existing lung cavities, especially after TB infection.

Some species of \textit{Aspergillus} produce \textit{A}flatoxins (associated with hepatocellular carcinoma).

Treatment: voriconazole or echinocandins (2nd-line).

Allergic bronchopulmonary aspergillosis (ABPA) \textit{F}—hypersensitivity response to \textit{Aspergillus} growing in lung mucus. Associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia.

Cryptococcus neoformans


Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Highlighted with India ink (clear halo \textit{G}) and mucicarmine (red inner capsule \textit{H}).

Latex agglutination test detects polysaccharide capsular antigen and is more sensitive and specific.

Causes cryptococcosis, which can manifest with meningitis, pneumonia, and/or encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised.

Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

Mucor and Rhizopus spp

Irregular, broad, nonseptate hyphae branching at wide angles \textit{I}.

Causes mucormycosis, mostly in patients with DKA and/or neutropenia (eg, leukemia). Inhalation of spores \rightarrow fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face \textit{J}; may have cranial nerve involvement.

Treatment: surgical debridement, amphotericin B or isavuconazole.
Rabies virus

Bullet-shaped virus A. Negri bodies (cytoplasmic inclusions) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity. Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors. Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.

Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.

Ebola virus

A filovirus A. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock. Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.

Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of healthcare-associated infection. Supportive care, no definitive treatment. Vaccination of contacts, strict isolation of infected individuals, and barrier practices for healthcare workers are key to preventing transmission.

Severe acute respiratory syndrome coronavirus 2

SARS-CoV-2 is a novel ssRNA coronavirus and the cause of the COVID-19 pandemic. Clinical course varies; often asymptomatic. Symptoms include
- Common: fever, dry cough, shortness of breath, fatigue.
- More specific: anosmia (loss of smell), dysgeusia (altered taste).

Complications include acute respiratory distress syndrome, hypereagulability (thrombotic complications including cryptogenic and/or ischemic stroke), shock, organ failure, death. Risk factors for severe illness or death include increasing age (strongest risk factor), obesity, diabetes, hypertension, chronic kidney disease, severe cardiopulmonary illness. Diagnosed by NAAT (most commonly RT-PCR). Tests detecting viral antigen are typically less sensitive than NAATs, but can be performed rapidly and may be more accessible.

Spreads through respiratory droplets and aerosols. Host cell entry occurs by attachment of viral spike protein to ACE2 receptor on cell membranes. Anti-spike protein antibodies confer immunity. Vaccination induces humoral and cellular immunity, which decreases risk of contracting or transmitting the virus and prevents more serious disease, hospitalization, and death. Supplemental oxygen and supportive care remain the mainstay of therapy for hospitalized patients. Dexamethasone, remdesivir, and IL-6 pathway inhibitors may benefit some severely ill patients.
### Normal Aging

Time-dependent progressive decline in organ function resulting in ↑ susceptibility to disease. Associated with genetic (eg, telomere shortening), epigenetic (eg, DNA methylation), and metabolic (eg, mitochondrial dysfunction) alterations.

<table>
<thead>
<tr>
<th>System</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>↓ arterial compliance (↑ stiffness), ↑ aortic diameter, ↓ left ventricular cavity size and sigmoid-shaped interventricular septum (due to myocardial hypertrophy), ↑ left atrial cavity size, aortic and mitral valve calcification, ↑ maximum heart rate.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>↓ LES tone, ↓ gastric mucosal protection, ↓ colonic motility.</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>↓ bone marrow mass, ↑ bone marrow fat; less vigorous response to stressors (eg, blood loss).</td>
</tr>
<tr>
<td>Immune</td>
<td>Predominant effect on adaptive immunity: ↓ naive B cells and T cells, preserved memory B cells and T cells. Immunosenescence impairs response to new antigens (eg, pathogens, vaccines).</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>↓ skeletal muscle mass (sarcopenia), ↓ bone mass (osteopenia), joint cartilage thinning.</td>
</tr>
<tr>
<td>Nervous</td>
<td>↓ brain volume (neuronal loss), ↓ cerebral blood flow; function is preserved despite mild cognitive decline.</td>
</tr>
<tr>
<td>Special senses</td>
<td>Impaired accommodation (presbyopia), ↓ hearing (presbycusis), ↓ smell and taste.</td>
</tr>
<tr>
<td>Skin</td>
<td>Atrophy with flattening of dermal-epidermal junction; ↓ dermal collagen and ↓ elastin (wrinkles, senile purpura), ↓ sweat glands (heat stroke), ↓ sebaceous glands (xerosis cutis).</td>
</tr>
<tr>
<td></td>
<td>- Intrinsic aging (chronological aging)—↓ biosynthetic capacity of dermal fibroblasts.</td>
</tr>
<tr>
<td></td>
<td>- Extrinsic aging (photoaging)—degradation of dermal collagen and elastin from sun exposure (UVA); degradation products accumulate in dermis (solar elastosis).</td>
</tr>
<tr>
<td>Renal</td>
<td>↓ GFR (↓ nephrons), ↓ RBF, ↓ hormonal function. Voiding dysfunction (eg, urinary incontinence).</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Males—testicular atrophy (↓ spermatogenesis), prostate enlargement, slower erection/ejaculation, longer refractory period. Less pronounced ↓ in libido as compared to females.</td>
</tr>
<tr>
<td></td>
<td>Females—vulvovaginal atrophy; vaginal shortening, thinning, dryness, ↑ pH.</td>
</tr>
<tr>
<td>Respiratory</td>
<td>↑ lung compliance (↑ elastic recoil), ↑ chest wall compliance (↑ stiffness), ↓ respiratory muscle strength; ↓ FEV₁, ↓ FVC, ↑ RV (TLC is unchanged); ↓ A-a gradient, ↑ V/Q mismatch. Ventilatory response to hypoxia/hypercapnia is blunted. Less vigorous cough, slower mucociliary clearance.</td>
</tr>
</tbody>
</table>
Quantifying risk (continued)

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
<th>FORMULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate</td>
<td>Number of deaths (in general or due to specific cause) within a population over a defined period</td>
<td>If 80 people in a town of 10,000 die over 2 years, mortality rate is 4 per 1000 per year.</td>
<td>Deaths/1000 people per year.</td>
</tr>
<tr>
<td>Attack rate</td>
<td>Proportion of exposed people who become ill.</td>
<td>If 80 people in a town are exposed and 60 people become ill, attack rate is 75%.</td>
<td>People who become ill/Total people exposed</td>
</tr>
</tbody>
</table>

Demographic transition

As a country proceeds to higher levels of development, birth and mortality rates decline to varying degrees, changing the age composition of the population.

Population pyramid

<table>
<thead>
<tr>
<th>AGE</th>
<th>POPULATION %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
</tbody>
</table>

Birth rate
Mortality rate
Life expectancy
Population

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth rate</td>
<td></td>
<td>j</td>
</tr>
<tr>
<td>Mortality rate</td>
<td></td>
<td>j</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Population</td>
<td>Growing</td>
<td>Stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Declining</td>
</tr>
</tbody>
</table>

Likelihood ratio

\[ LR^+ = \frac{\text{probability of positive result in patient with disorder}}{\text{probability of positive result in patient without disorder}} = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{\text{TP rate}}{\text{FP rate}} \]

\[ LR^- = \frac{\text{probability of negative result in patient with disorder}}{\text{probability of negative result in patient without disorder}} = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{\text{FN rate}}{\text{TN rate}} \]

LR+ > 10 indicates a highly specific test, while LR- < 0.1 indicates a highly sensitive test.

Pretest probability \( \times \) LR = posttest odds. Posttest probability = posttest odds / (posttest odds + 1).

Kaplan-Meier curve

Graphic representation of event probability (y-axis) vs length of time (x-axis). Useful for displaying “time-to-event” data. Outcomes examined may include any event, but frequently include mortality. Survival probability = 1 – (event probability).

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**High-output heart failure**

Uncommon form of HF characterized by ↑ CO. High-output state is due to ↓ SVR from either vasodilation or arteriovenous shunting. Causes include severe obesity, advanced cirrhosis, severe anemia, hyperthyroidism, wet beriberi, Paget disease of bone.

Presents with symptoms and signs of pulmonary and/or systemic venous congestion.

---

**Shock**

Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function. Initially may be reversible but life threatening if not treated promptly.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CAUSED BY</th>
<th>MECHANISM</th>
<th>SKIN</th>
<th>CVP (RIGHT HEART PRELOAD)</th>
<th>PCWP (LEFT HEART PRELOAD)</th>
<th>CO</th>
<th>SVR (AFTERLOAD)</th>
<th>SVO2 (MIXED VENOUS CONTENT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Hemorrhage, dehydration, burns</td>
<td>Volume depletion</td>
<td></td>
<td>↓</td>
<td></td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>MI, HF, vascular dysfunction, arrhythmia</td>
<td>Left heart dysfunction</td>
<td></td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Obstructive</td>
<td>Cardiac tamponade, PE, tension pneumothorax</td>
<td>Right heart dysfunction</td>
<td></td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Distributive</td>
<td>Sepsis (early anaphylaxis)</td>
<td>Systemic vasodilation</td>
<td></td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td>normal/↑</td>
</tr>
</tbody>
</table>

Double arrow = primary physiologic disorder driving the shock.

^↑ in cardiac tamponade

---

**Cardiac tamponade**

Compression of the heart by fluid (eg, blood, effusions) → ↓ CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans (due to “swinging” movement of heart in large effusion). Echocardiogram shows pericardial effusion (arrows in B), systolic RA collapse, diastolic RV collapse, and IVC plethora.

Treatment: pericardiocentesis or surgical drainage.

**Pulsus paradoxus** — ↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. ↑ venous return during inspiration → ↑ RV filling → interventricular septum bows toward LV (due to ↓ pericardial compliance) → ↑ LV ejection volume → ↓ systolic BP. Seen in constrictive pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), cardiac Tamponade (pea COAT).
**Syndrome of inappropriate antidiuretic hormone secretion**

Characterized by excessive free water retention, euvolemic hyponatremia with continued urinary Na⁺ excretion, urine osmolality > serum osmolality.

Body responds to water retention with ↑ aldosterone and ↑ ANP and BNP → ↑ urinary Na⁺ secretion → normalization of extracellular fluid volume → euvolemic hyponatremia.

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

SIADH causes include (HEELD-up water):
- Head trauma/CNS disorders
- Ectopic ADH (eg, small cell lung cancer)
- Exogenous hormones (eg, vasopressin, desmopressin, oxytocin)
- Lung disease
- Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

**Primary polydipsia and diabetes insipidus**

Characterized by the production of large amounts of dilute urine +/- thirst. Urine specific gravity < 1.006. Urine osmolality usually < 300 mOsm/kg. Central DI may be transient if damage is below hypothalamic median eminence or in the posterior pituitary (ADH in hypothalamus can still be secreted systemically via portal capillaries in median eminence).

<table>
<thead>
<tr>
<th></th>
<th>Primary polydipsia</th>
<th>Central DI</th>
<th>Nephrogenic DI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFINITION</strong></td>
<td>Excessive water intake</td>
<td>↓ ADH release</td>
<td>ADH resistance</td>
</tr>
<tr>
<td><strong>CAUSES</strong></td>
<td>Psychiatric illnesses, hypothalamic lesions affecting thirst center</td>
<td>Idiopathic, brain injury (trauma, hypoxia, tumor, surgery, infiltrative diseases)</td>
<td>Hereditary (ADH receptor mutation), drugs (eg, lithium, demeclocycline), hypercalcemia, hypokalemia</td>
</tr>
<tr>
<td><strong>SERUM OSMOLALITY</strong></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>ADH LEVEL</strong></td>
<td>↓ or normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>WATER RESTRICTION</strong></td>
<td>Significant ↑ in urine osmolality (&gt; 700 mOsm/kg)</td>
<td>No change or slight ↑ in urine osmolality</td>
<td>No change or slight ↑ in urine osmolality</td>
</tr>
<tr>
<td><strong>DESMOPRESSIN ADMINISTRATION</strong></td>
<td>—</td>
<td>Significant ↑ in urine osmolality (&gt; 50%)</td>
<td>Minimal change in urine osmolality</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Water restriction</td>
<td>Desmopressin (DDAVP)</td>
<td>Manage the underlying cause: low-solute diet, HCTZ, amiloride, indomethacin</td>
</tr>
</tbody>
</table>

*No water intake for 2–3 hours followed by hourly measurements of urine volume and osmolality as well as plasma Na⁺ concentration and osmolality.

*Desmopressin (ADH analog) is administered if serum osmolality ≥ 295–300 mOsm/kg, plasma Na⁺ ≥ 145 mEq/L, or urine osmolality does not increase despite ↑ plasma osmolality.
Normal gastrointestinal embryology

Foregut—esophagus to duodenum at level of pancreatic duct and common bile duct insertion (ampulla of Vater).
Midgut—lower duodenum to proximal 2/3 of transverse colon.
Hindgut—distal 1/3 of transverse colon to anal canal above pectinate line.

Midgut:
- 6th week of development—physiologic herniation of midgut through umbilical ring
- 10th week of development—returns to abdominal cavity + rotates around superior mesenteric artery (SMA), total 270° counterclockwise
Platelet plug formation (primary hemostasis)

INJURY
Endothelial damage → transient vasoconstriction via neural stimulation reflex and endothelin (released from damaged cell)

EXPOSURE
vWF binds to exposed collagen; vWF is from Weibel-Palade bodies of endothelial cells and α-granules of platelets

ADHESION
Platelets bind vWF via GpIIb receptor at the site of injury only (specific); platelets undergo conformational change

ACTIVATION
ADP binding to P2Y12 receptor induces GpIIb/IIIa expression at platelet surface → rapid irreversible platelet aggregation

AGGREGATION
Fibrinogen binds GpIIb/IIIa receptors and links platelets

Platelets release ADP and Ca²⁺ (necessary for coagulation cascade); TXA₂

ADP helps platelets adhere to endothelium

Coagulation cascade (secondary hemostasis)

Thrombogenesis

Formation of insoluble fibrin mesh.
Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA₂ synthesis.
Clpidogrel, prasugrel, ticagrelor, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by blocking P2Y₁₂ receptor.
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.
Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome. Desmopressin promotes the release of vWF and factor VIII from endothelial cells.
vWF carries/protects factor VIII; volkswagen factories make gr8 cars.
Other blistering skin disorders

**Dermatitis herpetiformis**
Pruritic papules, vesicles, and bullae (often found on elbows, knees, buttocks) A. Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.

**Erythema multiforme**
Associated with infections (eg, *Mycoplasma pneumoniae*, HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin). Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) B.

**Stevens-Johnson syndrome**
Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction (⊕ Nikolsky), high mortality rate. Typically mucous membranes are involved C D. Targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. **Toxic epidermal necrolysis (TEN)** E F is more severe form of SJS involving > 30% body surface area. 10–30% involvement denotes SJS-TEN.

---

**Lower extremity ulcers**

<table>
<thead>
<tr>
<th></th>
<th>Venous ulcer</th>
<th>Arterial ulcer</th>
<th>Neuropathic ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETIOLOGY</td>
<td>Chronic venous insufficiency; most common ulcer type</td>
<td>Peripheral artery disease (eg, atherosclerotic stenosis)</td>
<td>Peripheral neuropathy (eg, diabetic foot)</td>
</tr>
<tr>
<td>LOCATION</td>
<td>Gaiter area (ankle to midcalf), typically over malleoli</td>
<td>Distal toes, anterior shin, pressure points</td>
<td>Bony prominences (eg, metatarsal heads, heel)</td>
</tr>
<tr>
<td>APPEARANCE</td>
<td>Irregular border, shallow, exudative A</td>
<td>Symmetric with well-defined pouch-out appearance B</td>
<td>Hyperkeratotic edge with undermined borders C</td>
</tr>
<tr>
<td>PAIN</td>
<td>Mild to moderate</td>
<td>Severe</td>
<td>Absent</td>
</tr>
<tr>
<td>ASSOCIATED SIGNS</td>
<td>Telangiectasias, varicose veins, edema, stasis dermatitis (erythematos eczematous patches)</td>
<td>Signs of arterial insufficiency including cold, pale, atrophic skin with hair loss and nail dystrophy, absent pulses</td>
<td>Claw toes, Charcot joints, absent reflexes</td>
</tr>
</tbody>
</table>
### Common cranial nerve lesions

**CN V motor lesion**
Jaw deviates **toward** side of lesion due to unopposed force from the opposite pterygoid muscle.

**CN X lesion**
Uvula deviates **away** from side of lesion. Weak side collapses and uvula points away.

**CN XI lesion**
Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius).

**CN XII lesion**
LMN lesion. Tongue deviates **toward** side of lesion (“lick your wounds”) due to weakened tongue muscles on affected side.

### Facial nerve lesions

**Bell palsy** is the most common cause of peripheral facial palsy. Usually develops after HSV reactivation. Treatment: glucocorticoids +/- acyclovir. Most patients gradually recover function, but aberrant regeneration can occur. Other causes of peripheral facial palsy include Lyme disease, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus.

#### Upper motor neuron lesion
- **Location:** Motor cortex, connection from motor cortex to facial nucleus in pons
- **Affected Side:** Contralateral
- **Muscles Involved:** Lower muscles of facial expression
- **Forehead Involved:** Spared, due to bilateral UMN innervation
- **Other Symptoms:** Variable; depends on size of lesion

#### Lower motor neuron lesion
- **Location:** Facial nucleus, anywhere along CN VII
- **Affected Side:** Ipsilateral
- **Muscles Involved:** Upper and lower muscles of facial expression
- **Forehead Involved:** Affected
- **Other Symptoms:** Incomplete eye closure (dry eyes, corneal ulceration), hyperacusis, loss of taste sensation to anterior tongue
### Neurodegenerative disorders

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DESCRIPTION</th>
<th>HISTOLOGIC/GROSS FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal dementia</td>
<td>Formerly called Pick disease. Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia). May have associated movement disorders.</td>
<td>Frontotemporal lobe degeneration 6. Inclusions of hyperphosphorylated tau (round Pick bodies 7) or ubiquitinated TDP-43.</td>
</tr>
</tbody>
</table>
Renal clearance

\[ C_x = \frac{U_x V}{P_x} \]

- 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.

\[ C_{\text{inulin}} = \text{GFR} = \frac{U_{\text{inulin}} V}{P_{\text{inulin}}} = K_f \left[ (P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}}) \right] \]

- \( P_{\text{GC}} \) = glomerular capillary hydrostatic pressure;
- \( P_{\text{BS}} \) = Bowman space hydrostatic pressure;
- \( \pi_{\text{GC}} \) = glomerular capillary oncotic pressure;
- \( \pi_{\text{BS}} \) = Bowman space oncotic pressure (\( \pi_{\text{BS}} \) 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**: ↑ arterial pressure → stretch of afferent arteriole → mechanical activation of vascular smooth muscle → vasoconstriction of afferent arteriole → ↓ RBF
- **Tubuloglomerular**: ↑ NaCl or tonicity of the filtrate sensed by macula densa cells → paracrine-driven vasoconstriction of afferent arteriole → ↓ RBF

Effective renal plasma flow

Effective renal plasma flow (eRPF) can be estimated using para-aminomellipuric acid (PAH) clearance. Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney.

\[ \text{eRPF} = \frac{U_{\text{PAH}} V}{P_{\text{PAH}}} = C_{\text{PAH}} \]

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

Usually 20–25% of cardiac output, remaining constant due to autoregulation.
eRPF underestimated true renal plasma flow (RPF) slightly.
Uterine rupture

Full-thickness disruption of uterine wall. Risk factors: prior C-section (usually occurs during labor in a subsequent pregnancy), abdominal trauma.
Presents with painful vaginal bleeding, fetal heart rate abnormalities (eg, bradycardia), easily palpable fetal parts, loss of fetal station. May be life threatening for both mother and fetus.

Postpartum hemorrhage

Greater-than-expected blood loss after delivery. Leading cause of maternal mortality worldwide.
Etiology (4 T’s): Tone (uterine atony → soft, boggy uterus; most common), Trauma (eg, lacerations, incisions, uterine rupture), Tissue (retained products of conception), Thrombin (coagulopathy).
Treatment: uterine massage, oxytocin. If refractory, surgical ligation of uterine or internal iliac arteries (fertility is preserved since ovarian arteries provide collateral circulation).

Ectopic pregnancy

Implantation of fertilized ovum in a site other than the uterus, most often in ampulla of fallopian tube. Risk factors: tubal pathologies (eg, scarring from salpingitis [PID] or surgery), previous ectopic pregnancy, IUD, IVF.
Presents with first-trimester bleeding and/or lower abdominal pain. Often clinically mistaken for appendicitis. Suspect in patients with history of amenorrhea, lower-than-expected rise in hCG based on dates. Confirm with ultrasound, which may show extraovarian adnexal mass.
Treatment: methotrexate, surgery.
Placental disorders

**Placenta accreta spectrum**

Formerly called morbidly adherent placenta. Abnormal invasion of trophoblastic tissue into uterine wall. Risk factors: prior C-section or other uterine surgery (areas of uterine scarring impair normal decidualization), placenta previa, ↑ maternal age, multiparity. Three types depending on depth of trophoblast invasion:

- **Placenta accreta**—attaches to myometrium (instead of overlying decidua basalis) without invading it. Most common type.
- **Placenta increta**—partially invades into myometrium.
- **Placenta percreta**—completely invades (“perforates”) through myometrium and serosa, sometimes extending into adjacent organs (e.g., bladder → hematuria).

Presents with difficulty separating placenta from uterus after fetal delivery and severe postpartum hemorrhage upon attempted manual removal of placenta (often extracted in pieces).

**Placenta previa**

Attachment of placenta over internal cervical os (a “previ”ew” of the placenta is visible through cervix). Risk factors: prior C-section, multiparity.

Presents with painless vaginal bleeding in third trimester.

**Low-lying placenta**—located < 2 cm from, but not covering, the internal cervical os.

**Vasa previa**

Fetal vessels run over, or < 2 cm from, the internal cervical os. Risk factors: velamentous insertion of umbilical cord (inserts in chorioamniotic membrane rather than placenta → fetal vessels travel to placenta unprotected by Wharton jelly), bilobed or succenturiate placenta.

Presents with painless vaginal bleeding (fetal blood from injured vessels) upon rupture of membranes accompanied by fetal heart rate abnormalities (e.g., bradycardia). May lead to fetal death from exsanguination.

**Placental abruption**

Also called abruptio placentae. Premature separation of placenta from uterus prior to fetal delivery.

Risk factors: maternal hypertension, preeclampsia, smoking, cocaine use, abdominal trauma.

Presents with abrupt, painful vaginal bleeding in third trimester; can lead to maternal hypovolemic shock (due to hemorrhage) and DIC (due to release of tissue factor from injured placenta), fetal distress (e.g., hypoxia). May be life threatening for both mother and fetus.