THE ABSITE REVIEW

7th EDITION

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Dedicated to Garrett, Elle, and the rest of my wonderful family

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PREFACE TO THE FIRST EDITION

Each year, thousands of general surgery residents across the country express anxiety over preparation for the American Board of Surgery In-Training Examination (ABSITE), an exam designed to test residents on their knowledge of the many topics related to general surgery.

This exam is important to the future career of general surgery residents for several reasons. Academic centers and private practices searching for new general surgeons use ABSITE scores as part of the evaluation process. Fellowships in fields such as surgical oncology, trauma, and cardiothoracic surgery use these scores when evaluating potential fellows. Residents with high ABSITE results are looked upon favorably by general surgery program directors, as high scorers enhance program reputation, helping garner applications from the best medical students interested in surgery.

General surgery programs also use the ABSITE scores, with consideration of feedback on clinical performance, when evaluating residents for promotion through residency. Clearly, this examination is important to general surgery residents.

Much of the anxiety over the ABSITE stems from the issue that there are no dedicated outline-format review manuals available to assist in preparation. *The ABSITE Review* was developed to serve as a quick and thorough study guide for the ABSITE, such that it could be used independently of other material and would cover nearly all topics found on the exam. The outline format makes it easy to hit the essential points on each topic quickly and succinctly, without having to wade through the extraneous material found in most textbooks. As opposed to question-and-answer reviews, the format also promotes rapid memorization.

Although specifically designed for general surgery residents taking the ABSITE, the information contained in *The ABSITE Review* is also especially useful for certain other groups:

- General surgery residents preparing for their written American Board of Surgery certification examination
- Surgical residents going into another specialty who want a broad perspective of general surgery and surgical subspecialties (and who may also be required to take the ABSITE)
- Practicing surgeons preparing for their American Board of Surgery recertification examination

PREFACE TO THE SEVENTH EDITION

The seventh edition of *The ABSITE Review* dives deeper in found in the ABSITE with new information on surgical oncology, trauma, vascular, critical care, nutrition, and a number of other topics. Like previous editions, *The ABSITE Review* provides a quick, easy review of important surgical topics while still providing sufficient explanation, so readers do not feel lost.

Again, I thank all of the residents who gave me feedback on the books or who I met at surgical meetings saying, "I used your books in residency and they were great." I am glad I could help out.

Thank you again and good luck on the ABSITE.

1 Cell Biology

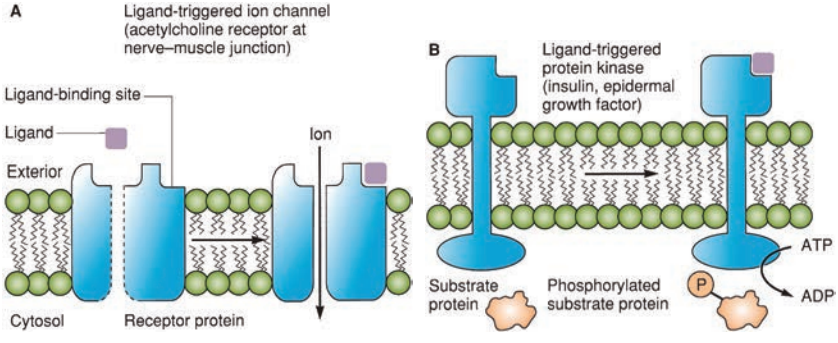
CELL MEMBRANE

- A **lipid bilayer** that contains protein channels, enzymes, and receptors
- **Cholesterol** increases membrane fluidity.
- Cells are negative inside compared to outside; based on Na/K ATPase (3 Na^+ out/2 K^+ in)
- The **Na^+ gradient** that is created is used for **co-transport** of glucose, proteins, and other molecules.

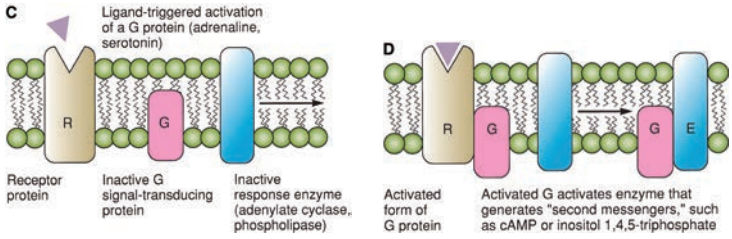
Electrolyte Concentrations of Intracellular and Extracellular Fluid Compartments

	Extracellular Fluid (mEq/L)	Intracellular Fluid (mEq/L)
CATIONS		
Na^+	140	12
K^+	4	150
Ca^{2+}	5	10^{-4}
Mg^{2+}	2	7
ANIONS		
Cl^-	103	3
HCO_3^-	24	10
SO_4^{2-}	1	–
HPO_4^{3-}	2	116
Protein	16	40
Organic anions	5	–

- **Desmosomes/hemidesmosomes** – adhesion molecules (cell–cell and cell–extracellular matrix, respectively), which anchor cells
- **Tight junctions** – cell–cell occluding junctions; form an impermeable barrier (eg epithelium)
- **Gap junctions** – allow communication between cells (connexin subunits)
- **G proteins** (are GTPases) – intramembrane proteins; transduce signal from receptor to response enzyme
- **Ligand-triggered protein kinase** – receptor and response enzyme are a single transmembrane protein (eg receptor tyrosine kinase)



Types of cell surface receptors. (A) Ligand-activated ion channel; binding results in a conformational change, opening or activating the channel. **(B)** Ligand-activated protein kinase; binding activates the kinase domain, which phosphorylates substrate proteins. *(continued)*



Types of cell surface receptors. *(continued)* **(C and D)** Ligand activation of a G protein, which then activates an enzyme that generates second, or intracellular, messengers.

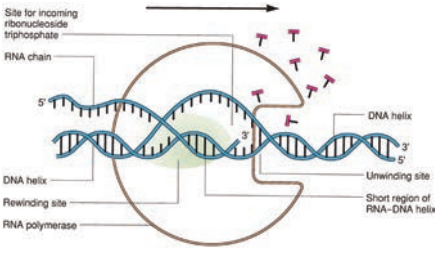
- **ABO blood-type antigens** – glycolipids on cell membrane
- **HLA-type antigens** – glycoproteins (Gp) on cell membrane
- **Osmotic equilibrium** – water will move from an area of low solute concentration to an area of high solute concentration and approach osmotic equilibrium

CELL CYCLE

- **G1**, **S** (protein synthesis, chromosomal duplication), **G2**, **M** (mitosis, nucleus divides)
- G1 most variable, determines cell cycle length
- **Growth factors** affect cell during G1.
- Cells can also go to G0 (quiescent) from G1.
- **Mitosis**
  - **Prophase** – centromere attachment, centriole and spindle formation, nucleus disappears
  - **Metaphase** – chromosome alignment
  - **Anaphase** – chromosomes pulled apart
  - **Telophase** – separate nucleus reforms around each set of chromosomes

NUCLEUS, TRANSCRIPTION, AND TRANSLATION

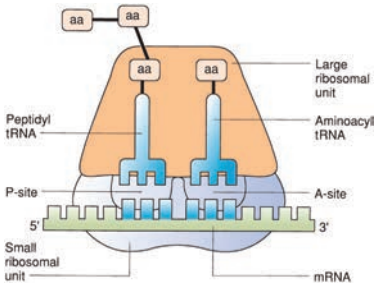
- **Nucleus** – double membrane, outer membrane continuous with rough endoplasmic reticulum
- **Nucleolus** – inside the nucleus, no membrane, **ribosomes** are made here
- **Transcription** – DNA strand is used as a template by **RNA polymerase** for synthesis of an mRNA strand



Transcription of DNA. RNA polymerase acts to unwind the DNA helix, catalyzes the formation of a transient RNA–DNA helix, and then releases the RNA as a single-strand copy while the DNA rewinds. In the process, the polymerase moves along the DNA from a start sequence to a stop sequence.

- **Transcription factors** – bind DNA and help the transcription of genes
  - **Steroid hormone** – binds receptor in cytoplasm, then enters nucleus and acts as transcription factor
  - **Thyroid hormone** – binds receptor in nucleus, then acts as a transcription factor
  - Other transcription factors – AP-1, NF-κB, STAT, NFAT
- **Initiation factors** – bind RNA polymerase and initiate transcription
- **DNA polymerase chain reaction** – uses oligonucleotides to amplify specific DNA sequences
- **Purines** – guanine, adenine
- **Pyrimidines** – cytosine, thymidine (only in DNA), uracil (only in RNA)
  - Guanine forms 3 hydrogen bonds with cytosine.
  - Adenine forms 2 hydrogen bonds with either thymidine or uracil.
- **Translation** – mRNA used as a template by **ribosomes** for the synthesis of **protein**

Ribosomes – have small and large subunits that read mRNA, then bind appropriate tRNAs that have amino acids, and eventually make proteins



Schematic view of the elongation phase of protein synthesis on a ribosome. As the ribosome moves along the mRNA, incoming aminoacyl–tRNA complexes bind to the A-site on the ribosome, after which a new peptide bond is formed with the nascent polypeptide chain previously attached to the peptide tRNA. The ribosome then moves, ejecting the now-empty tRNA and opening the A-site for the next aminoacyl–tRNA complex.

CELLULAR METABOLISM

- **Glycolysis** – 1 glucose molecule generates 2 ATP and 2 pyruvate molecules
- **Mitochondria** – 2 membranes, Krebs cycle on inner matrix, NADH/$FADH_2$ created
  - **Krebs cycle** (citric acid cycle) – the 2 pyruvate molecules (from the breakdown of 1 glucose) create NADH and $FADH_2$
  - NADH and $FADH_2$ enter the electron transport chain, leading to formation of a H^+ gradient and creation of ATP by ATP synthase.
  - Overall, 1 molecule of glucose produces 36 ATP.
  - Amino acids, ketones, and short-chain fatty acids can also enter the Krebs cycle to produce ATP.
- **Gluconeogenesis** – mechanism by which **lactic acid** (Cori cycle) and **amino acids** (#1 alanine) are converted to glucose
  - Used in times of starvation or stress (basically the glycolysis pathway in reverse)
  - **Fat and lipids** are not available for gluconeogenesis because acetyl CoA (breakdown product of fat metabolism) cannot be converted back to pyruvate.
- **Cori cycle** – mechanism in which the **liver** converts **muscle lactate** into new **glucose**; pyruvate plays a key role in this process

OTHER CELL ORGANELLES, ENZYMES, AND STRUCTURAL COMPONENTS

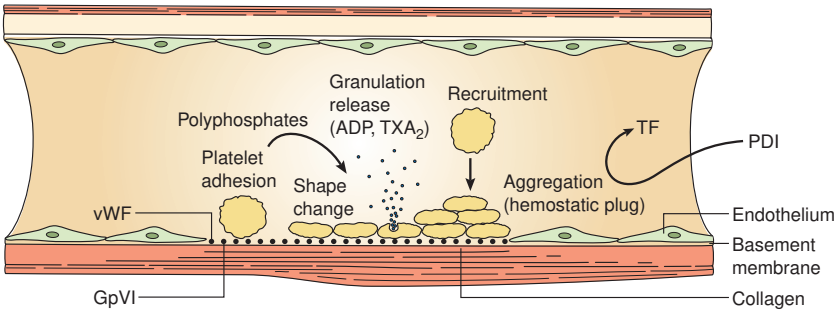
- **White blood cells** – contain nuclear material
- **Red blood cells** and **platelets** – do not contain nuclear material
- **Rough endoplasmic reticulum** – synthesizes proteins that are exported (increased in pancreatic acinar cells)
- **Smooth endoplasmic reticulum** – lipid/steroid synthesis, detoxifies drugs (increased in liver and adrenal cortex)
- **Golgi apparatus** – modifies proteins with **carbohydrates**; proteins are then transported to the cellular membrane, secreted, or targeted to lysosomes
- **Lysosomes** – have digestive enzymes that degrade engulfed particles and worn-out organelles
- **Phagosomes** – engulfed large particles; these fuse with lysosomes
- **Endosomes** – engulfed small particles; these fuse with lysosomes
- **Major signaling pathways** – phospholipase C, protein kinase A, and MAPK/ERK pathway
  - Utilize second messengers for signal transduction
- **Phospholipase C** – cleaves phospholipid phosphatidylinositol 4,5-bisphosphonate (PIP_2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3)
  - IP_3 causes release of calcium from the smooth endoplasmic reticulum.

Protein kinase C – activated by **calcium** and **diacylglycerol** (DAG); phosphorylates other enzymes and proteins
Protein kinase A – activated by **cAMP**; phosphorylates other enzymes and proteins

- **MAPK/ERK** – very complex pathway
- **Myosin** – thick filaments, uses ATP to slide along actin to cause **muscle contraction**
- **Actin** – thin filaments, interact with myosin above
- **Intermediate filaments** – keratin (hair/nails), desmin (muscle), vimentin (fibroblasts)
- **Microtubules** – form specialized cellular structures such as cilia, neuronal axons, and mitotic spindles; also involved in the transport of organelles in the cell (form a latticework inside the cell)
  - **Centriole** – a specialized microtubule involved in cell division (forms spindle fibers, which pull chromosome apart)

2 Hematology

INTRODUCTION



Primary hemostasis is achieved initially with a platelet aggregation as illustrated. Note that platelet adhesion, shape change, granule release followed by recruitment, and the hemostatic plug at the area of subendothelial collagen and collagen exposure are the initial events for thrombus formation.

NORMAL COAGULATION

Three initial responses to vascular injury: vascular vasoconstriction, platelet adhesion, and thrombin generation

Intrinsic pathway: exposed **collagen** + **prekallikrein** + **HMW kininogen** + **factor XII**
↓
activate XI
↓
activate IX, then add VIII
↓
activate X, then add V
↓
convert **prothrombin** (factor II) to **thrombin**
↓
thrombin then converts **fibrinogen** to **fibrin**

Extrinsic pathway: **tissue factor** (injured cells) + **factor VII**
↓
activate X, then add V
↓
convert **prothrombin** to **thrombin**
↓
thrombin then converts **fibrinogen** to **fibrin**

Prothrombin complex (for intrinsic and extrinsic pathways)
X, **V**, **Ca**, **platelet factor 3**, and **prothrombin**
Forms on platelets
Catalyzes the formation of thrombin

Factor X is the convergence point and is common for both paths.
Tissue factor pathway inhibitor – inhibits factor X

Fibrin – links platelets together (binds GpIIb/IIIa molecules) to form platelet plug → hemostasis
XIII – helps crosslink fibrin

Thrombin
Key to coagulation
Converts **fibrinogen** to **fibrin** and fibrin split products
Activates **factors V** and **VIII**
Activates **platelets**

NORMAL ANTICOAGULATION

Antithrombin III (AT-III)
- **Key to anticoagulation**
- Binds and inhibits **thrombin**
- Inhibits **factors IX**, **X**, and **XI**
- Heparin activates **AT-III** (up to 1000× normal activity).

Protein C – vitamin K–dependent; degrades **factors V** and **VIII**; degrades **fibrinogen**

Protein S – vitamin K–dependent, protein C cofactor

Fibrinolysis
- **Tissue plasminogen activator** – released from endothelium and converts plasminogen to plasmin
- **Plasmin** – degrades **factors V** and **VIII**, **fibrinogen**, and **fibrin** → lose platelet plug
- **Alpha-2 antiplasmin** – natural inhibitor of plasmin, released from endothelium

- **Factor VII** – shortest half-life
- **Factors V** and **VIII** – labile factors, activity lost in stored blood, activity not lost in FFP
- **Factor VIII** – only factor *not* synthesized in liver (synthesized in **endothelium** along with von Willebrand's Factor [vWF])
- **Factor II** – prothrombin
- **Vitamin K–dependent factors** – II, VII, IX, and X; proteins C and S
- **Vitamin K** – IV form takes 12 hours to start effect and **24 hours** for full effect
- **FFP** – effect is immediate after infusion (takes **2 hours** to thaw and complete infusion)
- **PCC** (prothrombin complex concentrate; eg Kcentra) – effect is immediate after infusion (which takes **30 minutes**)
- **Normal half-life** – RBCs: 120 days; platelets: 7 days; PMNs: 1–2 days
- **Prostacyclin** (PGI_2)
  - From **endothelium**
  - Decreases platelet aggregation and promotes vasodilation (antagonistic to TXA_2)
  - Increases cAMP in platelets
- **Thromboxane** (TXA_2)
  - From **platelets**
  - Increases platelet aggregation and promotes vasoconstriction
  - Triggers release of **calcium** in platelets → exposes **GpIIb/IIIa receptor** and causes platelet-to-platelet binding; platelet-to-collagen binding also occurs (**GpIb receptor**)

COAGULATION FACTORS

- **Cryoprecipitate** – contains highest concentrations of **vWF** and **factor VIII**; used in von Willebrand's disease and hemophilia A (factor VIII deficiency), also high levels of **fibrinogen**
- **FFP** (fresh frozen plasma) – has high levels of all coagulation factors, protein C, protein S, and AT-III
- **DDAVP** and **conjugated estrogens** – cause release of **VIII** and **vWF** from endothelium

COAGULATION MEASUREMENTS

- **PT/INR** (prothrombin time; extrinsic pathway) – measures II, V, VII, and X; fibrinogen; best for **liver synthetic function**
  - Measures **warfarin** anticoagulation (want **INR 2–3** for routine anticoagulation)
- **PTT** (partial thromboplastin time; intrinsic pathway) – measures most factors ***except VII and XIII*** *(thus does not pick up factor VII deficiency)*; also measures fibrinogen
  - Measures **heparin** anticoagulation (want **PTT 60–90 sec** for routine anticoagulation)

- **ACT** = activated clotting time
  - Want **ACT 150–200 sec** for routine anticoagulation, > **400 sec** for cardiopulmonary bypass
- INR > 1.5 – relative contraindication to performing surgical procedures
- INR > 1.3 – relative contraindication to central line placement, percutaneous needle biopsies, and eye surgery
- **Bleeding time** – tests platelet function
- **TEG** (Thromboelastography)
  - **Elevated R** (reaction time) Tx: **FFP**
  - **Elevated K** (K time) Tx: **cryoprecipitate**
  - **Low angle** (clot kinetics) Tx: **cryoprecipitate**
  - **Low MA** (maximum altitude) Tx: **platelets/DDAVP**
  - **High LY30** (lysis 30 minutes after MA) Tx: **aminocaproic acid** or **tranxemic acid**

BLEEDING DISORDERS

- **Incomplete hemostasis** – most common cause of surgical bleeding
- **von Willebrand's disease**
  - ***Most common congenital bleeding disorder***
  - MC Sx – epistaxis
  - Types I and II are autosomal dominant; type III is autosomal recessive.
  - **vWF** links **GpIb receptor** on **platelets** to **collagen**.
  - PT normal; PTT can be normal or abnormal.
  - Have long **bleeding time** (ristocetin test)
  - **Type I** is **most common** (70% of cases) and often has only mild symptoms.
  - **Type III** causes the **most severe bleeding**.
  - **Type I** – reduced quantity of vWF
    - Tx: recombinant VIII:vWF, **DDAVP**, cryoprecipitate
  - **Type II** – defect in vWF molecule itself, vWF does not work well
    - Tx: recombinant VIII:vWF, **cryoprecipitate**, **DDAVP**
  - **Type III** – complete vWF deficiency (rare)
    - Tx: recombinant VIII:vWF; **cryoprecipitate** (highest concentration of vWF:VIII)
    - *DDAVP will not work for type III*.
- **Hemophilia A** (VIII deficiency)
  - Sex-linked recessive
  - MC Sx – hemarthrosis
  - Need levels 100% preop; keep at 80%–100% for 10–14 days after surgery.
  - **Prolonged PTT** and normal PT (follow PTT Q 8 hours after surgery)
  - **Factor VIII** crosses **placenta** → newborns may not bleed at circumcision
  - Hemophiliac **joint bleeding** – ***do not aspirate***
    - Tx: ice, keep joint mobile with range of motion exercises, **factor VIII** concentrate or **cryoprecipitate**
  - Hemophiliac **epistaxis**, **intracerebral hemorrhage**, or **hematuria**
    - Tx: **recombinant factor VIII** or **cryoprecipitate**
- **Hemophilia B** (IX deficiency) – Christmas disease
  - Sex-linked recessive
  - Need level 100% preop; keep at 30%–40% for 2–3 days after surgery
  - **Prolonged PTT** and normal PT
  - Tx: **recombinant factor IX** or **FFP**
- **Factor VII deficiency** – **prolonged PT** and normal PTT, bleeding tendency. Tx: **recombinant factor VII** concentrate or **FFP**
- **Platelet disorders** – cause bruising, epistaxis, petechiae, purpura
  - **Acquired thrombocytopenia** – can be caused by H_2 blockers, heparin

- **Glanzmann's thrombocytopenia** – GpIIb/IIIa receptor deficiency on platelets (cannot bind to each other)
  - Fibrin normally links the GpIIb/IIIa receptors together.
  - Tx: **platelets**
- **Bernard Soulier** – GpIb receptor deficiency on platelets (cannot bind to collagen)
  - vWF normally links GpIb to collagen.
  - Tx: **platelets**
- **Uremia** (BUN > 60–80) – inhibits platelet function, mainly by inhibiting release of vWF
  - Tx: **hemodialysis** (1st-line Tx), DDAVP (for acute reversal), cryoprecipitate (for moderate to severe bleeding)

- **Heparin-induced thrombocytopenia** (HIT)
  - Thrombocytopenia due to **anti-heparin antibodies** (IgG heparin-PF4 antibody) results in platelet destruction.
  - Can also cause platelet aggregation and **thrombosis** (HIT**T**; **T** = thrombosis)
  - Clinical signs: platelets < 100, a drop in platelets > 50% admission levels, or thrombosis while on heparin
  - Forms a **white clot**
  - Can occur with low doses of heparin
  - Dx: ELISA for heparin Ab's (initial screen); serotonin release assay (confirmation)
  - Tx: ***Stop heparin***; start **argatroban** (direct thrombin inhibitor) to anticoagulate.
  - *Avoid giving platelets (risk of thrombosis).*
- **Disseminated intravascular coagulation** (DIC)
  - **Decreased platelets**, **low fibrinogen**, **high fibrin split products** (high D-dimer)
  - Prolonged PT and prolonged PTT
  - Often initiated by **tissue factor**
  - Tx: need to treat the underlying cause (eg sepsis)
- **ASA** – stop 7 days before surgery; patients will have prolonged bleeding time
  - **Inhibits cyclooxygenase** in platelets and **decreases TXA_2**
  - Platelets lack DNA, so they cannot resynthesize cyclooxygenase.
- **Clopidogrel** (Plavix) – stop 7 days before surgery; ADP receptor antagonist
  - Tx for **bleeding**: platelets
  - Coronary stent and need to stop Plavix for elective surgery – Tx: bridge with Integrilin (eptifibatide [GpIIb/IIIa inhibitor])
- **Coumadin** – stop 7 days before surgery, consider starting heparin while Coumadin wears off
  - Tx for **bleeding**: **PCC** (fastest) or **FFP**; Vit K if you have time
- **Platelets** – want them > 50,000 before surgery, > 20,000 after surgery
- **Prostate surgery** – can release **urokinase**, activates plasminogen → thrombolysis
- Tx: **ε-aminocaproic acid** (Amicar; inhibits fibrinolysis)
- **H and P** – best way to predict bleeding risk
- **Normal circumcision** – does not rule out bleeding disorders; can still have clotting factors from mother
- **Abnormal bleeding with tooth extraction or tonsillectomy** – picks up 99% patients with bleeding disorder
- **Epistaxis** – common with vWF deficiency and platelet disorders
- **Menorrhagia** – common with bleeding disorders

HYPERCOAGULABILITY DISORDERS

- Present as venous or arterial thrombosis/emboli (eg DVT, PE, stroke)
- **Factor V Leiden mutation** – 30% of spontaneous venous thromboses
  - ***Most common congenital hypercoagulability disorder***
  - Causes **resistance to activated protein C**; the defect is on **factor V**.
  - Tx: heparin, warfarin

- **Hyperhomocysteinemia** – Tx: **folic acid** and **B_{12}**
- **Prothrombin gene defect G20210 A** – Tx: heparin, warfarin
- **Protein C or S deficiency** – Tx: heparin, warfarin
- **Antithrombin III deficiency**
  - ***Heparin does not work in these patients.***
  - Can develop after previous heparin exposure
  - Tx: recombinant AT-III concentrate or FFP (highest concentration of AT-III) followed by heparin, then warfarin
- **Dysfibrinogenemia**, **dysplasminogenemia** – Tx: heparin, warfarin
- **Polycythemia vera** – from bone marrow overproduction; can get **thrombosis**
  - Keep Hct $<$ 48 and platelets $<$ 400 before surgery.
  - Tx: phlebotomy, ASA, hydroxyurea
- **Anti-phospholipid antibody syndrome**
  - Sx's: DVT/PE; loss of pregnancy; may have symptoms of lupus
  - Not all of these patients have SLE.
  - **Procoagulant** (get prolonged PTT but are **hypercoagulable**)
  - Caused by **antibodies** to phospholipids including **cardiolipin** (mitochondria) and **lupus anticoagulant** (cell membrane)
  - Dx: **prolonged PTT** (not corrected with FFP), positive Russell viper venom time, false-positive RPR test for syphilis
  - Tx: heparin, warfarin
- **Acquired hypercoagulability** – **tobacco** (most common factor causing acquired hypercoagulability), malignancy, inflammatory states, inflammatory bowel disease, infections, oral contraceptives, pregnancy, rheumatoid arthritis, postop patients, myeloproliferative disorders
- **Cardiopulmonary bypass** – factor XII (Hageman factor) activated; results in consumptive coagulopathy
  - Tx: heparin to prevent
- **Warfarin-induced skin necrosis**
  - Occurs when placed on Coumadin without being heparinized first
  - Due to short half-life of proteins C and S, which are first to decrease in levels compared with the procoagulation factors; results in relative hyperthrombotic state
  - *Patients with relative **protein C deficiency** are especially susceptible.*
  - Tx: heparin if it occurs; prevent by placing patient on heparin before starting warfarin.
- **Key elements in the development of venous thromboses** (Virchow's triad) – stasis, endothelial injury, and hypercoagulability
- **Key element in the development of arterial thrombosis** – endothelial injury

DEEP VENOUS THROMBOSIS (DVT)

- Stasis, venous injury, and hypercoagulability (Virchow's triad) are risk factors.
- The majority of adult surgery inpatients should receive DVT prophylaxis.
- **Duration of anticoagulation for DVT/PE**:
  - **3 months** for – 1st time calf DVT *or* a provoked DVT or PE (eg postop patient)
  - **Lifetime** for – 2nd time calf DVT, unprovoked proximal DVT or PE, cancer (until cured), or a hypercoagulable state
- **IVC filters** (some are removable) – indicated for patients with either:
  1. Contraindications to anticoagulation
  2. PE while on anticoagulation
  3. Free-floating IVC, ilio-femoral, or deep femoral DVT (controversial)
  4. Recent pulmonary embolectomy
     - Place IVC *below* the renal veins (caudad to renal veins).
     - PE with filter in place – likely arise from SVC (upper extremities), IVC above filter, or gonadal veins

PULMONARY EMBOLISM (PE)

- If clinical suspicion is high, do not wait on CT scan results, just **give heparin bolus** unless there is a contraindication.
- If the patient is in shock despite massive inotropes and pressors, go to OR for open removal or angiography for suction catheter Tx; otherwise, give heparin (thrombolytics have not shown an improvement in survival) or suction catheter–based intervention.
- Most commonly from the **ilio-femoral** region

HEMATOLOGIC DRUGS

- **Procoagulant agents** (anti-fibrinolytics)
  - ***ε*-Aminocaproic acid** (Amicar)
    - Inhibits fibrinolysis by inhibiting **plasmin**
  - Used in DIC, persistent bleeding following cardiopulmonary bypass, ***thrombolytic overdoses***
- **Anticoagulation agents**
  - **Warfarin** – inhibits VKORC (inhibition prevents decarboxylation of glutamic residues on vitamin K–dependent factors); need to follow INR level
    - Half-life – **40 hours**
    - *Contraindicated* in pregnancy
  - Dabigatran (**Pradaxa**), apixaban (**Eliquis**), and rivaroxaban (**Xarelto**) – novel oral anticoagulants (NOACs) that do not use INR levels; used for patients **with atrial fibrillation** not due to a heart valve problem and in patients with **DVT** or **PE**
    - Pradaxa is a **direct thrombin inhibitors**
    - **Half-life** and **reversal agents**:
      - Pradaxa (half-life **12 hours**) – **Praxbind** (idarucizumab; monoclonal Ab that binds drug), dialysis
      - Eliquis (half-life **12 hours**) and Xarelto (half-life **6 hours**) – **Andexxa** (andexanet alfa; decoy receptor for Eliquis/Xarelto)
      - PCC can give partial reversal.
  - **Sequential compression devices** – improve venous return but also induce fibrinolysis with compression (release of tPA [tissue plasminogen activator] from endothelium)
  - **Heparin**
    - Binds and activates **anti-thrombin III** (1000× more activity); increases neutralization of factors IIa (prothrombin) and Xa
    - Reversed with **protamine** (binds heparin)
    - Half-life of heparin is **60–90 minutes** (want PTT 60–90 seconds).
    - Is cleared by the **reticuloendothelial system** (spleen; macrophages)
    - **Long-term heparin** – osteoporosis, alopecia
    - Heparin does not cross placental barrier (can be used in pregnancy) → warfarin does cross the placental barrier (not used in pregnancy)
    - **Protamine** – cross-reacts with NPH insulin or previous protamine exposure; 1% get protamine reaction (hypotension, bradycardia, and decreased heart function)
  - **Low molecular weight heparin** (eg enoxaparin) – lower risk of HIT compared to unfractionated heparin; binds and activates antithrombin III but inhibits just factor **Xa**
    - *Weakly* reversed with protamine
    - Can check **anti-Factor Xa levels** (LMWH assay) to determine effectiveness
    - Half-life – **6 hours**
  - **Argatroban** – direct thrombin inhibitor; metabolized in the **liver**, half-life is 50 minutes, often used in patients w/ **HITT**
  - **Bivalirudin** (Angiomax) – direct thrombin inhibitor, metabolized by **proteinase enzymes** in the blood; half-life is 25 minutes; can be used in patients w/ **HITT**

- **Hirudin** (Hirulog; from leeches) – direct thrombin inhibitor; metabolized by **kidneys**; half-life is 40 minutes; is the most potent direct inhibitor of thrombin; high risk for bleeding complications

- **Thrombolytics** – usually used for thrombosis; given with heparin
  - **tPA** (MC; tissue plasminogen activator) and **streptokinase** (has high antigenicity)
  - Both activate **plasminogen** which breaks down **fibrinogen**.
  - Need to follow **fibrinogen levels** – fibrinogen < 100 associated with increased risk and severity of bleeding
  - *Tx for thrombolytic overdose* – ***ε-aminocaproic acid*** *(Amicar)*

Contraindications to Thrombolytic Use (Urokinase, Streptokinase, tPA)

Degree	Contraindications
Absolute	Active internal bleeding; recent CVA or neurosurgery (<3 mo); intracranial pathology, recent GI bleeding
Major	Recent (<10 d) surgery, organ biopsy, or obstetric delivery; left heart thrombus; active peptic ulcer; recent major trauma; uncontrolled hypertension, recent eye surgery
Minor	Minor surgery; recent CPR; atrial fibrillation with mitral valve disease; bacterial endocarditis; hemostatic defects (ie renal or liver disease); diabetic hemorrhagic retinopathy; pregnancy

3 Blood Products

INTRODUCTION

All blood products carry the risk of HIV and hepatitis except **albumin** and **serum globulins** (these are heat treated).
Donated blood is screened for HIV, HepB, HepC, HTLV, syphilis, and West Nile virus.
CMV-negative blood – use in low-birth-weight infants, bone marrow transplant patients, and other transplant patients
Type O blood – universal donor, contains no antigens
Type AB blood – contains both A and B antigens
Females of childbearing age should receive Rh-negative blood.
Stored blood is low in 2,3-DPG → causes left shift (increased affinity for oxygen)
Type and crossmatch – determines ABO compatibility
Type and screen – determines ABO compatibility and looks for preformed Ab's to minor antigens
One unit of **pRBCs** should raise the Hgb by 1 (Hct 3–5).
One six-pack of **platelets** should raise platelet count by 50,000.

HEMOLYSIS REACTIONS

- **Acute hemolysis** – from **ABO incompatibility**; antibody mediated (type II hypersensitivity)
  - Back pain, chills, tachycardia, fever, hemoglobinuria
  - Can lead to ATN, DIC, shock
  - **Haptoglobin < 50** mg/dL (binds Hgb, then gets degraded), **free hemoglobin > 5** g/dL, increase in **unconjugated bilirubin**
  - Tx: fluids, diuretics, HCO_3^-, pressors
  - In anesthetized patients, transfusion reactions may present as **diffuse bleeding**.
- **Delayed hemolysis** (mild jaundice) – antibody-mediated against minor antigens from donor
  - Tx: Observe if stable.
- **Nonimmune hemolysis** – from squeezed blood
  - Tx: fluids and diuretics

OTHER REACTIONS

- **Febrile nonhemolytic transfusion reaction** – ***most common transfusion reaction***
  - Usually **recipient antibody** reaction against **donor WBCs** (cytokine release)
  - Tx: Discontinue transfusion if patient had previous transfusions or if it occurs soon after transfusion has begun.
  - Use WBC filters for subsequent transfusions.
- **Urticaria** (rash) – usually nonhemolytic
  - Usually **recipient antibodies** against **donor plasma proteins** (eg peanuts) or **IgA** in an IgA-deficient patient
  - Tx: histamine blockers (Benadryl), supportive
- **Anaphylaxis** – bronchospasm, hypotension, angioedema, urticaria
  - Usually **recipient antibodies** against **donor IgA** in an IgA-deficient recipient
  - Can be an **airway emergency**
  - Tx: **epinephrine**, fluids, pressors, steroids, histamine blockers (Benadryl)
- **Transfusion-related acute lung injury** (TRALI) – rare
  - Caused by **donor antibodies** to **recipient's WBCs**, clot in pulmonary capillaries
  - Leads to noncardiogenic pulmonary edema in < 6 hours (ARDS)
  - *MCC of death from transfusion reaction*

OTHER TRANSFUSION PROBLEMS

- **Cold** – **poor clotting** can be caused by cold products or cold body temperature (coagulopathy due to slowing of enzyme reactions); patient needs to be warm to clot correctly
- Dilutional **thrombocytopenia** and dilution of **coagulation factors** occur with massive transfusion.
- **Hypocalcemia** – can cause poor clotting; occurs with massive transfusion; Ca is required for the clotting cascade; hypocalcemia can also cause hypotension
- **Citrate** used in stored blood binds Ca after transfusion and causes hypocalcemia.
- Most common bacterial contaminate – **GNRs** (usually ***E. coli***)
- Most common blood product source of contamination – **platelets** (not refrigerated)
- **Chagas' disease** – can be transmitted with blood transfusion

4 Immunology

T CELLS (THYMUS) – CELL-MEDIATED IMMUNITY

- **Helper T cells** (CD4)
  - Release **IL-2**, which mainly causes maturation of **cytotoxic T cells**
  - Release **IL-4**, which mainly causes **B-cell** maturation into **plasma cells**
  - Release **interferon-gamma** which activates **macrophages**
  - Involved in **delayed-type hypersensitivity** (type IV; brings in inflammatory cells by chemokine secretion)
- **Suppressor T cells** (CD8) – regulate CD4 and CD8 cells
- **Cytotoxic T cells** (CD8) – recognize and attack non–self-antigens attached to **MHC class I receptors** (eg viral gene products); responsible for the majority of liver injury due to HepB
- Cell-mediated immunity does not require Ab's.
- Effector cells in cell-mediated immunity – macrophages, cytotoxic T cells, natural killer cells
- **Intradermal skin test** (ie TB skin test) – used to test cell-mediated immunity; takes 2–3 days
- ***Infections associated with defects in cell-mediated immunity*** *– intracellular pathogens (TB, viruses)*

B CELLS (BONE) – ANTIBODY-MEDIATED IMMUNITY (HUMORAL)

- IL-4 from helper T cells stimulates B cells to become plasma cells (antibody secreting).
- 10% become memory B cells which can be reactivated.
- IgG (as opposed to IgM) is secreted with reinfection.

MHC CLASSES

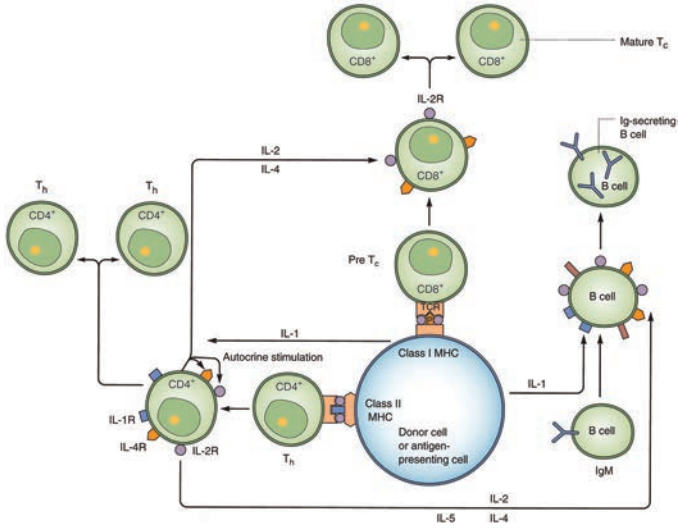
- **MHC class I** (A, B, and C)
  - **CD8** cell activation
  - Present on **all nucleated cells**
  - Single chain with 5 domains
  - ***Target for cytotoxic T cells*** *(bind T-cell receptor)*
- **MHC class II** (DR, DP, and DQ)
  - **CD4** cell activation
  - Present on **antigen-presenting cells** (APCs; eg dendrites [most important], monocytes)
  - 2 chains with 4 domains each
  - ***APCs activate helper T cells*** *(bind T-cell receptor) when passing through lymph nodes.*
  - ***Stimulates antibody formation*** *after interaction with B cells*

Viral infection – endogenous viral proteins produced, are bound to class I MHC, go to cell surface, and are recognized by CD8 cytotoxic T cells

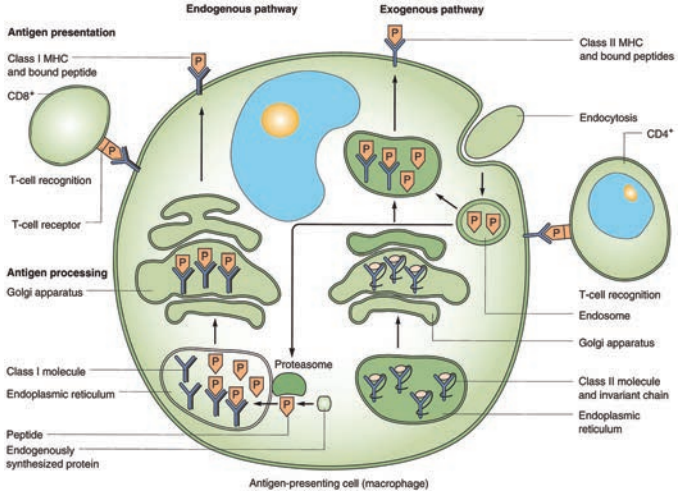
Bacterial infection – endocytosis, proteins get bound to class II MHC molecules, go to cell surface, recognized by CD4 helper T cells → B cells which have already bound to the antigen are then activated by the CD4 helper T cells; they then produce the antibody to that antigen and are transformed to plasma cells and memory B cells

NATURAL KILLER CELLS

- Not restricted by MHC, do not require previous exposure, do not require antigen presentation
- Not considered T or B cells
- *Recognize cells that* ***lack self-MHC***
- Part of the body's natural immunosurveillance for cancer
- Also attack cells with bound Ab (have Fc receptor)



T-cell and B-cell activation. Two signals are required. First, alloantigen binds to antigen-specific receptors—the TCR (T cells) or surface IgM (B cells). The second, or costimulatory, signal is provided by IL-1 released by the antigen-presenting cell. CD4 helper T cells (T_h) release IL-2 and IL-4, which provide help for CD8 T cells (T_c) and for B-cell activation.



Antigen processing and presentation. Endogenously synthesized or intracellular proteins are degraded into peptides that are transported to the ER. These peptides bind to **class I MHC** molecules and are transported to the surface of the antigen-presenting cell. $CD8^+$ cells recognize the foreign peptide bound to class I MHC by way of the TCR complex. Exogenous antigen is endocytosed and broken down into peptide fragments in endosomes. **Class II MHC** molecules are transported to the endosome, bind the peptide, and are delivered to the surface of the antigen-presenting cell, where they are recognized by $CD4^+$ cells.

ANTIBODIES

- **IgM** – initial antibody secreted after exposure to antigen (**primary** immune response). It is the largest antibody, having 5 domains (10 binding sites); MC Ab in the spleen
- **IgG** – most abundant antibody in body. Responsible for **secondary** immune response. Can cross the placenta and provides protection in newborn period. MC Ab overall
- **IgA** – found in secretions, in Peyer's patches in gut, and in breast milk (additional source of immunity in newborn); helps prevent microbial adherence and invasion in gut
- **IgD** – membrane-bound receptor on B cells (serves as an antigen receptor)
- **IgE** – allergic reactions, parasite infections (type I hypersensitivity reactions, see below)
- **IgM** and **IgG** are **opsonins**.
- **IgM** and **IgG** fix **complement** (requires 2 IgGs or 1 IgM).
- All Ab's have **2 antigen-binding sites** except **IgM** (which has 10 antigen-binding sites).
- **Variable region** – antigen recognition
- **Constant region** – recognized by PMNs, macrophages, and natural killer cells
  - Fc fragment does not carry variable region.
- **Polyclonal antibodies** have multiple binding sites to the antigen at multiple epitopes.
- **Monoclonal antibodies** have only 1 binding site to the antigen at 1 epitope.
- **Basophils** – major source of histamine in blood
- **Mast cells** – major source of histamine in tissue; main cell type for type I hypersensitivity
- **Primary lymphoid organs** – liver, bone, thymus
- **Secondary lymphoid organs** – spleen and lymph nodes
- **Immunologic chimera** – 2 different cell lines in one individual (eg bone marrow transplant patients)

Hypersensitivity Reactions

Type	Description	Examples
I	**Immediate hypersensitivity reaction** (allergic reaction; anaphylaxis) – **IgE** receptors on **mast cells** and **basophils** react with the antigen and cause release of **histamine**, serotonin, and bradykinin	Bee stings, peanuts, hay fever, Lymphazurin blue dye; Sx's – urticaria, hypotension, bronchoconstriction, angioedema; Tx: epinephrine, airway management
II	**IgG or IgM reacts with cell-bound antigen.**	ABO blood incompatibility, hyperacute rejection, myasthenia gravis
III	**Immune complex deposition**	Serum sickness, SLE
IV	**Delayed-type hypersensitivity** – APCs present antigen to helper T cells, which then activate macrophages to destroy the antigen; only hypersensitivity reaction not to involve Ab's (cell-mediated immunity)	TB skin test (PPD), contact dermatitis Generally takes 2–3 days

IL-2

- Converts lymphocytes to **lymphokine-activated killer** (LAK) cells by enhancing their immune response to tumor
- Also converts lymphocytes into **tumor-infiltrating lymphocytes** (TILs)
- Has shown some success for melanoma

TETANUS

- **Non–tetanus-prone wounds** – give **tetanus toxoid** only if patient has received < 3 doses or tetanus status is unknown, or > 10 years since booster
- **Tetanus-prone wounds** (> 6 hours old; obvious contamination and devitalized tissue; crush, burn, frostbite, or missile injuries) – always give **tetanus toxoid** unless patient has had ≥ 3 doses and it has been < 5 years since last booster
- **Tetanus immune globulin** (given intramuscular near wound site) – give only with tetanus-prone wounds in patients who have not been immunized or if immunization status is unknown

5 Infection

INTRODUCTION

Malnutrition – most common immune deficiency; leads to infection

MICROFLORA

- Stomach – virtually sterile; some GPCs, some yeast
- Proximal small bowel – 10^5 bacteria, mostly GPCs
- Distal small bowel – 10^7 bacteria, GPCs, GPRs, GNRs
- Colon – 10^{11} bacteria, almost all anaerobes, some GNRs, GPCs
- **Anaerobes** (anaerobic bacteria)
  - Most common organisms in the GI tract
  - More common than aerobic bacteria in the colon (1,000:1)
  - Need low-oxygen environment (lack superoxide dismutase and catalase, making them vulnerable to oxygen radicals)
  - ***Bacteroides fragilis*** – most common anaerobe in the colon
- ***Escherichia coli*** – most common aerobic bacteria in the colon

FEVER

- MC fever source **within 48 hours** — **Atelectasis**
- MC fever source **48 hours – 5 days** — **Urinary tract infection**
- MC fever source **after 5 days** — **Wound infection**
- **Fever sources** (sequentially over time) – atelectasis, urinary tract infection, pneumonia, DVT, wound infection, intra-abdominal abscess

GRAM-NEGATIVE SEPSIS

- ***E. coli*** most common
- **Endotoxin** (lipopolysaccharide **lipid A**) is released.
- Endotoxin triggers the release of **TNF-α** (most potent stimulus; released from macrophages, triggers inflammation), activates complement, and activates coagulation cascade.
- Early gram-negative sepsis – ↓ insulin, ↑ glucose (impaired utilization)
- Late gram-negative sepsis – ↑ insulin, ↑ glucose secondary to insulin resistance
- **Hyperglycemia** – often occurs just before the patient becomes clinically septic
- **Optimal glucose level in a septic patient**: < 180 mg/dL

CLOSTRIDIUM DIFFICILE COLITIS (PSEUDOMEMBRANOUS COLITIS)

- Sx's: foul-smelling diarrhea; nursing home or ICU patients
- Dx: ELISA for **toxin A**; elevated WBCs (often in 30–40's)
- Tx: **oral** – vancomycin or Flagyl; **IV** – Flagyl; lactobacillus can also help
- Pregnancy – oral vancomycin (no systemic absorption)
- Fluid resuscitation; stop other antibiotics or change them.
- Fulminant (eg severe sepsis, perforation) pseudomembranous colitis – Tx: total abdominal colectomy with ileostomy

ABSCESSES

- 90% of abdominal abscesses have anaerobes.
- 80% of abdominal abscesses have both anaerobic and aerobic bacteria.
- Abscesses are treated by **drainage** (usually percutaneous).
- Usually occur **7–10 days** after operation

- Antibiotics for an abscess are needed in patients with diabetes, cellulitis, clinical signs of sepsis, fever, or who have bioprosthetic hardware (eg mechanical valves, hip replacements).

WOUND INFECTION (SURGICAL SITE INFECTION)

- **Clean** (hernia): 2%
- **Clean contaminated** (elective colon resection with prepped bowel): 3%–5%
- **Contaminated** (gunshot wound to colon with repair): 5%–10%
- **Gross contamination** (abscess): 30%
- **Prophylactic antibiotics** are given to **prevent surgical site infections**.
  - Give antibiotics **within 1 hour** of incision.
  - Stop **within 24 hours** of end operation time, except cardiac, which is stopped within 48 hours of end operation time.
- ***Staphylococcus aureus*** – coagulase-positive
  - **Most common organism overall** in surgical site infections
- ***Staphylococcus epidermidis*** – coagulase-negative
- **Exoslime** released by staph species is an **exopolysaccharide matrix**.
- ***E. coli*** – most common **GNR** in surgical wound infections
- ***B. fragilis*** – most common **anaerobe** in surgical wound infections
  - Recovery from tissue indicates necrosis or abscess (only grows in low redox state).
  - Also implies translocation from the gut
- $\geq 10^5$ bacteria needed for wound infection; less bacteria is needed if foreign body present
- **Risk factors for wound infection**: long operations, hematoma or seroma formation, advanced age, chronic disease (eg COPD, renal failure, liver failure, diabetes mellitus), malnutrition, immunosuppressive drugs
- **Tx wound infection** (erythema, warmth, tenderness) – antibiotics, may need to open wound if wound abscess is present (get U/S if not sure)
- **Surgical infections within 48 hours of procedure**
  - **Injury to bowel** with leak
  - **Invasive soft tissue infection** – *Clostridium perfringens* and beta-hemolytic strep can present within hours postoperatively (produce exotoxins)
- Most common infection in surgery patients – **urinary tract infection**
  - Biggest risk factor – **urinary catheters**; most commonly ***E. coli*** *(GNRs)*
  - Tx: remove urinary catheter, abx's
- Leading cause of infectious death after surgery – **nosocomial pneumonia**
  - Related to the length of ventilation; aspiration from duodenum thought to have a role
  - Most common organisms in ICU pneumonia – **#1 *S. aureus***, #2 *Pseudomonas*, #3 *E. coli*
  - GNRs #1 class of organisms in ICU pneumonia

LINE INFECTIONS

- **#1 *S. epidermidis***, #2 *S. aureus*, #3 yeast
- **Femoral lines** at higher risk for infection compared to subclavian and intrajugular lines; subclavian lines have the lowest risk
- 50% line salvage rate with antibiotics (important for patients requiring long-term central access; 2 weeks of antibiotics); much less likely with yeast line infections
- **Suspected line infection** (temporary line) → move to new site or pull out the central line and place peripheral IVs if central line not needed

NECROTIZING SOFT TISSUE INFECTIONS

- Beta-hemolytic *Streptococcus* (group A), *C. perfringens*, or mixed organisms
- Usually occur in patients who are immunocompromised (eg diabetes mellitus, AIDS) or who have poor blood supply
- Can present very quickly after injury or surgical procedures (within hours)

- Pain out of proportion to skin findings (infection starts deep to the skin), mental status changes, WBCs > 20, thin gray drainage that is foul-smelling, can have skin blistering/necrosis, induration and edema, crepitus or soft tissue gas on x-ray, can be septic
- **Necrotizing fasciitis** – usually **beta-hemolytic group A strep** or **MRSA**
  - Overlying skin can look normal in the early stages (spreads along fascial planes).
  - Overlying skin progresses from pale red to purple with blister or bullae development.
  - Thin, gray, foul-smelling drainage; crepitus
  - GPCs without PMNs
  - Beta-hemolytic group A strep and MRSA have **exotoxin**.
  - Tx: **early debridement**, high-dose penicillin; may want broad spectrum if thought to be poly-organismal
- ***C. perfringens* infections**
  - **Necrotic tissue** decreases oxidation-redux potential, setting up environment for *C. perfringens*.
  - *C. perfringens* has **alpha toxin** (major source of morbidity).
  - Pain out of proportion to exam; may not show skin cellulitis (is a deep infection)
  - Gram stain shows GPRs without WBCs.
  - **Myonecrosis** and **gas gangrene** – common presentations
  - Can occur with farming injuries (dirty wounds)
  - Tx: **early debridement**, high-dose penicillin
- **Fournier's gangrene**
  - Severe infection in perineal and scrotal region
  - Risk factors – diabetes mellitus and immunocompromised state
  - Caused by mixed organisms (GPCs, GNRs, anaerobes)
  - Tx: **early debridement**; try to preserve testicles if possible; antibiotics

FUNGAL INFECTION

- Need fungal coverage for positive blood cultures, 2 sites other than blood, 1 site with severe symptoms, endophthalmitis, or patients on prolonged bacterial antibiotics with failure to improve
- **Actinomyces** (not a true fungus) – pulmonary symptoms most common; can cause tortuous abscesses in cervical, thoracic, and abdominal areas; characteristic yellow sulfur granules on Gram stain
  - Tx: **drainage** and **penicillin G**
- **Nocardia** (not a true fungus) – pulmonary and CNS symptoms most common
  - Tx: **drainage** and **sulfonamides** (Bactrim)
- **Candida** – common inhabitant of the respiratory tract; MCC of fungemia
  - Tx: **fluconazole** (some *Candida* resistant), **anidulafungin** for severe infections
  - Candiduria – Tx: remove urinary catheter only (anti-fungal not necessary)
- **Aspergillosis**
  - Tx: **voriconazole** for severe infections
- **Histoplasmosis** – pulmonary symptoms usual; Mississippi and Ohio River valleys
  - Tx: **liposomal amphotericin** for severe infections
- **Cryptococcus** – CNS symptoms most common; usually in AIDS patients
  - Tx: **liposomal amphotericin** for severe infections
- **Coccidioidomycosis** – pulmonary symptoms; Southwest
  - Tx: **liposomal amphotericin** for severe infections
- **Mucormycosis** – extensive burns or widespread trauma patients at risk; area turns black
  - Tx: debridement; **liposomal amphotericin**

SPONTANEOUS BACTERIAL PERITONITIS (SBP; PRIMARY)

- Sx's: mental status changes, fever, abdominal pain in a cirrhotic patient
- **Low protein** (< 1 g/dL) in peritoneal fluid – risk factor
- **Monobacterial** (50% ***E. coli***, 30% *Streptococcus*, 10% *Klebsiella*)

- Secondary to decreased host defenses (intrahepatic shunting, impaired bactericidal activity in ascites); not due to transmucosal migration
- Fluid cultures are negative in many cases.
- **Peritoneal fluid with PMNs > 250 or positive cultures are** diagnostic.
- Tx: **ceftriaxone** or other 3rd-generation cephalosporin
- Need to rule out intra-abdominal source (eg bowel perforation) if not getting better on antibiotics or if cultures are polymicrobial
- Liver transplantation not an option with active infection
- Weekly **fluoroquinolones** good for **SBP prophylaxis** (norfloxacin; indicated **for ascities** total protein < 1 g/dL or a previous history of SBP)
- Cirrhotic patients with **active UGI bleeds** should be placed on Abx's (eg norfloxacin) for a **7 day** course

SECONDARY BACTERIAL PERITONITIS

- Intra-abdominal source (implies perforated viscus)
- Polymicrobial – *B. fragilis*, *E. coli*, *Enterococcus* most common organisms
- Tx: usually need laparotomy to find source

HIV

- AIDS – loss of cell mediated immunity (decreased CD4 cells) leading to opportunistic infections
- RNA virus with reverse transcriptase
- **Exposure risk**
  - HIV blood transfusion 70%
  - Infant from positive mother 30%
  - Needle stick from positive patient 0.3%
  - Mucous membrane exposure 0.1%
  - Seroconversion occurs in 6–12 weeks.
  - **AZT** (zidovudine, reverse transcriptase inhibitor) and **ritonavir** (protease inhibitor) can help decrease seroconversion after exposure.
  - Antivirals should be given within 1–2 hours of exposure.
- **Opportunistic infections** – most common indication for laparotomy in HIV patients (CMV infection most common)
  - Neoplastic disease – 2nd most common reason for laparotomy (lymphoma most common)
- **CMV colitis** – most common intestinal manifestation of AIDS (can present with pain, bleeding, or perforation)
- **Kaposi's sarcoma** – MC neoplasm in AIDS patients (although surgery rarely needed)
- **Lymphoma in HIV patients** – stomach most common followed by rectum
  - MC malignancy requiring laparotomy
  - Mostly non-Hodgkin's (B cell)
  - Tx: chemotherapy usual; may need surgery with significant bleeding or perforation
- **GI bleeds** – **lower GI bleeds** are more common than upper GI bleeds in HIV patients
  - **Upper GI bleeds** – Kaposi's sarcoma, lymphoma
  - **Lower GI bleeds** – CMV, bacterial, HSV
- **CD4 counts**: 800–1,200 normal; 300–400 symptomatic disease; < 200 opportunistic infections

HEPATITIS C

- Now rarely transmitted with blood transfusion (0.0001%/unit)
- 1%–2% of population infected
- Fulminant hepatic failure rare
- Chronic infection in 60%; cirrhosis in 15%; hepatocellular carcinoma in 1%–5%
- MC indication for liver TXP
- Now curable with Sovaldi (sofosbuvir) in combination with ribavirin

CMV INFECTION

- Transmitted via **leukocytes**
- MC infection in TXP patients
- MC manifestation – **febrile mononucleosis** (sore throat, adenopathy)
- Most deadly form – **CMV pneumonitis**
- Dx: biopsy – shows characteristic **cellular inclusion bodies**; CMV serology
- Tx: **ganciclovir**; **CMV immune globulin** (Cytogam) indicated for severe infections or a CMV-negative patient receiving a CMV-positive organ

OTHER INFECTIONS

- **Aspiration pneumonia** – MC in the superior segment of the right lower lobe
  - Strep pneumonia MC organism; also need to cover anaerobes
- Highest sensitivity test for **osteomyelitis** – MRI (avoid bone Bx)
- **Brown recluse spider bites** – Tx: oral **dapsone** initially; avoid early surgery; may need resection of area and skin graft for large ulcers later
- **Acute septic arthritis** – *Gonococcus*, staph, *H. influenzae*, strep
  - Tx: **drainage**, 3rd-generation cephalosporin and vancomycin until cultures show organism
- **Diabetic foot infections** – mixed staph, strep, GNRs, and anaerobes
  - Tx: broad-spectrum antibiotics (Unasyn, Zosyn)
- **Cat/dog/human bites** – polymicrobial infection usual (MC – *Strep pyogenes*)
  - ***Eikenella*** found only in human bites; can cause permanent joint injury
  - ***Pasteurella multocida*** found in cat and dog bites
  - Tx: broad-spectrum antibiotics (Augmentin)
- **Impetigo**, **erysipelas**, **cellulitis**, and **folliculitis** – staph (most common) and strep
- **Furuncle** – boil; usually *S. epidermidis* or *S. aureus*. Tx: drainage ± antibiotics
- **Carbuncle** – a multiloculated furuncle
- **Peritoneal dialysis catheter infections**
  - Sx's: cloudy fluid, abdominal pain, fever; usually monobacterial
  - *S. epidermidis* (#1), *S. aureus*, and *Pseudomonas* most common organisms
  - Fungal infections hard to treat
  - Tx: intraperitoneal vancomycin and gentamicin; increased dwell time and intraperitoneal heparin may help; IV antibiotics not as effective as intraperitoneal
  - Removal of catheter for peritonitis that lasts for 4–5 days
  - Fecal peritonitis requires laparotomy to find perforation.
  - Some say need removal of peritoneal dialysis catheter for all fungal, tuberculous, and *Pseudomonas* infections.
- **Sinusitis**
  - **Risk factors** – nasoenteric tubes, intubation, patients with severe facial fractures
  - Usually polymicrobial
  - CT head shows air–fluid levels in the sinus.
  - Tx: broad-spectrum antibiotics; rare to have to tap sinus percutaneously for systemic illness
- **Prevention of nosocomial infections** (hospital-acquired infections)
  - Hand washing – best prevention strategy
  - Highest risk patients – burn patients
  - If patient is on isolation, leave gloves and gown in the room.
- **Prevention of surgical site infections**
  - Use **clippers** preoperatively instead of razors.
  - Keep glucose 80–120.
  - Keep PO_2 elevated (give 100% oxygen).
  - Keep patient warm (keep OR 70°F; warm air conduction [Bair Hugger] best for warming patients).
  - Chlorhexidine prep with iodine-impregnated drapes

6 Antibiotics

INTRODUCTION

- **Antiseptic** – kills and inhibits organisms on body
- **Disinfectant** – kills and inhibits organisms on inanimate objects
- **Sterilization** – all organisms killed
- **Common antiseptics in surgery**
  - **Iodophors** (Betadine) – good for GPCs and GNRs; poor for fungi
  - **Chlorhexidine gluconate** (Hibiclens) – good for GPCs, GNRs, and fungi

ANTIBIOTIC MECHANISM OF ACTION

- **Inhibitors** of **cell wall synthesis** – penicillins, cephalosporins, carbapenems, monobactams, vancomycin
- **Inhibitors** of the **30s ribosome and protein synthesis** – tetracycline, aminoglycosides (tobramycin, gentamicin)
- **Inhibitors** of the **50s ribosome and protein synthesis** – erythromycin, clindamycin, Synercid, linezolid
- **Inhibitor** of **DNA helicase** (DNA gyrase) – quinolones
- **Inhibitor** of **RNA polymerase** – rifampin
- **Produces oxygen radicals** that **breakup DNA** – metronidazole (Flagyl)
- **Sulfonamides** – PABA analogue, inhibits purine synthesis
- **Trimethoprim** – inhibits dihydrofolate reductase, which inhibits purine synthesis
- **Bacteriostatic antibiotics** – tetracycline, clindamycin, erythromycin (all have reversible ribosomal binding), Bactrim
- **Aminoglycosides** – have irreversible binding to ribosome and are considered **bactericidal**

MECHANISM OF ANTIBIOTIC RESISTANCE

- **PCN resistance** – due to plasmids for beta-lactamase (eg *Staphylococcus aureus*)
- **Transfer of plasmids** – most common method of antibiotic resistance
- **Methicillin-resistant *S. aureus*** (MRSA) – resistance caused by a **mutation of cell wall–binding protein**
- **Vancomycin-resistant *Enterococcus*** (VRE) – resistance caused by a **mutation in cell wall–binding protein**
- **Gentamicin resistance** – resistance due to modifying enzymes leading to a **decrease in active transport of gentamicin** into the bacteria

APPROPRIATE DRUG LEVELS

- **Vancomycin** – peak 20–40 μg/mL; trough 5–10 μg/mL
- **Gentamicin** – peak 6–10 μg/mL; trough < 1 μg/mL
- **Peak too high** → decrease amount of each dose
- **Trough too high** → decrease frequency of doses (increase time interval between doses)

SPECIFIC ANTIBIOTICS

- **Penicillin**
  - **GPCs** – streptococci, syphilis, *Neisseria meningitides* (GPR), *Clostridium perfringens* (GPR), beta-hemolytic *Streptococcus*, anthrax
  - Not effective against *Staphylococcus* or *Enterococcus*
- **Oxacillin**, **methicillin**, and **nafcillin**
  - **Anti-staph** penicillins (staph only)

- **Ampicillin** and **amoxicillin**
  - Same as penicillin but also picks up enterococci
- **Unasyn** (ampicillin/sulbactam) and **Augmentin** (amoxicillin/clavulanic acid)
  - Broad spectrum – pick up **GPCs** (staph and strep), **GNRs**, ± anaerobic coverage
  - Effective for enterococci; not effective for *Pseudomonas*, *Acinetobacter*, or *Serratia*
  - **Sulbactam** and **clavulanic acid** are beta-lactamase inhibitors.
- **Ticarcillin** and **piperacillin** (antipseudomonal penicillins)
  - **GNRs** – enterics, *Pseudomonas*, *Acinetobacter*, and *Serratia*
  - Side effects: **inhibits platelets**; high salt load
- **Timentin** (ticarcillin/clavulanic acid) and **Zosyn** (piperacillin/tazobactam)
  - Broad spectrum – pick up **GPCs** (staph and strep), **GNRs**, and **anaerobes**
  - Effective for enterococci; effective for *Pseudomonas*, *Acinetobacter*, and *Serratia*
  - Side effects: **inhibits platelets**; high salt load
  - **Zosyn** has **QID dosing**.
- **First-generation cephalosporins** (cefazolin, cephalexin)
  - **GPCs** – staph and strep
  - Not effective for *Enterococcus*; does not penetrate CNS
  - Ancef (cefazolin) has the longest half-life → best for prophylaxis
- **Second-generation cephalosporins** (cefoxitin, cefotetan)
  - **GPCs**, **GNRs**, ± anaerobic coverage; lose some staph activity
  - Not effective for *Enterococcus*, *Pseudomonas*, *Acinetobacter*, or *Serratia*
  - Effective only for community-acquired GNRs
  - Cefotetan has longest half-life → best for prophylaxis
- **Third-generation cephalosporins** (ceftriaxone, cefepime)
  - **GNRs** mostly, ± anaerobic coverage
  - Not effective for *Enterococcus*; effective for *Pseudomonas*, *Acinetobacter*, and *Serratia*
  - Side effects: **cholestatic jaundice**, sludging in gallbladder (ceftriaxone)
- **Monobactam** (aztreonam)
  - **GNRs**; picks up *Pseudomonas*, *Acinetobacter*, and *Serratia*
- **Carbapenems** (meropenem, imipenem) – is given with cilastatin
  - Broad spectrum – **GPCs**, **GNRs**, and **anaerobes**
  - Not effective for **MEP**: **M**RSA, ***E****nterococcus*, and ***P****roteus*
  - **Cilastatin** – prevents renal hydrolysis of the drug and increases half-life
  - Side effects: **seizures**
- **Bactrim** (trimethoprim/sulfamethoxazole)
  - **GNRs**, ± GPCs
  - Not effective for *Enterococcus*, *Pseudomonas*, *Acinetobacter*, and *Serratia*
  - Side effects (numerous): teratogenic, allergic reactions, renal damage, Stevens–Johnson syndrome (erythema multiforme), hemolysis in G6PD-deficient patients
- **Quinolones** (ciprofloxacin, levofloxacin, norfloxacin)
  - Some **GPCs**, mostly **GNRs**
  - Not effective for *Enterococcus*; picks up *Pseudomonas*, *Acinetobacter*, and *Serratia*
  - 40% of MRSA sensitive; same efficacy PO and IV
  - **Ciprofloxacin** has **BID** dosing; **levofloxacin** has **QD** dosing.
  - Side effects: **tendon ruptures**
- **Aminoglycosides** (gentamicin, tobramycin)
  - **GNRs**
  - Good for *Pseudomonas*, *Acinetobacter*, and *Serratia*; not effective for anaerobes (need O_2)
  - Resistance due to **modifying enzymes** leading to **decreased active transport**
  - Synergistic with ampicillin for *Enterococcus*
  - Beta-lactams (ampicillin, amoxicillin) facilitate aminoglycoside penetration.
  - Side effects: reversible **nephrotoxicity**, irreversible **ototoxicity**

- **Erythromycin** (macrolides)
  - **GPCs**; best for community-acquired pneumonia and atypical pneumonias
  - Side effects: **nausea** (PO), **cholestasis** (IV)
  - Also binds motilin receptor and is **prokinetic** for bowel
- **Vancomycin** (glycopeptides)
  - **GPCs**, *Enterococcus*, *Clostridium difficile* (with PO intake), MRSA
  - Binds cell wall proteins
  - Resistance develops from a **change in cell wall–binding protein**.
  - Side effects: HTN, **Redman syndrome** (histamine release), nephrotoxicity, ototoxicity
- **Synercid** (streptogramin – quinupristin-dalfopristin)
  - **GPCs**; includes MRSA, VRE
- **Linezolid** (oxazolidinones)
  - **GPCs**; includes MRSA, VRE
- **Tetracycline**
  - **GPCs**, **GNRs**, **syphilis**
  - Side effects: tooth discoloration in children
- **Clindamycin**
  - **Anaerobes**, some GPCs
  - Good for aspiration pneumonia
  - Can be used to treat *C. perfringens*
  - Side effects: pseudomembranous colitis
- **Metronidazole** (Flagyl)
  - **Anaerobes**
  - Side effects: disulfiram-like reaction, **peripheral neuropathy** (long-term use)
- **Antifungal drugs**
  - **Amphotericin** – binds **ergosterols** in wall and alters membrane permeability
    - Side effects: **nephrotoxic**, fever, hypokalemia, hypotension, anemia
    - Liposomal type has fewer side effects.
  - **Voriconazole** – inhibits ergosterol synthesis (needed for cell wall)
  - **Anidulafungin** (Eraxis), micafungin, caspofungin – inhibit synthesis of **cell wall glucan**
  - **Prolonged broad-spectrum antibiotics** ± fever → **anidulafungin** (or other fungin drug)
  - **Invasive aspergillosis** → **voriconazole**
  - **Candidemia** → **anidulafungin** (or other fungin drug)
  - **Fungal sepsis** other than candida and aspergillus → **liposomal amphotericin**
- **Antituberculosis drugs**
  - **Isoniazid** – inhibits mycolic acids (give with pyridoxine)
    - Side effects: hepatotoxicity, **B_6 deficiency**
  - **Rifampin** – inhibits RNA polymerase
    - Side effects: hepatotoxicity; GI symptoms; high rate of resistance
  - **Pyrazinamide**
    - Side effect: hepatotoxicity
  - **Ethambutol**
    - Side effect: **retrobulbar neuritis**
- **Antiviral drugs**
  - **Acyclovir** – inhibits viral DNA polymerase; used for **HSV** infections, EBV
  - **Ganciclovir** – inhibits viral DNA polymerase; used for **CMV** infections
    - Side effects: decreased bone marrow, CNS toxicity
- Broad-spectrum antibiotics can lead to **superinfection**.
- **Effective for *Enterococcus*** – ampicillin/amoxicillin, vancomycin, Timentin/Zosyn
  - *Enterococcus is resistant to all cephalosporins.*
- **Effective for VRE** (vancomycin-resistant *Enterococcus*) – Synercid, linezolid

- **Effective for *Pseudomonas***, ***Acinetobacter***, and ***Serratia*** – ticarcillin/piperacillin, Timentin/Zosyn, third-generation cephalosporins, aminoglycosides (gentamicin and tobramycin), meropenem/imipenem, or fluoroquinolones
- **Effective for MRSA** – vancomycin, Synercid, linezolid
- **Double cover *Pseudomonas***
  - Has an alginate mucoid biolayer; can colonize tubes and lines

7 Medicines and Pharmacology

INTRODUCTION

- **Sublingual** and **rectal drugs** – do not pass through liver first (no first-pass metabolism); have higher bioavailability compared to oral drugs
- **Skin absorption** – based on lipid solubility through the epidermis
- **CSF absorption** – restricted to nonionized, lipid-soluble drugs
- **Albumin** – largely responsible for binding drugs (PCNs and warfarin 90% bound)
- **Sulfonamides** – will displace unconjugated bilirubin from albumin in newborns (avoid in newborns; can cause kernicterus [damages brain])
- **Tetracycline** and **heavy metals** – stored in bone
- **0 order kinetics** – constant amount of drug is eliminated regardless of dose
- **1st order kinetics** – drug eliminated proportional to dose
- **Takes 5 half-lives** for a drug to reach steady state
- **Volume of distribution** = amount of drug in the body divided by amount of drug in plasma or blood
  - Drugs with a high volume of distribution have higher concentrations in the **extravascular compartment** (eg fat tissue) compared with intravascular concentrations.
- **Bioavailability** – fraction of unchanged drug reaching the systemic circulation
  - Assumed to be 100% for intravenous drugs, less for other routes (ie oral)
- **ED_{50}** – drug level at which desired effect occurs in 50% of patients
- **LD_{50}** – drug level at which death occurs in 50% of patients
- **Tolerance** – decline in potency with continued use
- **Hyperactive** – effect at an unusually low dose
- **Tachyphylaxis** – tolerance after only a few doses
- **Potency** – dose required for effect
- **Efficacy** – ability to achieve result without untoward effect
- **Drug metabolism** (hepatocyte smooth endoplasmic reticulum, P-450 system)
  - **Phase I** – demethylation, oxidation, reduction, hydrolysis reactions (mixed function oxidases, requires NADPH/oxygen)
  - **Phase II** – **glucuronic acid** (**#1**) and sulfates attached (forms **water-soluble metabolite**); usually inactive and ready for excretion. Biliary excreted drugs may become deconjugated in intestines with reabsorption, some in active form (termed entero-hepatic recirculation; eg cyclosporine).
  - **Inhibitors of P-450** – cimetidine, isoniazid, ketoconazole, erythromycin, Cipro, Flagyl, allopurinol, verapamil, amiodarone, MAOIs, disulfiram
  - **Inducers of P-450** – cruciform vegetables, ETOH, cigarette smoke, phenobarbital (barbiturates), Dilantin, theophylline, warfarin
- **Kidney** – most important organ for eliminating most drugs (glomerular filtration and tubular secretion); #2 biliary system
- **Polar drugs** (ionized) – water soluble; more likely to be eliminated in unaltered form
- **Nonpolar drugs** (nonionized) – fat soluble; more likely metabolized before excretion
- **Gout** – caused by high **uric acid** in blood (negatively birefringent crystals); end product of purine metabolism; causes exquisite pain, swelling, and redness
  - **Podagra** – when it affects the big toe joint space (1st MTP joint); MC area affected (50% of cases)
  - **Colchicine** – anti-inflammatory; binds **tubulin** and inhibits migration (chemotaxis) of WBCs
  - **Indomethacin** – NSAID; inhibits prostaglandin synthesis (reversible cyclooxygenase inhibitor)
  - **Allopurinol** – xanthine oxidase inhibitor, blocks uric acid formation from xanthine
  - **Probenecid** – increases renal secretion of uric acid

- **Lipid-lowering agents**
  - **Cholestyramine** – binds bile acids in gut, forcing body to resynthesize bile acids from cholesterol, thereby lowering body cholesterol; can bind vitamin K and cause bleeding tendency
  - **HMG-CoA reductase inhibitors** (statin drugs) – can cause liver dysfunction, rhabdomyolysis
  - **Niacin** (inhibits cholesterol synthesis) – can cause flushing. Tx: **ASA**
- **GI drugs**
  - **Metoclopramide** (Reglan, prokinetic) – **inhibits dopamine receptors**; can be used to increase gastric and gut motility
  - **Erythromycin** (prokinetic) – binds and activates motilin receptor
  - **Alvimopan** (prokinetic) – **antagonist to mu-opioid receptor**; used for postop ileus and to improve bowel recovery
  - **Loperamide** – slows gut motility; agonist to **mu-opioid receptors**
  - **Lomotil** (diphenoxylate/atropine) – slows gut; agonist to **opioid receptors**
  - **Promethazine** (Phenergan, antiemetic) – **inhibits dopamine receptors**; S/E: **tardive dyskinesia** (Tx: **diphenhydramine** [Benadryl])
  - **Ondansetron** (Zofran, antiemetic) – central-acting **serotonin receptor inhibitor**
  - **Omeprazole** – proton pump inhibitor; **blocks H/K ATPase** in stomach parietal cells
  - **Cimetidine/ranitidine** – histamine **H_2 receptor blockers**; decrease acid in stomach
  - **Octreotide** – long-acting **somatostatin analogue**; decreases gut secretions
- **Cardiac drugs**
  - **Digoxin**
    - **Inhibits Na/K ATPase** and increases myocardial **calcium**
    - **Slows atrial-ventricular conduction**
    - Also acts as an **inotrope**
    - Decreases **blood flow** to intestines – has been implicated in causing **mesenteric ischemia**
    - **Hypokalemia** increases sensitivity of heart to digitalis; can precipitate arrhythmias or AV block
    - **Is <u>not</u> cleared with dialysis**
    - Other side effects: visual changes (yellow hue), fatigue, arrhythmias
  - **Amiodarone** – good for acute atrial and ventricular arrhythmias
    - S/Es: **pulmonary fibrosis** w/ prolonged use; can also cause **hypo-** and **hyperthyroidism**
  - **Magnesium** – used to treat torsades de pointes (ventricular tachycardia)
  - **Adenosine** – causes transient interruption of the AV node
  - **ACE inhibitors** (angiotensin-converting enzyme inhibitors) – captopril
    - Best single agent shown to improve survival in patients with <u>CHF</u>
    - Can prevent CHF after myocardial infarction
    - Can prevent progression of renal dysfunction in patients with hypertension and DM
    - Can precipitate renal failure in patients with renal artery stenosis
  - **Beta-blockers** – may prolong life in patients with severe LV failure
    - Reduce risk of **MI** and **atrial fibrillation** postoperatively
    - Best single agent shown to improve survival after <u>myocardial infarction</u>
  - **Atropine** – acetylcholine antagonist; increases heart rate
- **Metyrapone** and **aminoglutethimide** – inhibit adrenal steroid synthesis
  - Used in patients with adrenocortical CA
- **Leuprolide** – analogue of GnRH and LHRH
  - Inhibits release of LH and FSH from pituitary when given continuously (paradoxic effect); used in patients with metastatic prostate CA
- **Tamsulosin** (Flomax) – alpha-adrenergic receptor antagonist used for BPH

- **NSAIDs**: nonselective COX inhibitors (indomethacin, ibuprofen)
  - Inhibit prostaglandin synthesis and lead to ↓ mucus and HCO_3^- secretion and ↑ acid production (mechanism of **gastritis**, **ulcer formation**, and **GI bleeding**)
  - Decreased prostaglandin synthesis also leads to constriction of renal afferent arterioles, leading to **renal insufficiency**.
- **NSAIDs**: selective COX-2 inhibitors (celecoxib)
  - Only binds inducible cyclooxygenase 2
  - Fewer GI side effects compared to nonselective agents
  - Increased risk of cardiovascular events (stroke, myocardial infarction)
- **Misoprostol** – a PGE_1 derivative; a **protective prostaglandin** used to prevent peptic ulcer disease; consider use in patients on chronic NSAIDs
- **Haldol** – antipsychotic, inhibits dopamine receptors
  - Can cause **extrapyramidal** (tardive dyskinesia) manifestations (Tx: Benadryl)
  - Can cause **prolonged QT syndrome** and **ventricular tachycardia** (Tx: amiodarone or DC cardioversion if unstable)
- **Furosemide** (Lasix) – loop diuretic
  - Side effects (over-diuresis) – metabolic alkalosis, hypokalemia, ototoxicity
- **Spironolactone** – inhibits aldosterone
  - Side effects (over-diuresis) – metabolic acidosis, hyperkalemia
- **Infliximab** (Remicade) – antibody to TNF-alpha (given IV)
  - Used in inflammatory bowel disease
  - Most significant Cx is infection risk (TB reactivation or new infection).
  - CHF can also occur.
  - Should not be used in patients with an active infection
- **ASA poisoning** – tinnitus, headaches, nausea, and vomiting
  - 1st – respiratory alkalosis
  - 2nd – metabolic acidosis
- **Gadolinium** – MC side effect: nausea
  - Do not use with renal insufficiency; can cause acute renal failure and nephrogenic systemic fibrosis
- **Iodine contrast**
  - MC side effect – **nausea**
  - MC side effect requiring medical Tx – **dyspnea**
- **Tylenol overdose** – Tx: *N*-acetylcysteine

8 Anesthesia

ANESTHESIA INDUCTION

- Results in loss of consciousness, lack of sensation, and anesthesia
- Can use inhalational (MC – sevoflurane) or intravenous agent (MC – propofol)

INHALATIONAL INDUCTION AGENTS

- **MAC** – minimum alveolar concentration = smallest concentration of inhalational agent at which 50% of patients will not move with incision
  - Small MAC → more lipid soluble = more potent
  - Speed of induction is inversely proportional to solubility.
  - Nitrous oxide is fastest but has high MAC (low potency).
- Inhalational agents cause unconsciousness, amnesia, and some analgesia (pain relief).
- Blunt hypoxic drive
- Most have some **myocardial depression**, ↑ cerebral blood flow, and ↓ renal blood flow.
- **Nitrous oxide** (NO_2) – fast, minimal myocardial depression; tremors at induction
  - Diffuses into closed spaces (avoid in patients with small bowel obstruction or pneumothorax)
- **Halothane** – slow onset/offset, highest degree of cardiac depression and arrhythmias; least pungent, which is good for children
  - Halothane hepatitis – fever, eosinophilia, jaundice, ↑ LFTs
- **Sevoflurane** – fast, less laryngospasm and less pungent; good for mask induction
- **Isoflurane** – good for neurosurgery (lowers brain O_2 consumption; no increase in ICP)
  - Pungent (not used for induction)
- **Enflurane** – can cause seizures
- MCC intraop **bradycardia** – inhalational anesthesia (Tx: atropine)

INTRAVENOUS INDUCTION AGENTS

- **Propofol** – very rapid distribution and on/off; provides anesthesia and amnesia; sedative
  - Side effects: hypotension, respiratory depression, metabolic acidosis (avoid prolonged use in children)
  - **Not an analgesic**
  - Do not use in patients with egg allergy, pregnancy, or Parkinson's.
  - Metabolized in liver and by plasma cholinesterases
- **Ketamine** – dissociation of thalamic/limbic systems; places patient in a cataleptic state (amnesia, analgesia)
  - No respiratory depression
  - Side effects: **hallucinations**, catecholamine release (↑ CO_2, tachycardia, HTN), ↑ airway secretions
  - *Considered safe* with **head injury**
  - Good for **children**
- **Etomidate** – fewer hemodynamic changes; fast acting
  - Fewest cardiac side effects (good for patients with CHF or angina)
  - Not analgesic
  - Continuous infusions can lead to adrenocortical suppression.
- **Rapid sequence intubation** – can be indicated for recent oral intake, GERD, delayed gastric emptying, pregnancy, bowel obstruction (pre-oxygenate, etomidate, succinylcholine typical sequence), cricoid pressure

- **Dexmedetomidine (Precedex)** – sedation agent for intubated patients (not an induction agent)
  - Provides **anesthesia** and **analgesia** without blunting hypoxic drive
  - Good for early extubation protocols (eg cardiac surgery)
  - Use not recommended for more than 24 hours
  - Is a CNS alpha-2 receptor agonist

MUSCLE RELAXANTS (PARALYTICS)

- **Diaphragm** – last muscle to go down and 1st muscle to recover from paralytics
- **Neck muscles and face** – 1st to go down and last to recover from paralytics
- **Depolarizing agents** – only one is **succinylcholine**; depolarizes neuromuscular junction
- **Succinylcholine** – fast, short acting; causes fasciculations, ↑ ICP; degraded by plasma pseudocholinesterases (can not be reversed); many side effects →
  - **Malignant hyperthermia**
    - Caused by a defect in calcium metabolism
    - Calcium released from sarcoplasmic reticulum causes **muscle excitation** – **contraction syndrome** (ryanodine receptor defect)
    - Side effects: 1st sign is ↑ **end-tidal CO_2**, then fever, tachycardia, rigidity, acidosis, hyperkalemia, rhabdomyolysis.
    - Tx: **dantrolene** (10 mg/kg) inhibits Ca release and decouples excitation complex; cooling blankets, HCO_3, glucose, supportive care
  - **Hyperkalemia** – depolarization releases K
    - **Do not use** in patients with severe burns, neurologic injury, neuromuscular disorders, spinal cord injury, massive trauma, or acute renal failure (all have up-regulation of acetylcholine receptors which can release significant amounts of K).
  - **Open-angle glaucoma** can become closed-angle glaucoma.
  - **Atypical pseudocholinesterases** – cause prolonged paralysis (Asians)
- **Nondepolarizing agents**
  - Inhibit neuromuscular junction by competing with acetylcholine
  - Can get prolongation of these agents with myasthenia gravis
  - **Cis-atracurium** – undergoes **Hoffman elimination**
    - Can be used in **liver** and **renal failure** (drug is broken down in the blood)
    - Histamine release (hypotension)
  - **Rocuronium** – fastest, intermediate duration; hepatic metabolism
  - **Vecuronium** – fast; intermediate duration; hepatic metabolism
  - **Pancuronium** – slow acting, long-lasting; renal metabolism
    - Most common side effect – ***tachycardia*** *(no hypotension)*
  - **Reversing drugs for nondepolarizing agents**
    - **Sugammadex** – selective relaxant binding agent (binds the paralytic drug)
      - Used to reverse Rocuronium and Vecuronium only
      - Does *not* require glycopyrrolate or atropine (although atropine given if bradycardia occurs)
    - **Neostigmine** – blocks **acetylcholinesterase**, increasing acetylcholine
    - **Edrophonium** – blocks **acetylcholinesterase**, increasing acetylcholine
    - **Glycopyrrolate** or **Atropine** should be given with neostigmine or edrophonium to counteract effects of generalized acetylcholine overdose.

LOCAL ANESTHETICS

- Work by **increasing action potential threshold**, preventing Na influx
- Sensory block > motor block
- Can use 0.5 cc/kg of 1% lidocaine
- Maximum dosing
  - **Lidocaine** 4 mg/kg (7 mg/kg with epi)
  - **Bupivacaine** 2 mg/kg (3 mg/kg with epi)
- Can re-administer after 2 hours

- **Infected tissues** are hard to anesthetize secondary to **acidosis**.
- **Length of action** – bupivacaine > lidocaine > procaine
- Side effects: perioral paresthesias (1st sign), tremors, seizures, tinnitus, arrhythmias (CNS symptoms occur before cardiac)
- **Epinephrine** allows higher doses to be used, stays locally.
  - **No epinephrine** with arrhythmias, unstable angina, uncontrolled hypertension, poor collaterals (penis and ear), uteroplacental insufficiency
- **Amides** (all have an "i" in first part of the name) – lidocaine, bupivacaine, mepivacaine; rarely cause allergic reactions
- **Esters** – tetracaine, procaine, cocaine; ↑ allergic reactions due to PABA analogue

NARCOTICS (OPIOIDS)

- Morphine, fentanyl, Demerol (meperidine), codeine, hydromorphone (Dilaudid)
- Are all CNS **mu-opioid receptor agonists**
- Profound analgesia, respiratory depression (↓ CO_2 drive), no cardiac effects, blunt sympathetic response; overdose – pinpoint pupils, somnolent
- Metabolized by the liver and excreted via kidney
- Overdose of narcotics – Tx: **Narcan** (naloxone; works for all; mu-opioid receptor antagonist)
- Avoid use of narcotics (especially Demerol) in patients on **MAOIs** → can cause **hyperpyrexic coma** (serotonin release syndrome – fever, tachycardia, seizures, coma)
- **Morphine** – analgesia, euphoria, respiratory depression, miosis, constipation, histamine release (causes hypotension), ↓ cough
- **Demerol** – analgesia, euphoria, respiratory depression, miosis, tremors, fasciculations, convulsions
  - **No histamine release**
  - Can cause **seizures** (buildup of **normeperidine** analogues) – *avoid in patients with* ***renal failure*** and be careful with total amount given for other patients
- **Methadone** – simulates morphine, less euphoria; agonist to CNS mu-opioid receptor
- **Fentanyl** – fast acting; 80× strength of **morphine** (does not cross-react in patients with morphine allergy); no histamine release
- **Sufentanil** and **remifentanil** – very fast-acting narcotics with short half-lives
- Most potent narcotic – ***sufentanil***
- Careful with combining opioids and benzodiazepines (synergistic effect)

BENZODIAZEPINES

- Anticonvulsant, amnesic, anxiolytic, **respiratory depression**; not analgesic; liver metabolism
- Agonist to the GABA receptor in the CNS (most prevalent inhibitory brain receptor)
- **Versed** (midazolam) – short acting; contraindicated in pregnancy, crosses placenta
- **Valium** (diazepam) – long acting
- **Ativan** (lorazepam) – long acting
- Overdose of these drugs – Tx: **flumazenil** (competitive inhibitor; may cause seizures and arrhythmias; contraindicated in patients with elevated ICP or status epilepticus)

EPIDURAL AND SPINAL ANESTHESIA

- **Epidural anesthesia** – allows analgesia by **sympathetic denervation** (sensory blockade); vasodilation
  - Has been shown to decrease respiratory Cx and cardiac events; no change in mortality
  - **Morphine** in epidural can cause **respiratory depression** (use Dilaudid to avoid this).
  - **Lidocaine** in epidural can cause **decreased heart rate** and **blood pressure**.
  - Dilute concentrations allow sparing of motor function.
  - Tx for **acute hypotension** and **bradycardia**: turn epidural down; fluids, phenylephrine, atropine

- T-5 epidural can affect cardiac accelerator nerves.
- Epidural contraindicated with hypertrophic cardiomyopathy or cyanotic heart disease → **sympathetic denervation** causes decreased afterload, which worsens these conditions
- **Thoracotomy** insertion level: T6–T9
- **Laparotomy** insertion level: T8–T10

- **Spinal anesthesia** – injection into subarachnoid space, spread determined by baricity and patient position
  - Inject below L2 to avoid hitting the spinal cord.
  - Can perform any surgery below the umbilicus with spinal anesthesia alone
  - Neurologic blockade is above motor blockade.
  - Spinal contraindicated with hypertrophic cardiomyopathy, cyanotic heart disease
- **Caudal block** – through sacrum, good for pediatric hernias and perianal surgery
- **Epidural and spinal complications** – hypotension, headache, urinary retention (MC complication; need urinary catheter in these patients), abscess/hematoma formation, respiratory depression (with high spinal)
- **Spinal headaches** – caused by CSF leak after spinal/epidural; headache gets worse sitting up; Tx: rest, fluids, caffeine, analgesics; **blood patch** to site if it persists > 24 hours

PERIOPERATIVE COMPLICATIONS

- Preop **renal failure** (#1) and **CHF** – associated with most postop hospital **mortality**
- **Postop MI** – may have no chest pain; can have hypotension, arrhythmias, ↑ filling pressures, oliguria, bradycardia; can happen intraop or postop (usually 2–3 days after surgery)
  - **Dx** – EKG and troponins (best test)
  - Initial Tx (BMOAN) – beta-blocker, morphine, oxygen, ASA, sublingual nitrates
  - **ST elevation MI (STEMI)** – emergently go to the cardiac cath lab for percutaneous coronary intervention (PCI)
- **Patients who need cardiology workup preop** – aortic stenosis, angina, previous MI, shortness of breath, CHF, walks < 2 blocks due to shortness of breath or chest pain, FEV_1 < 70% predicted, severe valvular disease, PVCs > 5/min, high-grade heart block, age > 70, DM, renal insufficiency, patients undergoing major vascular surgery (peripheral and aortic)

ASA Physical Status (PS) Classes

Class	Description
1	Healthy
2	Mild disease without limitation (controlled hypertension, obesity, diabetes mellitus, significant smoking history, older age)
3	Severe disease (angina, previous MI, poorly controlled hypertension, diabetes mellitus with complications, moderate COPD)
4	Severe constant threat to life (unstable angina, CHF, renal failure, liver failure, severe COPD)
5	Moribund (ruptured AAA, saddle pulmonary embolus)
6	Donor
E	Emergency

- Most **aortic** and **peripheral vascular surgeries** are considered high risk.
- **Carotid endarterectomy** (CEA) is considered moderate risk surgery.
- **Biggest risk factors for postop MI**: uncompensated CHF (#1, S3 gallop, JVD), recent MI, age > 70, DM, previous MI, unstable angina, Cr > 2, stroke/TIA
- **Beta-blocker** – most effective agent to prevent intraop and postop cardiovascular events
- Wait **6–8 weeks** after MI before elective surgery.
- Best determinant of esophageal vs. tracheal intubation – **end-tidal CO_2** ($ETCO_2$)

Cardiac Risk[a] Stratification for Noncardiac Surgical Procedures

High (cardiac risk > 5%) – emergent operations (especially in elderly); aortic, peripheral, and other major vascular surgery (*except* CEA); long procedure with large fluid shifts

Intermediate (cardiac risk < 5%) – CEA; head and neck surgery; intraperitoneal and intrathoracic surgery; orthopedic surgery; prostate surgery

Low[b] (cardiac risk < 1%) – endoscopic procedures; superficial procedures; cataract surgery; breast surgery

[a]Combined incidence of cardiac death and nonfatal myocardial infarction.
[b]Do not generally require further preoperative cardiac testing.

- Intubated patient undergoing surgery with **sudden transient rise in $ETCO_2$**
  - Dx: most likely **hypoventilation**
  - Tx: ↑ tidal volume or ↑ respiratory rate
  - Could also be due to **CO_2 embolus** (would have associated hypotension, followed by a massive drop in **$ETCO_2$** from lack of blood flow to lungs)
  - Could also be due to **malignant hyperthermia**
  - Could also be due to **capnothorax**
- **Capnothorax** (CO_2 pneumothorax)
  - From upper GI laparoscopic procedure (eg Nissen) with CO_2 pneumothorax due to **pleural tear**
  - Causes **trouble ventilating**; may see **bulging diaphragm**; elevated **$ETCO_2$**
  - If **hypotensive**, likely **tension capnothorax** – enlarge pleural tear to decompress
  - Tx: **Stop insufflation** and add **PEEP** (generally resolves in 30 minutes).
    - If it doesn't resolve – **thoracentesis** to remove CO_2
    - If it resolves – resume procedure at **lower insufflation**
    - If **lung** was injured when pleura was entered – place **chest tube** at end of procedure
  - **Small PTX** noticed after laparoscopic Nissen (< 2 cm) – observe (repeat CXR in 8 hours)
- Intubated patient with **sudden drop in $ETCO_2$** – likely became **disconnected from the vent**
  - Could also be due to pulmonary embolism, air embolism, cardiac arrest, or some other massive drop in cardiac output (patient would also have **hypotension**)
- **Air embolus**
  - MC occurs with air sucking through a central line or central line site.
  - CO_2 embolus can occur with laparoscopic procedures.
  - Sx's: sudden drop in **$ETCO_2$**, hypotension, tachycardia, mill wheel murmur (air lock prevents venous return)
  - Tx: Stop CO_2 insufflation if laparoscopic procedure.
    - Trendelenburg (head down) and left lateral decubitus position (keeps air in right ventricle)
    - Hyperventilate with 100% oxygen (helps reabsorb air embolus faster).
    - Aspirate central line if present (try to remove air).
    - Pressors and inotropes
    - Prolonged CPR
- **Endotracheal tube** – should be placed 2 cm above the carina
- MC **PACU complication** – ***nausea*** *and vomiting*
- MCC postop **hypoxemia** – **atelectasis** (alveolar hypoventilation)
- MCC postop **hypercarbia** – **poor minute ventilation** (need to take bigger breaths or increase tidal volumes)
- **Safest surgical setting** – bipolar cautery (only affects area between circuit)
- **Adequate pain control** – 3/10 or less
  - Signs of inadequate pain control – tachycardia, diaphoresis, splinting, hypertension
- **Visceral pain** Tx: opioids
- **Somatic pain** Tx: NSAIDs and opioids
- **Higher volume hospitals** are associated with lower mortality for abdominal aortic aneurysm repair and for pancreatic resection.

9 Fluids and Electrolytes

TOTAL BODY WATER

- Roughly ⅔ of the total body weight is water (men).
  - **Infants** have a little more body water; **women** have a little less.
- ⅔ of water weight is intracellular (mostly muscle).
- ⅓ of water weight is extracellular.
  - ⅔ of extracellular water is interstitial.
  - ⅓ of extracellular water is intravascular.
- Third space fluid is **interstitial fluid**.
- **Proteins** – determine plasma/interstitial compartment oncotic pressures
- **Na** – determines intracellular/extracellular osmotic pressure
- **Volume overload** – most common cause is iatrogenic; first sign is **weight gain**
- **Cellular catabolism** – can release a significant amount of H_2O
- **0.9% normal saline**: Na 154 and Cl 154; **3% normal saline**: Na 513 and Cl 513
- **Lactated Ringer's** (LR; ionic composition of plasma): Na 130, K 4, Ca 2.7, Cl 109, lactate 28 (lactate is converted to HCO_3^- in the body)
- **Serum osmolality**: (2 × Na) + (glucose/18) + (BUN/2.8)
  - Normal: 280–295
- **Water** shifts from areas of low solute concentration (low osmolarity) to areas of high solute concentration (high osmolarity) to achieve **osmotic equilibration**.

MAINTENANCE IV FLUIDS

- 4 cc/kg/h for 1st 10 kg
- 2 cc/kg/h for 2nd 10 kg
- 1 cc/kg/h for each kg after that
- **IV maintenance fluids** after **major adult gastrointestinal surgery**
  - During operation and 1st 24 hours, use **LR**.
  - After 24 hours, switch to **D5 ½ NS with 20 mEq K^+**.
    - 5% dextrose will stimulate **insulin release** and **prevent protein breakdown** (prevents protein catabolism).
    - D5 ½ NS @ 125/h provides 150 g glucose per day (525 kcal/day).
- During open abdominal operations, fluid loss is **0.5–1.0 L/h** unless there are measurable blood losses.
- Usually do not have to replace blood lost unless it is **> 500 cc**
- Best indicator of adequate volume replacement is **urine output**.
- **Urine output** – should be kept at least 0.5 cc/kg/h; should not be replaced, usually a sign of normal postoperative diuresis
- **Insensible fluid losses** – 10 cc/kg/day; 75% **skin** (#1; sweat), 25% respiratory, pure water
  - Increases in insensible losses – fever, burns, large open wounds, ventilated patients

FLUID RESUSCITATION (FOR SIGNIFICANT DEHYDRATION)

- **Sweat** loss (eg marathon runner) – Tx: normal saline
- **Gastric fluid** loss (eg gastric outlet obstruction) – Tx: normal saline
- **Pancreas**, **biliary**, or **small bowel** fluid loss – Tx: lactated ringers (may need extra HCO_3^-)
- **Large bowel** (eg massive diarrhea) – Tx: lactated ringers (may need extra K^+)
- **GI fluid losses** should generally be replaced **cc/cc**.
- *Avoid* albumin unless special circumstances such as large volume paracentesis replacement or hepatorenal syndrome.
  - Concern over **leakage of colloid** into interstitial space due **to increased capillary permeability** resulting in **interstitial/pulmonary edema**

GI FLUID SECRETION

- Stomach 1–2 L/day
- Biliary system 500–1,000 mL/day
- Pancreas 500–1,000 mL/day
- Duodenum 500–1,000 mL/day

GI ELECTROLYTE LOSSES

- Sweat – hypotonic (Na concentration 35–65)
- Saliva – K^+ (*highest concentration of K^+ in body*)
- Stomach – H^+ and Cl^-
- Pancreas – HCO_3^-
- Bile – HCO_3^-
- Small intestine – HCO_3^-, some K^+
- Large intestine – K^+
- Dialysis can remove K, Ca, Mg, PO_4, urea, and creatinine.
- **Normal body K^+ requirement**: 0.5–1.0 mEq/kg/day
- **Normal body Na^+ requirement**: 1–2 mEq/kg/day

POTASSIUM (NORMAL 3.5–5.0)

- **Hyperkalemia** – peaked T waves on EKG (arrhythmias); often occurs with **renal failure**
  - Tx: **calcium gluconate** (1st drug to give; membrane stabilizer for heart)
  - **Sodium bicarbonate** (causes alkalosis, K enters cell in exchange for H)
  - **10 U insulin** and **1 ampule of 50% dextrose** (K driven into cells with glucose)
  - **Kayexalate**
  - **Lasix**
  - **Albuterol**
  - **Dialysis** if refractory
- **Hypokalemia** – T waves disappear (usually from **over-diuresis** [eg too much Lasix])
  - Can also occur with **diarrhea**
  - Fatigue, weakness, muscle cramps/twitches
  - May need to replace Mg^+ before you can correct K^+
- **Pseudohyperkalemia** – hemolysis of blood sample

SODIUM (NORMAL 135–145)

- **Hypernatremia** – usually from **poor fluid intake** (concentrated urine)
  - Restlessness, irritability, seizures
  - If dehydrated, replace volume loss with **D5 ½ normal saline**.
  - If using **D5 water**, give slowly to avoid **brain swelling**.
- **Hyponatremia** – usually from **fluid overload** (dilute urine)
  - Headaches, nausea, vomiting, seizures
  - **Water restriction** is first-line treatment for fluid overload hyponatremia, then **diuresis**.
  - Correct Na slowly to avoid **central pontine myelinolysis** (no more than 1 mEq/h).
  - **Hyperglycemia** (eg DKA) and **hyperlipidemia** (eg from acute pancreatitis) can cause **pseudohyponatremia**.
  - **Hyponatremia** can occur from **isotonic fluid loss** (usually from GI tract) compensated by water retention – treatment is isotonic fluids (lactated Ringer's if pH is normal/acidotic or normal saline if pH is alkalotic).
- **Diabetes insipidus** (low ADH) – **hypernatremia** and **increased urine output** (low urine specific gravity [dilute urine]), high serum osmolality
  - Can occur with ETOH, head injury
  - First line Tx: **free water**
  - Tx if refractory and severe: **DDAVP** (synthetic analogue of ADH)

- **SIADH** (high ADH) – **hyponatremia** and **low urine output** (high urine osmolality [concentrated urine]), low serum osmolality
  - Can occur with head injury
  - First line Tx: **fluid restriction** and **diuresis** (slowly)
  - Tx if refractory and severe: **conivaptan**, **tolvaptan** (competitive antagonist for kidney V2 receptor)

CALCIUM (NORMAL 8.5–10.0; NORMAL IONIZED CA 1.0–1.5)

- **Hypercalcemia** (Ca usually > 13 for symptoms)
  - Acute hypercalcemia causes lethargic state, N/V, hypotension.
  - **Breast cancer** most common malignant cause
  - **Hyperparathyroidism** most common benign cause (also MCC overall)
  - **MCC hypercalcemic crisis** – undiagnosed **hyperparathyroidism** with stressor (eg surgery); as a group, **hypercalcemia of malignancy** is likely #1
  - No lactated Ringer's (contains Ca^{2+})
  - No thiazide diuretics (these retain Ca^{2+})
  - Tx: **Fluids** (normal saline at 200–300 cc/h) and **Lasix** (start after patient is euvolemic)
  - For **malignant disease** → calcitonin, alendronic acid (bisphosphonates; inhibit osteoclasts), glucocorticoids, dialysis
- **Hypocalcemia** (Ca usually < 8 or ionized Ca < 1 for symptoms) – perioral tingling and numbness (1st symptom), hyperreflexia, Chvostek's sign (tapping on facial nerve produces twitching), Trousseau's sign (carpopedal spasm with blood pressure cuff), prolonged QT interval
  - Can occur after **parathyroidectomy**
  - May need to replace Mg^{+} before you can correct Ca
  - **Albumin adjustment for calcium** – for every 1 g/dL decrease in albumin (normal is 4 g/dL), add 0.8 to Ca
  - **MCC** – previous **thyroidectomy** (injured the parathyroid glands at surgery)

MAGNESIUM (NORMAL 2.0–2.7)

- **Hypermagnesemia** – causes lethargic state; usually occurs in **renal failure** patients taking magnesium containing products (laxatives, antacids)
  - Tx: **calcium**
- **Hypomagnesemia** – causes irritability, confusion, hyperreflexia, seizures; usually occurs with **massive diuresis**, **chronic TPN** without magnesium replacement, or **ETOH abuse**; signs similar to hypocalcemia

PHOSPHATE (NORMAL 2.5–4.5)

- **Hyperphosphatemia** – most often associated with **renal failure**
  - Tx: sevelamer hydrochloride (Renagel), low-phosphate diet (avoid dairy), dialysis
- **Hypophosphatemia** – most often associated with **refeeding syndrome**; usually from PO_4 shift from extracellular to intracellular
  - Sx's: failure to wean from the ventilator, muscle weakness, confusion
  - Tx: **potassium phosphate**

RESPIRATORY ACIDOSIS

- **High CO_2** from low tidal volumes (TV) or low respiratory rate (RR; eg narcotic overdose)
- Tx: Increase minute ventilation (Narcan if overdose).

RESPIRATORY ALKALOSIS

- **Low CO_2** from hyperventilation (high TV and/or high RR; eg anxiety, high altitudes)
- Tx: lower minute ventilation; acetazolamide can be used for altitude sickness

METABOLIC ACIDOSIS

- **Anion gap = Na − (HCO_3 + Cl)**; Normal is < 10–15
- **High anion gap acidosis** – excessive production of fixed acids; "**MUDPILES**" = **m**ethanol, **u**remia, **d**iabetic ketoacidosis, **p**ar-aldehydes, **i**soniazid, **l**actic acidosis, **e**thylene glycol, **s**alicylates
- **Normal anion gap acidosis** – usually loss of Na/HCO_3^- (ileostomies, small bowel fistulas, lactulose), rapid infusion of HCO_3^--deficient fluids, primary hyperparathyroidism, diarrhea, mafenide acetate (Sulfamylon; inhibits carbonic anhydrase), acetazolamide (Diamox; inhibits carbonic anhydrase)
- Tx: underlying cause; keep pH > 7.20 with bicarbonate; severely ↓ pH can affect myocardial contractility
- Correction of acidosis can lead to **hypokalemia**.

METABOLIC ALKALOSIS

- Usually a contraction alkalosis (loss of fluid [eg NG tube suction, overdiuresis with Lasix])
  - **Nasogastric suction** – results in **hypochloremic**, **hypokalemic**, **metabolic alkalosis**, and **paradoxical aciduria** →
  - Loss of Cl^- and H ion from stomach secondary to nasogastric tube (hypochloremia and alkalosis)
  - Loss of water causes kidney to reabsorb Na in exchange for K^+ (Na/K ATPase), thus losing K^+ (hypokalemia).
  - Na^+/H^- exchanger activated in an effort to reabsorb water along with K^+/H^- exchanger in an effort to reabsorb K^+ → results in paradoxical aciduria
  - Tx: **normal saline** (most important to correct the Cl^- deficit)
- **Respiratory compensation** (CO_2 regulation) for acidosis/alkalosis takes **minutes**.
- **Renal compensation** (HCO_3^- regulation) for acidosis/alkalosis takes **hours to days**.

Acid–Base Balance

Condition	pH (7.4)	CO_2 (40)	HCO_3 (24)
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑

ACUTE RENAL FAILURE

- **FeNa** = (urine Na/Cr)/(plasma Na/Cr) − fractional excretion of Na; *best test for azotemia*
- **Prerenal** – FeNa < 1%, urine Na < 20, BUN/Cr ratio > 20, urine osmolality > 500 mOsm
  - 70% of renal mass must be damaged before ↑ Cr and BUN.
- **Contrast dyes** – prehydration best prevents renal damage; HCO_3^- and *N*-acetylcysteine
- **Myoglobin** – converted to ferrihemate in acidic environment, which is toxic to renal cells; Tx: hydration, alkalinize urine

TUMOR LYSIS SYNDROME

- Release of purines and pyrimidines leads to ↑ **PO_4**, **K**, and **uric acid**, leads to ↓ Ca.
- Can ↑ BUN and Cr (from renal damage; can lead to acute renal failure), EKG changes
- RFs – leukemias, lymphomas
- Tx: **hydration** (*best*), rasburicase (converts uric acid in inactive metabolite allantoin), allopurinol (↓ uric acid production), diuretics, alkalinization of urine

VITAMIN D (CHOLECALCIFEROL)

- Made in skin (UV sunlight converts 7-dehydrocholesterol to cholecalciferol)
- Goes to **liver** for **(25-OH)**, then **kidney** for **(1-OH)**. This creates the active form of vitamin D.
- **Active form of vitamin D** – increases **calcium-binding protein**, leading to increased **intestinal Ca absorption**

CHRONIC RENAL FAILURE

- ↑ K, Mg, PO_4, BUN, and creatinine
- ↓ Na and Ca
- ↓ **Active vitamin D** (↓ 1-OH hydroxylation) → ↓ Ca reabsorption from gut (↓ Ca-binding protein)
- **Anemia** – from low erythropoietin

Transferrin – transporter of iron
Ferritin – storage form of iron

10 Nutrition

INTRODUCTION

- **Caloric need** – approximately 20–25 calories/kg/day
- **Calories**:

Fat (lipids)	9 calories/g
Protein	4 calories/g
Oral carbohydrates	4 calories/g
Dextrose	3.4 calories/g

- **Nutritional requirements for average healthy adult male (70 kg)**
  - **20% protein** calories (**1 g protein/kg/day**; 20% should be essential amino acids)
  - **20% fat** calories – important for essential fatty acids
  - **60% carbohydrate** calories
  - 1,500–1,700 calories/day
- **Trauma**, **surgery**, or **sepsis** stress can increase kcal requirement 20%–40%.
- **Pregnancy** increases kcal requirement 300 kcal/day.
- **Lactation** increases kcal requirement 500 kcal/day.
- **Protein requirement** also increases with above.
- **Burns**
  - Calories: 25 kcal/kg/day + (30 kcal/day × % burn)
  - Protein: 1–1.5 g/kg/day + (3 g/day × % burn)
  - Don't exceed 3,000 kcal/day.
- Much of **energy expenditure** is used for **heat production**.
- **Fever** increases **basal metabolic rate** (10% for each degree above 38.0°C).
- If overweight and trying to calculate caloric need, use equation: weight = [(actual weight − ideal body weight) × 0.25] + IBW.
- **Harris–Benedict equation** calculates basal energy expenditure based on **weight**, **height**, **age**, and **gender**.
- **Central line TPN** – glucose based; maximum glucose administration −3 g/kg/h
- **Peripheral line parenteral nutrition** (PPN) – fat based
- **Short-chain fatty acids** (eg butyric acid) – fuel for **colonocytes**
- **Glutamine** – fuel for **small bowel enterocytes**
  - Most common amino acid in **bloodstream** and **tissue**
  - Most common amino acid released from **muscle** with **catabolism**
  - Releases NH_4 in kidney, thus helping with **nitrogen excretion**
  - Can be used for **gluconeogenesis**, as an **energy source**, or in the **urea cycle**
  - Enhances **immune function** by inhibiting small bowel mucosal breakdown and preventing bacterial translocation
- **Primary fuel for most neoplastic cells** – glutamine

PREOPERATIVE NUTRITIONAL ASSESSMENT

- **Approximate half-lives**
  - Albumin – 18 days
  - Transferrin – 8 days
  - Prealbumin – 2 days
- Normal **protein** level: 6.0–8.5
- Normal **albumin** level: 3.5–5.5
- Normal **prealbumin** level: 15–35
- **Acute indicators of nutritional status** – prealbumin (#1), retinal binding protein, transferrin
- **Ideal body weight** (IBW)
  - Men = 106 lb + 6 lb for each inch over 5 ft
  - Women = 100 lb + 5 lb for each inch over 5 ft

- **Preoperative signs of severe malnutrition**
  - Acute weight loss > 20% in 3 months
  - Albumin < 3.0
  - Transferrin < 200
  - Anergy to skin antigens
- **Low albumin** (< 3.0) – strong risk factor for **morbidity** and **mortality** after surgery
- **Preop nutrition** is indicated *only* for patients with **severe malnutrition** undergoing **major abdominal or thoracic procedures**.
- **Early enteral feeding** increases survival with **sepsis**, **pancreatitis**, and **burns**.

RESPIRATORY QUOTIENT (RQ; METABOLIC CART/INDIRECT CALORIMETRY)

- Ratio of CO_2 produced / O_2 consumed – is a measurement of energy expenditure
- **RQ > 1** = lipogenesis (overfeeding)
  - Tx: ↓ carbohydrates and caloric intake
  - High carbohydrate intake can lead to CO_2 buildup and difficulty weaning from ventilator.
  - CO_2 is produced when excess carbohydrates are converted to fats.
  - Too many **carbohydrates** can also cause **hyperglycemia** and **immunosuppression**.
  - Too many **fat calories** can cause excessive **inflammation** (omega 3 fatty acids [eg linolenic acid] have less inflammation).
- **RQ < 0.7** = ketosis and fat oxidation (starving)
  - Tx: ↑ carbohydrates and caloric intake
- Pure **fat utilization** – RQ = 0.7
- Pure **protein utilization** – RQ = 0.8
- Pure **carbohydrate utilization** – RQ = 1.0
- Balanced nutrition – RQ = 0.825

POSTOPERATIVE PHASES

- **Diuresis phase** – postoperative days 2–5
- **Catabolic phase** – postoperative days 0–3 (negative nitrogen balance)
- **Anabolic phase** – postoperative days 3–6 (positive nitrogen balance)

STARVATION OR MAJOR STRESS (SURGERY, TRAUMA, SYSTEMIC ILLNESS)

Metabolic Differences Between the Responses to Simple Starvation and to Injury

	Starvation	Injury
Basal metabolic rate	−	+ +
Presence of mediators (eg TNF-α, IL-1)	−	+ + +
Major fuel oxidized	Fat	Mixed (fat, protein)
Ketone body production	+ + +	±
Gluconeogenesis	+	+ + +
Protein metabolism	+	+ + +
Negative nitrogen balance	+	+ + +
Hepatic ureagenesis	+	+ + +
Muscle proteolysis	+	+ + +
Hepatic protein synthesis	+	+ + +

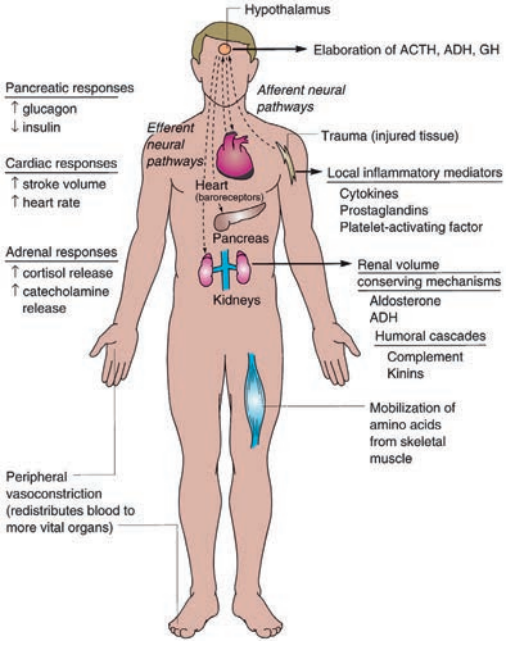
- The magnitude of metabolic response is proportional to the degree of injury.
- **Glycogen stores**
  - Depleted after **24–36 hours** of starvation (⅔ in **skeletal muscle**, ⅓ in liver) → body then switches to **fat**
  - Skeletal muscle lacks **glucose-6-phosphatase** (found only in **liver**).
  - Glucose-6-phosphate stays in muscle after breakdown from glycogen and is utilized there.
  - The **liver** is the source of systemic glucose during stress times or starvation.

- **Gluconeogenesis precursors** – amino acids (especially **alanine**, **#1**), lactate, pyruvate, glycerol; occurs in the **liver**
  - **Alanine** is the simplest amino acid precursor for gluconeogenesis.
    - Is the **primary substrate** for gluconeogenesis
  - **Alanine** and **phenylalanine** – only amino acids to increase during times of stress
  - **Late starvation** – gluconeogenesis occurs in kidney
- **Starvation**
  - Protein-conserving mechanisms **do not occur after trauma** (or surgery) secondary to catecholamines and cortisol.
  - Protein-conserving mechanisms do occur with **starvation**.
  - **Fat** (ketones) is the main source of energy in **starvation** and in **trauma**; however, with trauma the energy source is more mixed (fat and protein).
  - Fat is the body's largest potential energy source.
  - Most patients can tolerate a 15% weight loss without major complications.
  - Start **enteral nutrition** within **24–48 hours** after event (after resuscitation and stabilization) in **severely ill patients** (eg trauma, pancreatitis).
  - Patients can tolerate about **5–7 days** without eating; **start TPN** at that point if not able to start enteral nutrition.
  - Enteral nutrition *preferred* to avoid **bacterial translocation** (bacterial overgrowth, increased permeability due to starved enterocytes, bacteremia) and **TPN complications**
  - **PEG tube** – consider when regular feeding not possible (eg CVA) or predicted to not occur for **> 4 weeks**
  - **Tube feeds**
    - **Diarrhea** – slow rate, add fiber, less-concentrated feeds
    - **High gastric residuals** – Tx: Reglan, erythromycin
    - **Renal formulation** – contains low concentrations of K, PO_4, and protein
  - **Brain** – utilizes ketones with progressive starvation (normally uses **glucose**)
  - **Peripheral nerves**, **adrenal medulla**, **red blood cells**, and **white blood cells** are all **obligate glucose users**.
  - **Refeeding syndrome**
    - Occurs when feeding after prolonged starvation/malnutrition
    - **ETOH abuse** often present
    - Shift from fat to carbohydrate metabolism
    - Symptoms usually occur on **day 4** following re-feeding.
    - Results in decreased **K**, **Mg**, and **PO_4**; causes cardiac dysfunction, profound weakness, encephalopathy, CHF, failure to wean from the ventilator
    - Decreased ATP, the most significant problem
    - Prevent this by starting to re-feed at a **low rate** (10–15 kcal/kg/day).
  - **Cachexia** – anorexia, weight loss, wasting
    - Thought to be mediated by **TNF-α**
    - Glycogen breakdown, lipolysis, protein catabolism
  - **Kwashiorkor** – protein deficiency
  - **Marasmus** – starvation
- **Major stress**
  - Causes an increase in **catecholamines**, **cortisol**, and **cytokines** (eg TNF-α, IL-1)
  - Results in significant **protein breakdown** (negative nitrogen balance)
  - **Hepatic urea formation** occurs at high levels.

NITROGEN BALANCE

- Based on 24-hour urine nitrogen collection
- **6.25 g of protein** contains **1 g of nitrogen**.
- **N balance** = (N in − N out) = ([protein/6.25] − [24-hour urine N + 4 g])
  - **Positive N balance** – more protein ingested than excreted (anabolism)
  - **Negative N balance** – more protein excreted than taken in (catabolism)

- Total protein synthesis for a healthy, normal 70-kg male is **250 g/day**.
- **Liver**
  - Responsible for amino acid production and breakdown
  - Majority of protein breakdown from skeletal muscle is **glutamine** (#1) and **alanine**.
  - **Urea production** is used to get rid of **ammonia** (NH_3) from amino acid breakdown.
- **Urea cycle – glutamine** is the primary NH_3 donor; reactions occur in the **liver** and urea is removed by the **kidney**; accounts for 90% of all N loss



Homeostatic adjustments initiated after injury.

FAT DIGESTION

- **Triacylglycerides** (TAGs), **cholesterol**, and **lipids**
  - Broken down by pancreatic lipase, cholesterol esterase, and phospholipase to micelles and free fatty acids
  - **Micelles** – aggregates of bile salts, **long-chain free fatty acids**, and monoacylglycerides
    - Enter enterocyte by fusing with membrane
    - **Bile salts** – increase absorption area for fats, helping form **micelles**
    - **Cholesterol** – used to synthesize bile salts
    - **Fat-soluble vitamins** (A, D, E, K) – absorbed in micelles
  - **Medium-** and **short-chain fatty acids** – enter enterocyte by simple diffusion
- **Micelles and other fatty acids enter enterocytes.**
  - **Chylomicrons** are formed (90% TAGs, 10% phospholipids/proteins/cholesterol) which enter **lymphatics** (thoracic duct).
  - **Long-chain fatty acids** – enter **lymphatics** (terminal villous lacteals) along with chylomicrons
  - **Medium-** and **short-chain fatty acids** – enter **portal system** (same as amino acids and carbohydrates)
- **Lipoprotein lipase** – on endothelium in liver and adipose tissue; clears chylomicrons and TAGs from the blood, breaking them down to fatty acids and glycerol