DRUG INTERACTIONS (Ch. 6)

A drug can interact with:

- Drugs: occurs when a patient is taking 2+ drugs. They can be both intended or undesired.
- Foods
- Supplement
- Medical conditions

Possible effects:

- Decrease action of drug(s)
- Increase action of drug(s)
- Cause adverse effects

Drug Interaction Consequences

- Consequences depend on patient-related & drug administration-related factors
- Patient-related = diet, genetics, comorbidities
- Administration-related = route, dosage, order of administration

Consequences	Definition	Example
Potentiation	Drug B ↑ Drug A	β-lactamase inhibitors ↑ Ampicillin **(Beneficial)**
Additive	Total effect = Drugs A +B	Alcohol & Anxiolytics **(Harmful)**
Synergistic	Total effect > Drugs A + B	Codeine + NSAIDs for Pain **(Beneficial)** Aspirin + Warfarin for Anticoagulation **(Harmful)**
Antagonistic	Drug B ↓ Drug A	Naloxone ↓ Morphine/Heroin **(Beneficial)** Propranolol ↓ Albuterol **(Harmful)**
Unique	Effect unrelated to A or B	Disulfiram + Alcohol **(Harmful & Beneficial)**

*Beneficial = increased therapeutic effects or decrease in toxicity or cost ($) of therapy
*Harmful = decreased therapeutic effects or increased toxicity or cost ($)

The table lists the possible consequences of the different drug interactions:

- Potentiation (beneficial): when administered alone, ampicillin undergoes rapid inactivation by bacterial enzymes. Beta-lactamase inhibits those enzymes, and thereby prolongs and intensifies ampicillin's therapeutic effects.
- Potentiation (harmful): interaction between aspirin and warfarin represents detrimental potentiative interaction. Aspirin and warfarin both suppress the formation of blood clots. When given concurrently, the risk of bleeding is significantly increased.
- Additive: usually happens when two drugs do the same thing (ie. 2 CNS depressants)
- Synergistic: the total effect is greater than the sum of its parts. The effect is greater than A + B.
- Antagonistic: Drug B decreases the efficacy of Drug A.

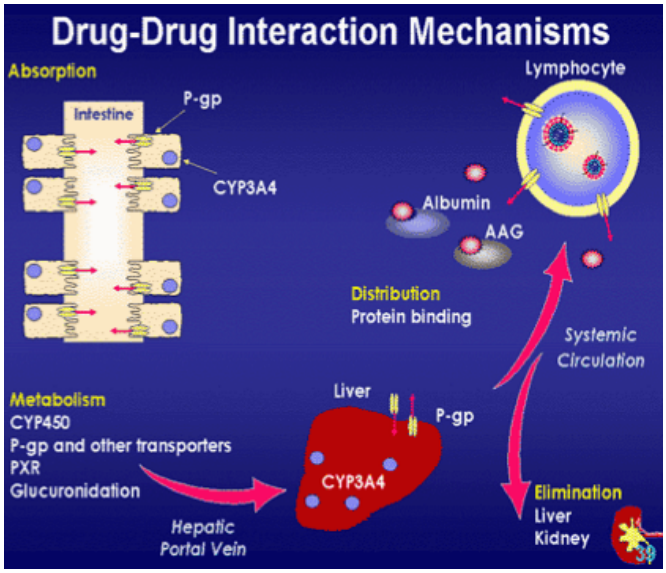
Chemical or Physical Interactions

- Most likely antagonistic consequences
- Most common when drugs combined in IV solution → frequently form precipitate
- Risks of chemical/physical interaction in body decreases thanks to body water dilution

Never combine 2+ drugs in a container unless you know for sure there are no interactions. Absence of precipitate DOES NOT mean no interactions.

Kinetic Interactions

Kinetic vs Dynamic: Kinetic has to be related to ADME.
Horizontal DRC shift: kinetic interaction usually slides the curve to the right or left (horizontally), because it changes your concentration (concentration is on the x-axis).



- Absorption:
  - Gastric pH alterations
  - Anything altering transit time
    - ex. Laxatives can reduce absorption of other oral drugs by accelerating their passage through to the intestine.
    - Drugs that depress peristalsis (ie. morphine, atropine) prolong drug transit time in the intestine, thereby increasing the time for absorption.
  - P-Glycoprotein affinity/concentration
- Distribution
  - Extracellular pH alterations → a drug with the ability to change extracellular pH can alter the distribution of other drugs. If a drug were to increase extracellular pH, that drug would increase the ionization of acidic drugs in extracellular fluids.

As a result, acidic drugs would be drawn from within cells (where the pH was below that of the extracellular fluid) into the extracellular space.

- Ex: aspirin toxicity → symptoms of aspirin toxicity can be reduced with sodium bicarbonate, a drug that elevates extracellular pH. By increasing the pH outside cells, bicab causes aspirin to move from intracellular sites into the interstitial fluid and plasma, thereby minimizing injury to cells.

- Plasma competition for protein binding: when two drugs bind to the same site on plasma albumin, coadministration of those drugs produces competition for binding. As a result, binding of one or both agents is reduced, causing plasma levels of free drug to rise. In theory, the increase in free drug can intensify effects.

- Metabolism
  - Hepatic enzyme induction: some drugs increase metabolism by inducing synthesis of hepatic drug-metabolizing enzymes
  - Hepatic enzyme inhibition: some drugs decrease the metabolism of other drugs by inhibiting those enzymes.
- Excretion
  - Anything altering glomerular filtration (ex. BP) - drugs that reduce cardiac output, which decreases renal perfusion, which decrease drug filtration at the glomerulus, which in turn decreases excretion.
  - Urinary pH alterations: one drug can alter the ionization of another and thereby increase or decrease the extent to which that drug undergoes passive tubular reabsorption
  - Tubular secretion transporters competition: competition between two drugs for active tubular secretion can decrease the renal excretion of both agents.
  - P-Glycoprotein: drugs can induce or inhibit PGP. Drugs that induce PGP have the following impact:
    - Reduced absorption: by increasing drug export from cells of the intestinal epithelium into the intestinal lumen.
    - Reduced fetal drug exposure: by increasing drug export from placental cells into the maternal blood
    - Reduced brain drug exposure: by increasing drug export from cells of brain capillaries into the blood.
    - Increased drug elimination: by increasing drug export from liver into the bile and from renal tubular cells into the urine

    drugs that inhibit have the opposite effect

P450 interactions

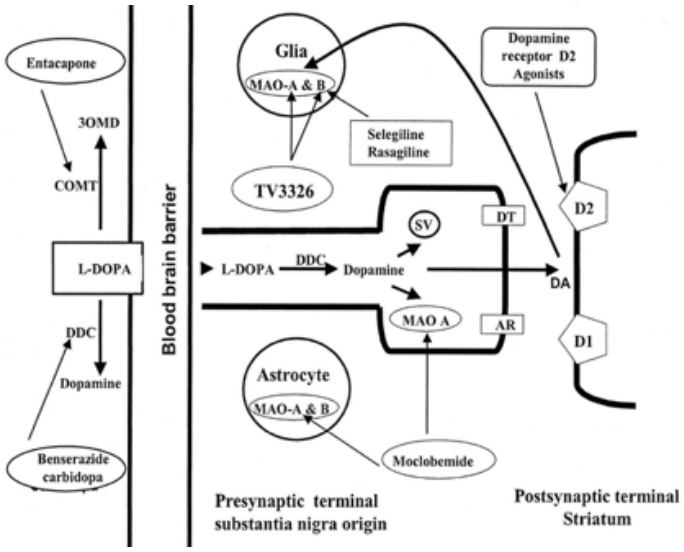
Top 5 P450 Enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4

The P450 enzymes have a 7 day induction onset & offset

- some drugs might increase the amount of a specific enzyme. It takes about a week to get the full effect.
    - Ex: increases the amount of CYP3A4 from 100 to 150. So all the other drugs that are metabolized by CYP3A4 are not being metabolized more quickly. We have more enzymes to do the work.
- The dosage needs to be adjusted every time a new drug is added or discontinued.

Dynamic Interactions

- Dynamic has to do with efficacy (found on the y-axis).
- Usually causes Vertical DRC Shifts (response alterations)
- The effect of the drug changes without any significant changes in drug concentration!



Example in the picture: L-Dopa doesn't cross the BBB very fast, therefore a lot gets metabolized by the 2 enzymes COMT and DDC. These enzymes are usually located on the outside of the brain, and therefore not a lot of L-Dopa reaches the brain in the end. However, we found out that carbidopa is able to inhibit the DDC enzyme. So, if you combine L-Dopa and carbidopa, DDC metabolism is blocked, and allows L-Dopa to cross the BBB at its slow rate, and more of it reaches the brain. So L-Dopa is much more efficient when combined with Carbidopa.

- Shift is vertical

Receptor Interactions

- Mostly antagonism: occurs when an antagonist drug blocks access of an agonist drug to its receptor
    - Ex: naloxone and morphine

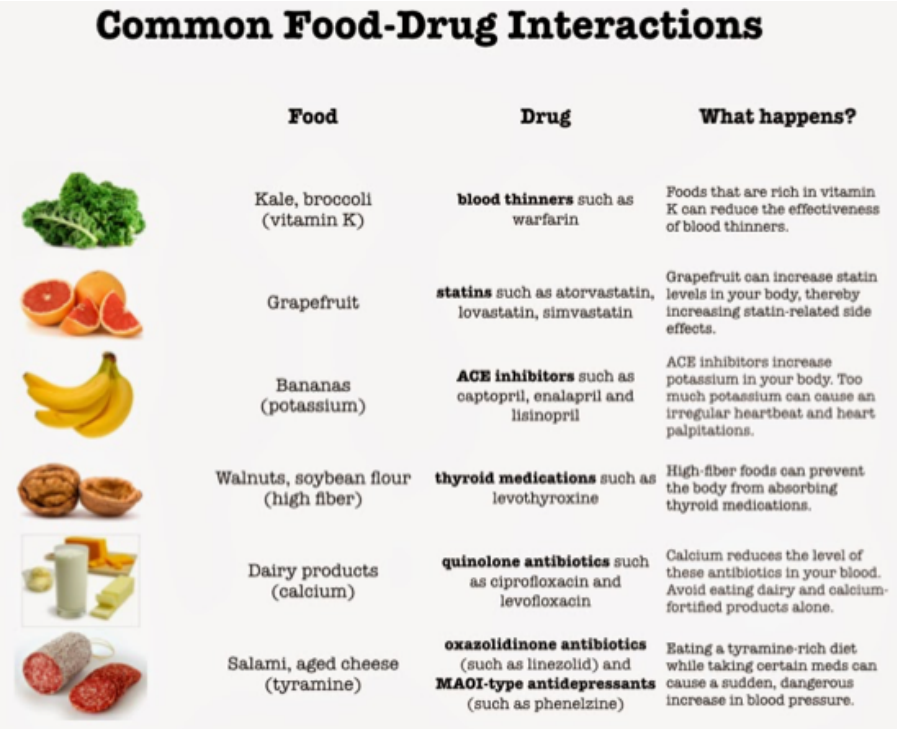
- Receptor regulation/tolerance
    - Ex: alcoholics have decreased GABA receptors

Physiologic Interactions

- Same physiologic effects via different mechanisms
- Ex:
    - Morphine & Diazepam = CNS depression synergy
        - These drugs act at different receptor sites but together act as a potentiation
    - L-DOPA + Carbidopa = increase efficacy (potentiation)
    - Proton Pump Inhibitors + Aspirin = decreases toxicity

Food-Drug Interactions

- Includes Dietary supplements/Natural Products



- Kale, broccoli: decreased drug response
- Grapefruit: metabolism interactions
- Walnuts, Dairy products, etc: absorption interactions
- Salami, aged cheese, etc: increased toxicity (ex: MAO inhibitors - can lead to life-threatening BP levels)

The Grapefruit Juice Effect

Grapefruit has 2 molecules that have a big interaction with CYP3A4 enzyme, found in the liver and intestinal wall. Any drug that is supposed to be metabolized by CYP3A4, mixed with grapefruit, will now be less metabolized.

- Grapefruit inhibits intestinal CYP3A4, decreasing the intestinal metabolism of many drugs, and thereby increasing the amount available for absorption (drug bioavailability). As a result, blood levels of these drugs rise, causing peak effects to be more intense.
- Because inhibition of CYP3A4 in the liver is minimal, grapefruit juice does not usually affect the metabolism of drugs after they have been absorbed.
- Grapefruit juice effect has little or no effect on drugs administered IV. Why? Because with IV administration, intestinal metabolism is not involved.
- Inhibition of CYP3A4 is dose dependent - the more grapefruit juice, the greater the inhibition
- Inhibition can persist up to 3 days.
- Avoid completely during course of Tx

Clinical considerations of Interactions

- High risk drug interaction cases
    - Polypharmacy → increases risk exponentially
    - Narrow therapeutic range drugs → therapeutic failure or toxicity
    - New/recent drugs → undocumented interactions
- Minimizing adverse reactions
    - Avoid polypharmacy whenever possible
    - Obtain a complete history of drugs taken by patients → undisclosed OTCs or illicit drugs
- Timing of meal and drug intake
    - Reduce stomach irritation or avoid interactions
    - "Empty stomach" indication = 1 hour before meals OR 2 hours after

ADVERSE REACTIONS & MEDICATION ERRORS (Ch. 7)

Definitions

- Adverse drug reaction (ADR): noxious, unintended and undesired effect occurring at normal dosage (only bad)
- Side effects (SE): Nearly unavoidable secondary drug effect at therapeutic dosage, can be good or bad
    - Often predictable & dose-dependent
    - Ex: gastric irritation from Aspirin; constipation from opioid painkillers
- Toxicity: Detrimental physiologic effects caused by excessive drug dosage

    - Clinical usage: any severe ADR regardless of dosage
    - Ex: coma from morphine overdose; neutropenia from anticancer therapeutic dose
- Allergic reactions (AR): Aberrant and harmful immune response triggered by a drug
    - AR intensity = dosage-independent, but patient-dependent
    - Most severe AR caused by Penicillins
- Idiosyncratic effect = uncommon DR resulting from genetic variation
    - Ex: G6PD Deficiency + Aspirin → RBC hemolysis
- Paradoxical effect: opposite effect than intended/expected
    - Ex: excitation following diazepam for sedation
- Iatrogenic disease = disease produced by a drug
    - Ex: antipsychotics → Parkinson-like symptoms
- Physical dependence = body adaptation to long-term physiologic drug effects
    - Ex: nasal sprays for airway openings; sedating effects of sleeping pills
- Psychological dependence = intense motivational cravings to consume a drug
    - Ex: opioids; nicotine dependence
- Carcinogenic effect = ability of a drug to induce cancer development
    - Usually undocumented until many years post-marketing
- Teratogenic effect = ability of a drug to induce birth defects (thalidomide!!!)
    - Scrutinized and tested during new drug development

<u>Hepatoxicity</u>

- Liver enzymes convert drugs into toxic metabolites
- Frequent cause of Acute Liver Failure
- Super hepatotoxic drugs = withdrawn from market
- Patients taking hepatotoxic drugs:
    - Frequent LFT → look for increased AST or ALT
    - Monitor liver injury symptoms (ie. jaundice, dark urine, light-colored stool, N/V)
    - Educate patients for liver symptom recognition

<u>QT interval Drugs</u>

- Q is the beginning of ventricular contraction and T is the ventricular repolarization. So if you start prolonging the QT interval → prolonging the duration of a heart beat. If this continues to happen over time, you're likely to cause arrhythmias.
- Prolonged QT interval time (FDA mandatory QT interval testing for all new drugs)
- QT > 470 msec → increased dysrhythmias (torsade de pointe) → increased V. fibrillation
- Women are at a higher risk of a prolonged QT interval compared to men, because women already have a longer QT interval normally.

- Avoid QT drugs whenever possible
- See page 66 of book for drug examples

Clinical considerations of ADR

- Identifying ADRs
  - Temporal relationship: ADR starts shortly after drug administration & ceases when discontinued
  - ADR cannot be explained by the illness or other drugs in the regimen
  - High vigilance with new drugs → report suspected ADRs
- Minimizing ADR
  - Know the major ADRs associated to drugs you administer/taken by patients under your care
  - Monitor organ functions if known specific toxicity (ex: liver, QT interval; kidneys; bone marrow)
  - Individualize therapy considering patient history (ex: allergies, pregnancy, etc)
- Guides & Box warnings
  - Medication guides = excellent patient education tool
  - Black box warning = serious life-threatening ADR risk

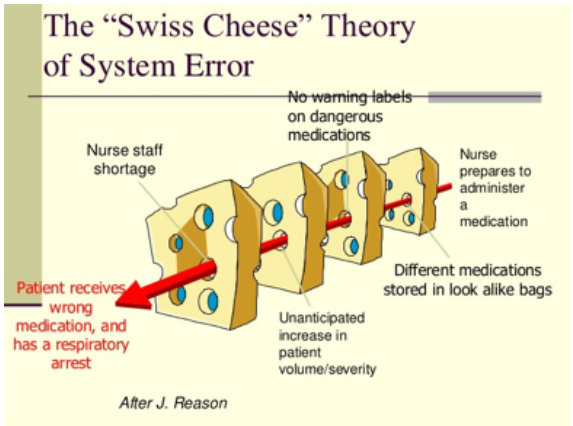
Medication Errors

Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the HCP, patient or consumer.

- Major cause of morbidity & mortality → injure ~ 1.5M & kill ~ 7000/year
- Huge financial burden → 3.5 billions/year

Types of Medication Errors

Wrong patient
Wrong drug
Wrong route
Wrong time
Wrong dose
Omitted dose
Wrong dosage form
Wrong diluent
Wrong strength/concentration
Wrong infusion rate
Wrong technique (includes inappropriate crushing of tablets)
Deteriorated drug error (dispensing a drug after its expiration date)
Wrong duration of treatment (continuing too long or stopping too soon)



Major causes:

- Human factors
- Communication mistakes - written or oral
- Name confusion
- Packaging, formulations, and delivery devices
- Labeling and reference materials

Clinical Considerations of Medication Errors

Who makes them?

- HCP makes the order → pharmacist verifies and prepares order → nurse practitioner administers order
- Nurses = last line of defense: last one to catch mistakes by others but no one can catch a nurse's mistake!

Minimizing medical errors

- Institution-wide processes = best /most effective
- Ex: computer order vs. hand-written; bar-code matching systems for drugs & patients' armbands.

How to report

- Report via MER program (not to blame) - is a nationwide system run by the ISMP. All reporting is confidential and done via phone or internet.

Medication Reconciliation (box 7-1)

- Compare list of medications currently taken with new medications that are about to be provided
- Done whenever a patient undergoes a transition in care
- Decrease medication errors during transition in care by 70% + ADRs by 15%
- Provide a list of all medications to be taken following discharge

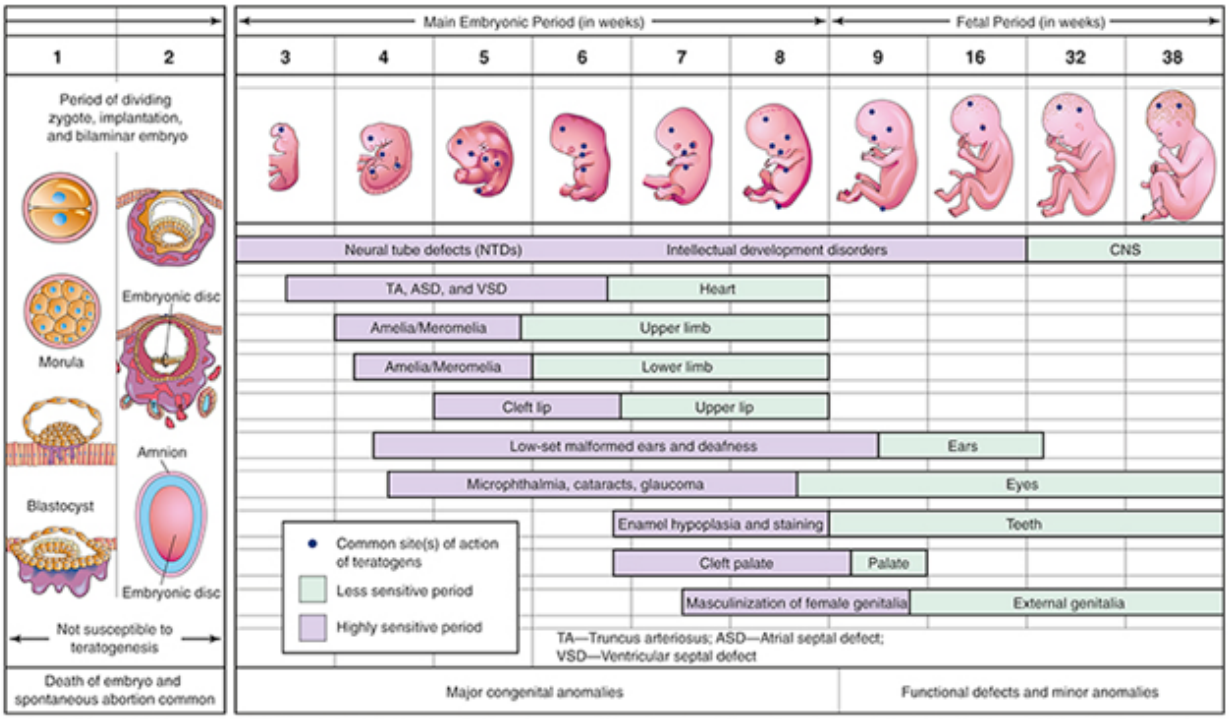
PREGNANCY & BREAST-FEEDING (Ch.9)

Basic Considerations

- ⅔ pregnant patients take at least 1 medication; majority takes more
- Reliable data on drug toxicity during pregnancy = very limited
- Risk-benefit analysis without knowing most of the risks..
- Health of the mother = crucial to fetus health → MUST treat!
- Pregnancy physiologic changes → dosage adjustments!
    - Ex: increased BP → increased GFR → increased excretion
    - Increased GI transit time (slowed) → more time for drugs to get reabsorbed → increased absorption
- Assume that drug taken during pregnancy reaches the fetus
    - Although polarity affects placental barrier crossing

Teratogenesis

Teratogenesis is the development of birth defects.



From Moore K, Persaud TVN, Torchia M: *The developing human: clinically oriented embryology*, ed 9, Philadelphia, 2012, Elsevier, with permission.

During the 1st two weeks, from fertilization until day 14, drugs cannot reach the fetus because the blood supply of the fetus is not fully attached to the mother yet. First it needs to implant, then the blood supply will become attached..

Starting from week 3, when the fetus is attached to the mother, the organs begin to develop. The fetus is especially vulnerable during the embryonic period.

- Major congenital anomalies typically occur in the first trimester

Window of vulnerability: different organs develop at different time frames in the pregnancy. It varies per organ/drug/defect/fetus

- For example, if the mother is taking a drug that affects the fetus at week 16, there's a very very low chance that the development of the limbs will be affected.

Teratogen exposure during the fetal period (2nd and 3rd trimester) usually disrupts function rather than gross anatomy.

Drug exposure = minor cause (<1%)

Teratogens

- Proof of teratogenecity = difficult → almost no direct human studies
- Animal safety = FDA requirement does not equal human safety (ex. thalidomide)

- Fast-acting: a single dose can cause malformations. Can be easily detected in the fetus or at birth.
- Slow-acting: needs repeated doses to cause malformations. The effects can only be detected later in life
    - for example, fertility problems only show up later and not at birth of the baby
- Behavioural teratogens = almost impossible to detect because this would occur much much later in life, and a correlation cannot be made to a medication taken during birth

Breast-feeding

Patient education advice:

- Avoid drugs from table 9-4 - favor those from table 9-5 (p.88)
- Administer immediately after (or even during) breast-feeding to minimize drug concentrations in milk at the next feeding
- Avoid Rx with long half-life or sustained-release formulations

Pregnancy Risks

- FDA categories → pregnancy & lactation labelling rules (PLLR)
    - Categories phased out by 2020 → replaced by PLLR (see table 9-3, p.85)
    - Drug-specific infos on exposure/risk/clinical considerations/scientific data
- Minimize teratogenesis
    - Discontinue unnecessary drugs for pregnant patients (including all recreational drugs)
    - Substitute teratogenic drug to less harmful option if applicable
    - Educate reproductive-age patients taking proven teratogen Rx to use contraceptives
- Responding to teratogen exposure
    - Reassure about the absolute low risk of birth malformation + most birth defects being drug-independent
    - Consult literature for anticipated malformations
    - Ultrasound to assess injury →
        - Severe = possible termination
        - Minor = possible surgical correction
- Food for thought: what do you do in the case of an epileptic patient where the anti-seizure drug is a teratogen but seizure attacks are also a known teratogen?
    - Treat the patient, give one epileptic drug at its smallest possible dose. Seizures are teratogenic for the fetus, and therefore still want to treat the seizures.

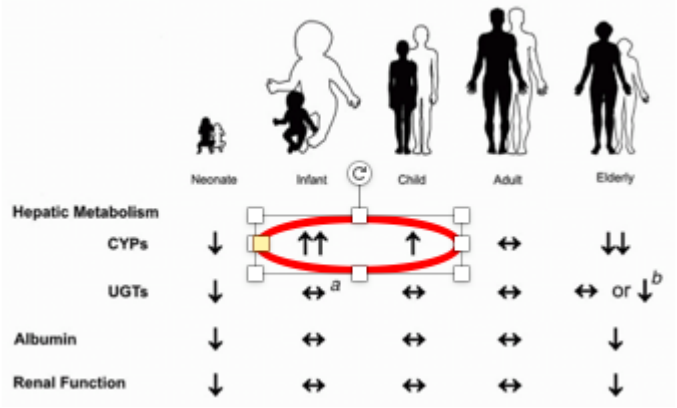
PEDIATRIC & GERIATRIC PATIENTS (Ch. 10 & 11)

Pediatric patients - basic considerations

- Organ immaturity → infant drug sensitivity > adults
- Very limited pediatric drug research
- New FDA Acts in 2000s' forced to increase pediatric research
    - Early results:
        - 20% of effective Rx in adults = ineffective in kids
        - 20% required different dosage than extrapolated
        - 30% of drugs had new serious ADR in kids
- Kids DO NOT EQUAL miniature adults

Pharmacokinetics

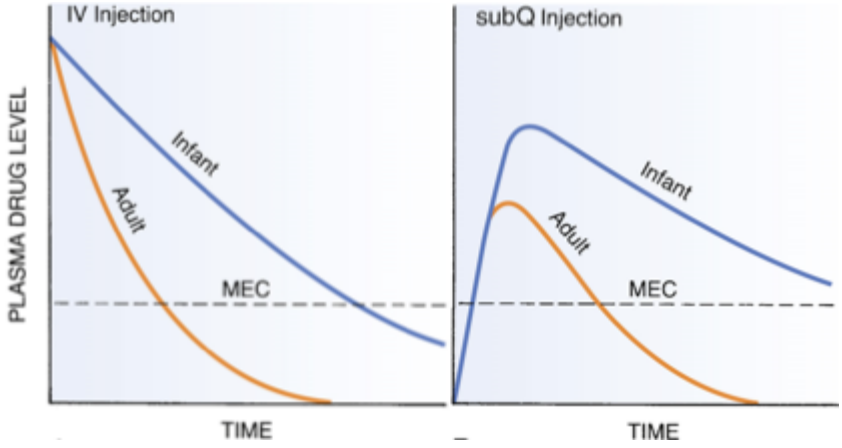
- One of the biggest differences in kids and adults isin the kinetics (see red circle)



- Everything is reduced because organs are immature.
- Neonates & infants immaturity in 5 major PK processes:
    - Absorption - gastric emptying is both prolonged and irregular in early infancy
    - Protein binding (distribution)
        - The amount of serum albumin is relatively low and endogenous compounds (fatty acids, bilirubin) compete with drugs for available binding site. As a result, the concentration of free levels of such drugs is relatively high in the infant, thereby intensifying effects. Dose will need to be decreased.
    - Permeable BBB (distribution)
        - BBB is more permeable in children than in adults, drugs can reach the brain more easily. They will need a smaller dose.
    - Hepatic metabolism
        - Drug-metabolizing capacity is low. Dosages must be reduced.
    - Renal excretion

- Renal blood flow, glomerular filtration, and active tubular secretion are all low during infancy. Therefore, dose will need to be reduced.

- CYP enzymes are working better in kids than in adults. One hypothesis is that kids and babies are always putting bacteria and harmful things in there mouth, therefore the CYP enzymes are thought to be increased.



Pediatric considerations

- ADRs
  - Altered kinetics increases intensity & prolonged drug effects
  - Avoid Rx from table 10-1 (p.92) whenever possible
- Dosage
  - Look for pediatric dosage whenever available
  - When unavailable use body surface area (BSA) approximation
    - (Child BSA x Adult dosage)/1.73m^2 = pediatric dosage
  - Adjust dosage accordingly following initial dose
- Adherence promotion (see table 10-2,p.92)
  - Child caregiver and child education = crucial!!
  - Select most advantageous route of administration + provide demonstration
  - Written instructions + conscientious participation of parents

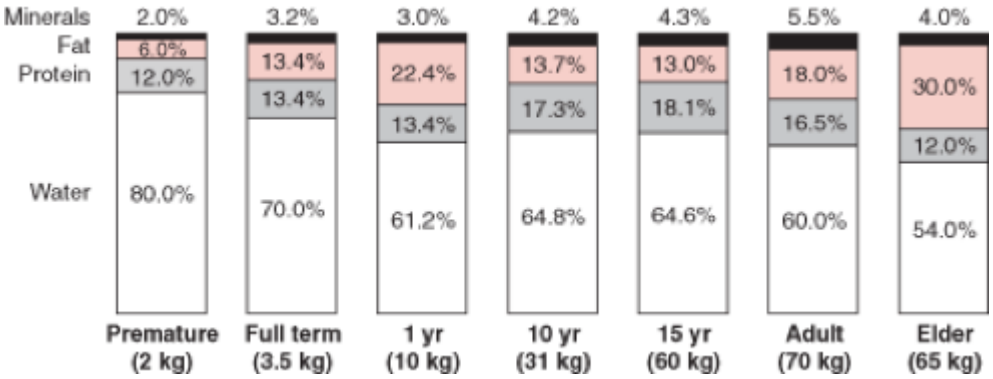
Geriatric Population

Kinetic Changes (p.95 Table 11.1)

- The kinetics of the elderly are very similar to babies/children.
- High individual variation depending on:
  - Physical fitness
  - Pathologies (organ degeneration)
  - Polypharmacy
- The excretion changes are the most important. Key factor: loss of kidney function.

- Decreased renal blood flow
- Decreased glomerular filtration rate
- Decreased tubular secretion
- Decreased number of nephrons

- Body water:Fat ratio changes with Age



Geriatric considerations

- Minimize ADRs
  - High risk population (7x more common!!) due to polypharmacy, comorbidities, poor adherence, etc.
  - Avoid drugs on Beers' list
  - Watch out for few dynamic alterations
    - Ex. Beta blockers decrease efficacy
    - Ex. warfarin increase efficacy
- Adherence promotion
  - Counter the most common adherence hurdles
  - Simplify dosage & administration
  - Recruit friends & family assistance
  - Intensive education → intentional nonadherence
- Factors decreasing adherence in elderly
  - Multiple disorders
  - Multiple prescriptions & prescribers
  - Multiple doses per day for each medication
  - Drug packaging difficult to open
  - Regimen changes
  - Low SES (literacy, $$, social support)
  - Personal conviction that a drug is unnecessary or the dosage too high
  - Cognitive or physical impairment (memory, vision, hearing, etc)
  - Presence of side effects
  - Recent discharge from hospital

ANTISEPTICS & DISINFECTANTS (Ch. 96)

General considerations

- Action antimicrobial agents → toxicity too large for internal use
- Definitions:
  - Antiseptics: living tissue (ex: hands, patient skin prior to intervention)
  - Disinfectants = non-living objects (ex: surgical instruments)
  - Sterilization = destruction of all microorganisms
  - Sanitization = contamination meeting public health standards
  - Germicide = kills microorganisms vs. germistatic drugs = inhibit growth
- Important characteristics
  - No perfect agent
    - Ex: safe + selective + effective + no odor + kills all germs + …
  - Variable time course of action
    - Ex: alcohol = 36 secs vs. 7 minutes of benzalkonium chloride
  - Effective prophylaxis → best usage = application on medical personnel & instruments
  - Infective vs. local (topical) infections

Individual properties of antiseptics & disinfectants

Antiseptics and Disinfectants: Chemical Category and Application

Chemical Category	Drug	Application	
		Antisepsis	Disinfection
Alcohols	Ethanol	✓	
	Isopropanol	✓	
Aldehydes	Glutaraldehyde		✓
	Formaldehyde		✓
Iodine Compounds	Iodine tincture	✓	
	Iodine solution	✓	
Iodophors	Povidone-iodine	✓	✓
Chlorine Compounds	Oxychlorosene	✓	
	Sodium hypochlorite	✓	✓
Phenolic Compound	Hexachlorophene	✓	
Miscellaneous Agents	Chlorhexidine	✓	
	Hydrogen peroxide	✓	✓
	Benzalkonium chloride	✓	✓

Focus on those that are used in the clinical section

Alcohols

	Characteristics
Prototype	Ethyl Alcohol
Main Usage	**Fast-Acting Antisepsis only** (ex.: Staff hand washing)
Antimicrobial Spectrum	Most Pathogenic Viruses & Bacteria Dissolve membranes + Protein precipitation
Weakness	Bacterial spores & Fungi **Thus poor Disinfectants**
Optimal Concentration	70% Solution (Higher % ↓ Efficacy)
Contraindications	**Do not use on open wounds!** Tissue damage + Coagulation Mass
Miscellaneous	↑ Efficacy of other Antiseptics (Ex.: Chlorhexidine & Benzal Chloride)

Iodine Compounds

	Characteristics
Prototype	Iodine
Main Usage	**Antiseptic only** Best for skin of patients prior to IV injections or blood sampling
Antimicrobial Spectrum	All microorganisms & spores
Optimal Concentration	Solution = 2% Iodine + 2.4% Sodium Iodide Tincture = Solution + 47% Ethanol (↑ Efficacy)
Contraindications	**Avoid tincture on open wounds** (Alcohol = Irritant)
Miscellaneous	Oldest Antiseptics (160 years old!!) Very cheap + Very low toxicity Only Free Elemental Iodine kills (≈ 0.15% of solution) Sodium Iodide works as a reservoir for sustained-release

- Tincture increases the efficacy because of iodine combined with ethanol, but cannot be used on open wounds

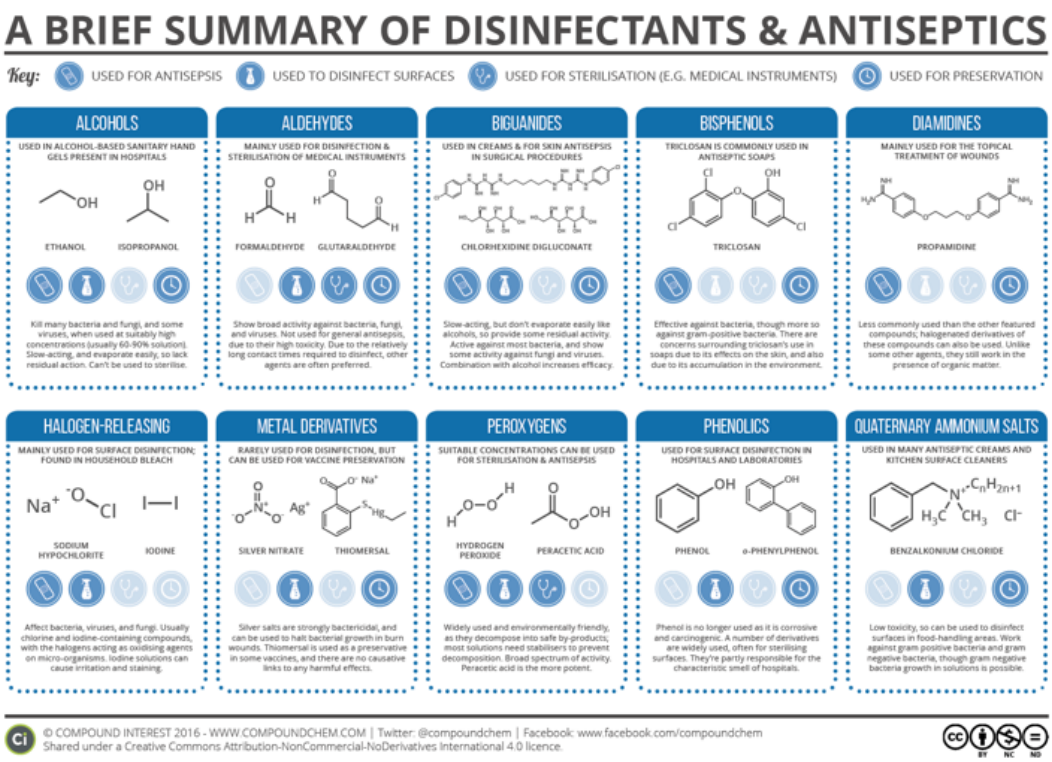
Chlorhexidine

	Characteristics
Main Usage	**Fast-Acting Antiseptic** (ex.: Preoperative preparation of skin & hand-wash)
Antimicrobial Spectrum	Most Pathogenic Viruses & Bacteria Low concentrations: Cell membrane leaks High Concentrations: Protein + Nucleic Acid Precipitation
Weakness	Bacterial spores
Miscellaneous	Preferred agent against central venous catheter infections Oral-rinse in gingivitis patients Very Safe!

September 19, 2019
William Archambault

Summary

*focus only on those discussed in class



Hand hygiene

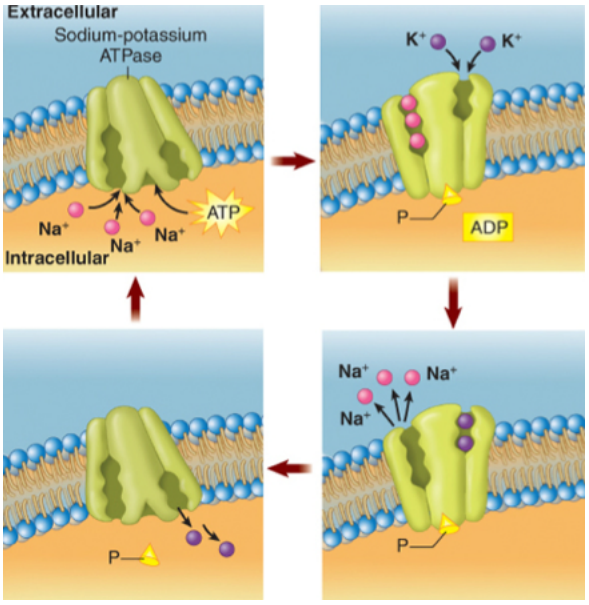
Specific CDC recommendations with highest evidence-based support (category 1A)

- Used antimicrobial soap + water when hands are visibly dirty
- Use alcohol-based hand rub when hands are not visibly dirty
- Decontaminate hands following body fluids or mucous membranes or wound dressing contact
- No artificial fingernails or extenders in ICU or OR
- Administration should provide healthcare workers with readily accessible alcohol-based products
- Alcohol-based products located at convenient locations (ex. Entrance of patients' rooms)

Antimicrobial Spectrum and Characteristics of Hand-Hygiene Antiseptic Agents

Group	Gram-Positive Bacteria	Gram-Negative Bacteria	Mycobacteria	Fungi	Viruses	Speed of Action	Comments
Alcohols	+++	+++	+++	+++	+++	Fast	Optimum concentration 60%–95%; no persistent activity; not lethal to bacterial spores, including those of *C. difficile*
Chlorhexidine (2% and 4% aqueous)	+++	++	+	+	+++	Intermediate	Persistent activity; rare allergic reactions
Iodine compounds	+++	+++	+++	++	+++	Intermediate	Causes skin burns; usually too irritating for hand hygiene
Iodophors	+++	+++	+	++	++	Intermediate	Less irritating than iodine; acceptance varies
Phenol derivatives	+++	+	+	+	+	Intermediate	Activity neutralized by nonionic surfactants

BODY FLUID & ION CONTENT AGENTS (Ch. 42)

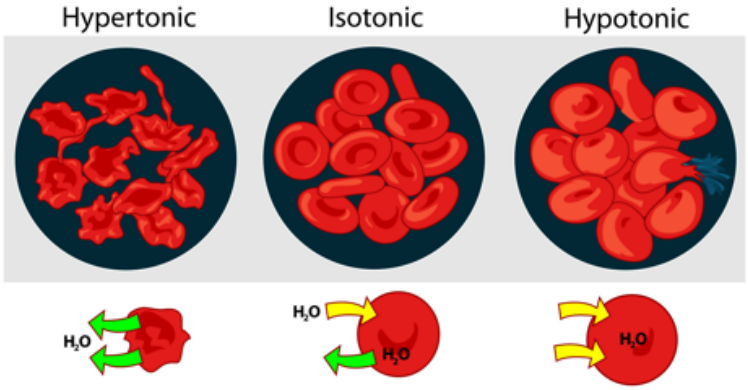


Patho Review - Active Transport

- Pump against concentration gradient
- Requires ATP
- Sodium-potassium pump
  - Generates electrical gradient
  - Essential for life!

Osmosis

- Depends on:
  - Hydrostatic pressure & solute concentration
  - Independent of size or weight
- Osmolarity = mOsm/L
- Tonicity = effective osmolarity/osmolality

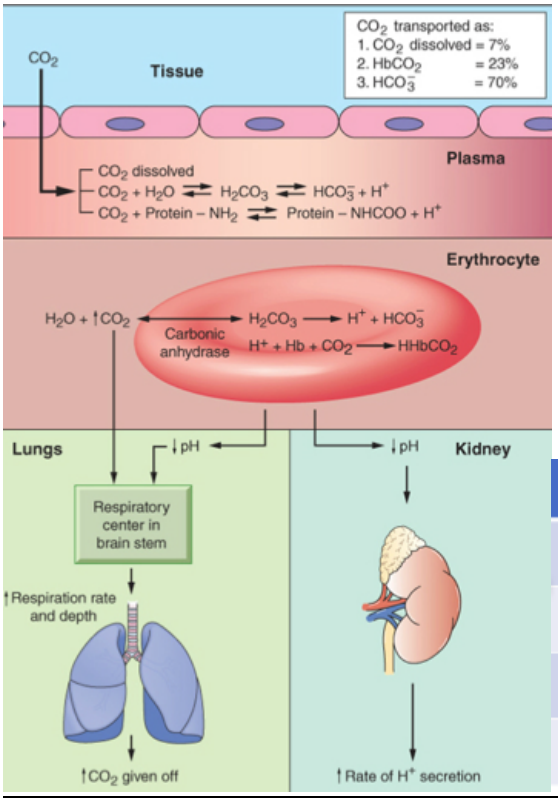


Fluid alterations

- Isotonic alterations
  - hypo/hypervolemia
- Hypertonic alterations
  - hypernatremia/dehydration
  - Leads to coma, fever, cognitive deficits
- Hypotonic alterations
  - hyponatremia/excessive water intake
  - Leads to coma, fever, cognitive deficits
- Many others… potassium, calcium, etc.

Acid-Base Regulation

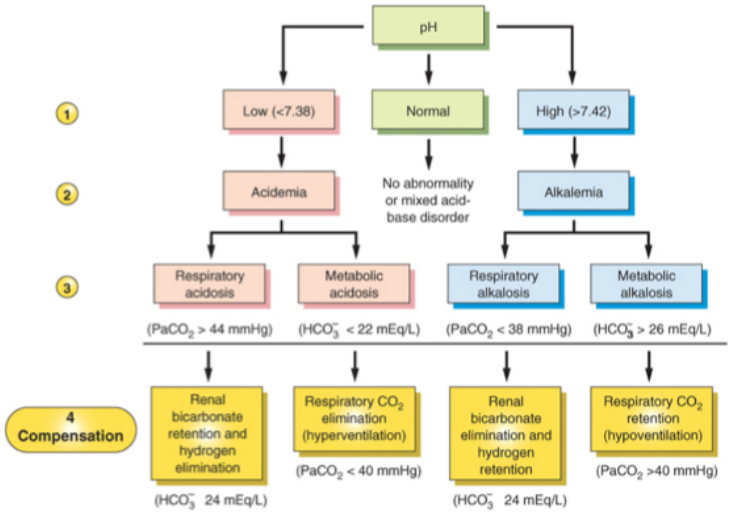
$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$



Fluid	pH
Gastric	1.0-3.0
Urine	5.0-6.0
Blood	7.35-7.45
CSF	7.28-7.32

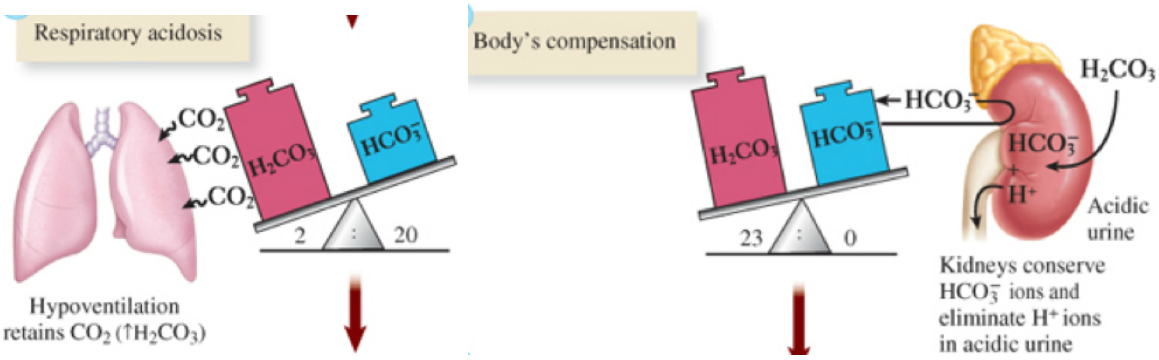
Acid-Base Disorders

To Understand you need: "H_20"+$CO_2 \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$ *& Le Chatelier'sPrinciple*



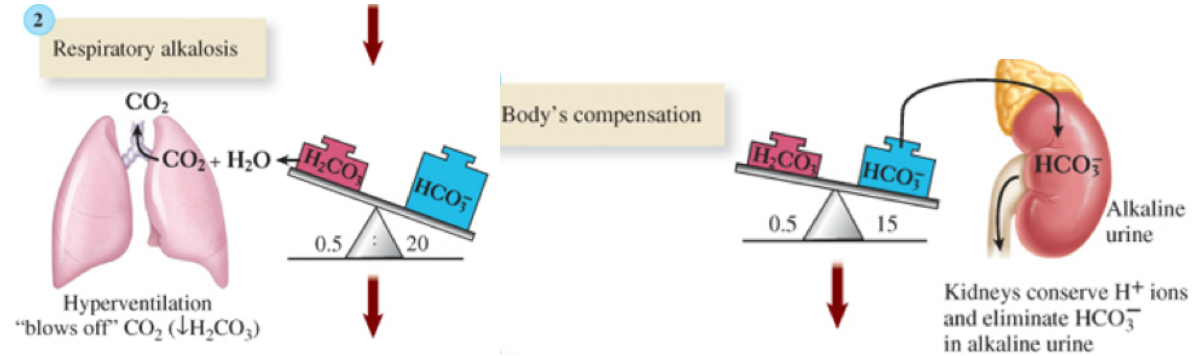
Respiratory Acidosis Scenario

Increase CO2 (ex. Hypoventilation) → increased H+ (acidosis!) → kidney compensation: increased bicarb retention & H+ excretion



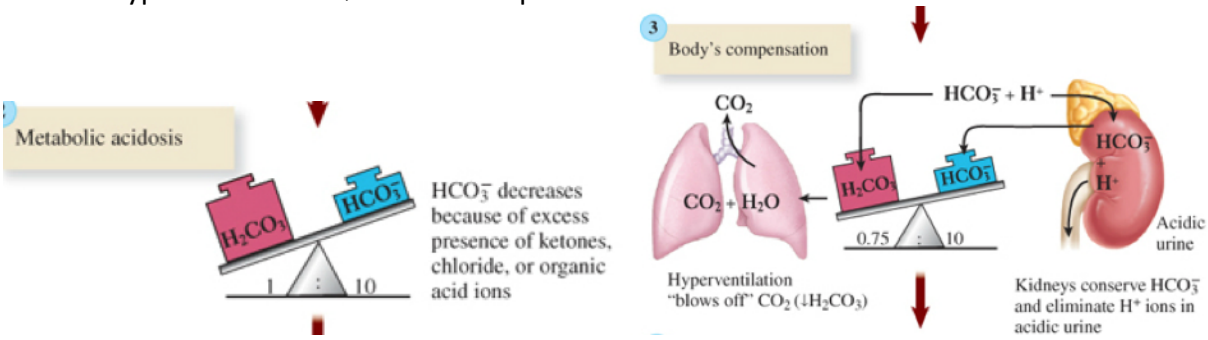
Respiratory Alkalosis Scenario

Decreased CO2 (ex: hyperventilation) → decreased H+ (alkalosis) → kidney compensation: increased bicarb excretion & H+ retention



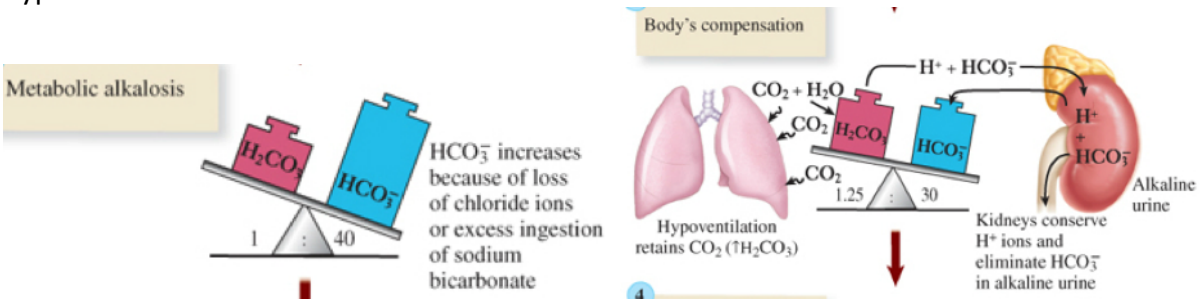
Metabolic Acidosis Scenario

Decreased bicarb (ex: renal failure) → increased H+ (acidosis) → lung compensation: decreased CO2 via hyperventilation → kussmal respirations



Metabolic Alkalosis Scenario

Increased bicarb (ex. vomiting) → decreased H+ (alkalosis) → lung compensation: hypoventilation to increase CO2



Acid-Base Disorders Summary

Disorder	pH	H^+	CO_2	HCO_3^-
Respiratory Acidosis	↓	↑	↑	↑
Respiratory Alkalosis	↑	↓	↓	↓
Metabolic Acidosis	↓	↑	↓	↓
Metabolic Alkalosis	↑	↓	↑	↑

Initial Event!!

BACK TO PHARM

Osmolarity Disorders

- Healthy [total plasma Osm] = 280-300 mEq/L
- Clinical setting:
  - Osmolarity in terms of [plasma Na+]
  - Healthy = 135-145 mEq/L ~ 50% TPO
- Isotonic contraction: equal loss of salt and water
  - Ex: hemorrhage
  - Slow administration - you need to give the body time to readapt and not overload it, because your body is actively adapting to the situation. You don't want to do the work for the body.
  - If administered rapidly, can cause pulmonary edema

- Volume expansion: when you have a water gain or a large sodium gain (significant enough to have a volume expansion)

Volume Expansion	H_2O Gain < or > or = Na^+ Gain
Causes	Therapeutic Fluid Overdose Heart Failure Liver Cirrhosis Ascites
Treatments	Diuretics Anti-Heart Failure Agents

Isotonic Contraction	Na^+ Loss = H_2O Loss
Causes	Cholera infection (Diarrhea; Vomiting) Diuretics ADR Kidney Disease
Treatments	Slow admin of Saline (0.9%) solution
Hypertonic Contraction	**Na^+ Loss < H_2O Loss**
Causes	↑↑↑ Sweating Burn Shock
Treatments	Hypotonic Saline (0.45%) solution Simply drinking tap water
Hypotonic Contraction	**Na^+ Loss > H_2O Loss**
Causes	↑↑↑ Kidney Na^+ Excretion Ex.: Low aldosterone Chronic Kidney Disease
Treatments	Hypertonic Saline (3%) solution until [Plasma Na^+] = 130 mEq/L Aldosterone replacement therapy

Acid-Base Alterations

- Treat only when compensation mechanisms FAIL/INSUFFICIENT

Respiratory Acidosis	↑ CO_2 → ↑ H^+
Causes	Hypoventilation Ex.: COPD; CNS (Medulla) Depression
Treatments	Treat Respiratory Impairment Severe : Sodium Bicarbonate infusion
Respiratory Alkalosis	**↓ CO_2 → ↓ H^+**
Causes	Hyperventilation Ex.: Hypoxia, Aspirin, Hysteria
Treatments	Mild: No need to treat Severe: Paper bag; sedative for hysteria

Metabolic Acidosis	↓ HCO_3^- → ↑ H^+
Causes	Renal failure; Severe diarrhea Ketoacidosis; Aspirin Poisoning
Treatments	Treat the cause Severe: Sodium Bicarbonate infusion
Metabolic Alkalosis	**↑ HCO_3^- → ↓ H^+**
Causes	Sodium Bicarbonate overdose Excessive vomiting
Treatments	NaCl + KCl infusions → ↓ HCO_3^- Severe: 0.1 N HCl infusion

Hyperkalemia

Healthy Concentrations	Regulation	Key Cellular Functions
• **Major Intracellular Ion** • Intracellular ≈ 150 mEq/L • Extracellular ≈ 4-5 mEq/L	• Insulin ↓ [Plasma K^+] (↑ Cell Uptake) • Alkalosis ↓ [Plasma K^+] • Acidosis ↑ [Plasma K^+] • Aldosterone & Diuretics ↑ Renal K^+ Excretion	1) Action Potential Conduction 2) Muscular Excitability 3) Acid-Base Regulation

Hyperkalemia = [Plasma K^+] > 5mEq/L	
Causes	Addison's Disease; Acidosis/Renal Failure; K^+-Sparring Diuretics or IV KCl Overdose
Symptoms	**Cardiac Electrical Dysfunctions → Dysrhythmias (see in 2 slides)** Mild: [Plasma K^+] ≈ 5-7mEq/L → Peak T-waves + Prolonged PR Interval Severe: [Plasma K^+] ≈ 8-9 mEq/L → Ventricular Tachycardia/Fibrillation & Arrest Non-Cardiac Sx: Confusion; Anxiety; Muscle Weakness/Tingling/Numbness
Treatment	1) Discontinue any potassium in food or drugs that ↑ [Plasma K^+] 2) Calcium Gluconate → Cancel Cardiac Effects of Potassium 3) Glucose or Insulin or Sodium Bicarb Infusions →↑ Cell Uptake of K^+ 4) If still insufficient: ***Sodium Polysterne Sulfonate (Kionex)*** → K^+ chelating agent

* In alkalosis, potassium moves into the cells, causing a reduction in extracellular K+

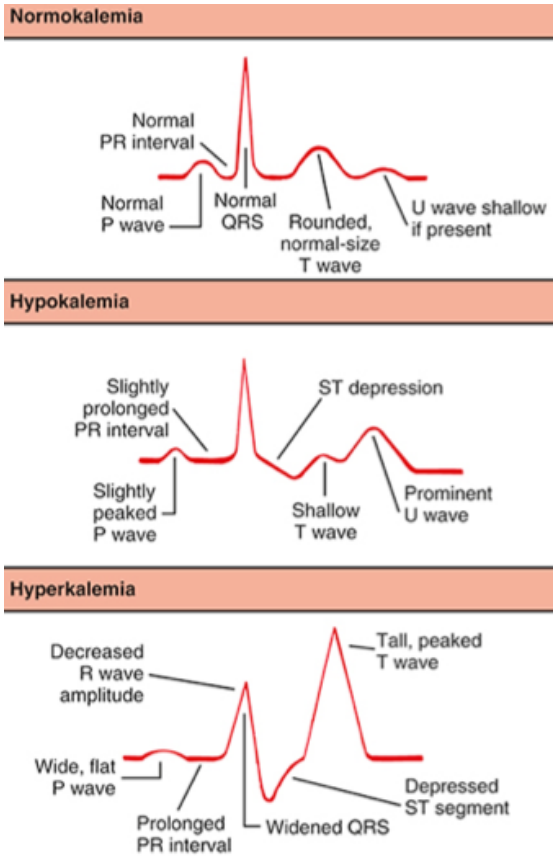
*In acidosis, potassium moves out of the cells, causing extracellular hyperkalemia.

Hypokalemia

Hypokalemia = [Plasma K^+] < 3.5 mEq/L	
Causes	Diuretics Therapy; Insulin poisoning; Alkalosis, etc.
Symptoms	↑ risk of HT, Strokes, fatal Dysrhythmias Muscle weakness & paralysis
Frequent Comorbidities	Loss of Cl^- → ***Hypokalemic Alkalosis***
Prevention & Treatment	***Potassium Chloride (preferred)*** or bicarbonate or phosphate
Oral KCl	Prevention (16-24 mEq/day) or Mild (40-100 mEq/day) Sustained-release = ↑ Patient Adherence (convenient + safer) **ADR**: GI Irritations (ex.: nausea; vomiting; diarrhea) **Rare ADRs**: GI Ulcers & Bleeding; Hyperkalemia
IV KCl	≤ 40 mEq/L solutions for Prevention (*PO* impossible) or Severe cases **ADR**: Hyperkalemia ***Nursing Tip***: monitoring of [Plasma K^+], renal functions & ECG for early toxicity ***SLOW Infusion ONLY** (< 10mEq/h) or else → Cardiac Arrest (ex.: lethal injections!!)**

Potassium Imbalances: ECG Alterations

- If you have less potassium, it takes longer for it to depolarize
- If you have too much potassium, the depolarization is overdone (high peak on the EKG)
    - The T wave heightens and the PR interval becomes prolonged



Magnesium Imbalances

- Healthy Concentrations
  - Intracellular = 40 mEq/L
  - Extracellular = 2 mEq/L
- Key cellular functions
  - Enzymatic cofactor
  - Ribosome-mRNA binding
  - Long-term potentiation
  - Muscle excitability

Hypomagnesemia	
Causes	Diarrhea; Kidney Disease
Symptoms	↑ Muscle & Neural Excitation Ex.: Tetany; Psychoses; Seizures ↑ Kidney stones formation
Frequent Comorbidities	Hypocalcemia Hypokalemia
Prevention	Magnesium Oxide Supplements >800mg/daily → Diarrhea
Treatment	**Magnesium Sulfate (IM or IV)**
Adverse Effects	Hypermagnesemia Sx (Resp. & Cardiac) Calcium Antidote should be pre-prepared!!

Hypermagnesemia	
Causes	Renal Insufficiency
Symptoms	Muscle Weakness; Sedation; Hypotension Respiratory Arrest ≈ 12-15 mEq/L; Cardiac Arrest > 25 mEq/L
Treatment	**IV Calcium Gluconate Antidote**