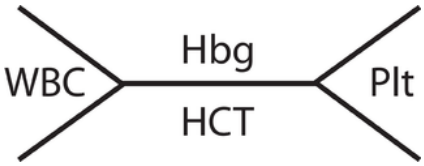
Exam 1: Pcol 1 Heme Toxicology Appendix Drugs	Exam 2 Pcol 2 GG drugs Monitor Solid Tumors Lung Cancer Melanoma Breast Cancer Colon Cancer	Exam 3 Intro CART ALL AML CLL CML FL DLBCL MM HL Lymphoma
Exam 4 Pharmaceutics VTE ESAs Neutropenia Oncologic Emergencies Nausea and Vomiting	Exam 5 Intro Hemodynamics Shock Management Sepsis PADIS NMBA ACS ADHF Stroke AIS Hemorrhagic Acid/Base Emergency Pharmaceutics	Exam 6 Nutrition Geriatrics Pediatrics Ophthalmology Dermatology Acne Psoriasis

Heme: Exam 1

Hematopoiesis

- process by which blood cells are formed
- pluripotent stem cells (PSC) or hematopoietic stem cells (HSC) are first in process; stem cells commit to myeloid or lymphoid line

Innate, Non-Specific Immunity (Myeloid Cell Line)	**Acquired, Specific Immunity (Lymphoid Cell Line)**
Granulocytes - Basophils - Neutrophils - Eosinophils - Mast cells	T Lymphocytes - Helper T cells - Cytotoxic T cells - Regulatory T cells - Memory T cells
Monocytes/Macrophages	B Cells - Plasma cells - Memory B cells
Erythrocytes	Natural Killer Cells
Thrombocytes	



Hb	F12-15 M13-17	↑Polycythemia ↓Anemia	
Plt	150-400k	↑Thrombocytosis ↓Thrombocytopenia	
WBC	4-10k w/ bands	↑Leukocytosis ↓Leukopenia (ANC <1000 ↓Neutropenia) ↑Leukocytosis with left shift	ANC = [(%neutrophils) + (%bands)] x WBC
MCV	80-100	↑Macrocytic ↓Microcytic	
Hct [35-50] Haptoglobin [36-195] Ferritin [15-300] Serum iron [50-170] TIBC [250-370] Cobalamin [200-900] Folate [5-16]			
Hemolysis		↓Hb ↓Hct **↓haptoglobin**	
Anemia of iron deficiency		↓Hb ↓Hct **↓MCV** **↓ferritin** **↑TIBC** ↓serum iron	if normal ferritin = anemia of chronic disease
Anemia of chronic disease		↓Hb ↓Hct —MCV —/↑ferritin ↓TIBC ↓serum iron	ferritin normal/high
Anemia of chronic kidney CKD		↓Hb ↓Hct —MCV —/↑ferritin ↓TIBC ↓serum iron; Burr cells	ferritin normal/high; normal MCV+haptoglobin
Anemia of cobalamin defic		↓Hb ↓Hct **↑MCV** ↓Cobalamin	
Anemia of folate deficiency		↓Hb ↓Hct **↑MCV** ↓Folate	

Objectives
Understand commonly-used hematology terminology
Describe and perform the ANC calculation
Recognize the most common hematologic abnormalities, their common etiologies, and clinical concerns associated with each abnormality

Elements of WBC (Leukocytes): neutrophils (several), lymphocytes, monocytes, eosinophils, basophils
CBC w/ diff: 60% segmented neutrophils, 2% band neutrophils, 25% lympthocytes, 8% monocytes, 3% eosinophils, 2% basophils

Neutrophils: primary defense against microbial invasion, phagocytic cells, most populous white cells, circulate 8hr vasculature (lifespan 1wk)
- maturation: myeloblast, promyelocyte, myelocyte, metamyelocyte, band, neutrophil - mature neutrophils fully-functional phagocytes (segmented nucleus)
- only polymorphonucleocytes (PMNs) and few band forms are present in peripheral band; more immature forms remain sequestered in bone marrow
- immature neutrophil forms are seen in peripheral blood during infection---presence of immature forms in peripheral blood is a "LEFT SHIFT"

Thrombocytosis: platelets above of normal range (150k - 400k/ul)
- concerns: CLOTTING, hemorrhage, migraine
- causes: infection "reactive" collagen-vascular diseases, inflammatory bowel disease, malignancy

Thrombocytopenia: platelets below normal range (150k - 400k/ul)
- concerns: bleeding, hemorrhage
- causes: impaired production (**drugs**, malignancy); accelerated destruction (hypersplenism, ITP, TTP, immunologic **drugs**)

Polycythemia/Erythrocytosis: hemoglobin above normal range (F12-15 M13-17 g/dl)
- concerns: increased blood viscosity, hypertension, thrombosis, bleeding
- causes: high altitude chronic hypoxia (**lung disease**), smoking; EPO-producing malignancy

Anemia: hemoglobin below normal range (F12-15 M13-17 g/dl)
- concerns: inadequate oxygen delivery, cardiovascular overdrive, fatigue
- hypoproduction (chronic disease, inflammation, drugs, deficiencies); blood loss (drugs, ulcers, malignancy); shorter lifespan (drugs, hypersplenism, hemolysis)

Leukocytosis: WBCs above normal range (4k - 10k/ul)
- concerns: usually clinically benign unless extreme; concern about underlying cause
- cause: increased production (infection, drugs, inflamm, malignancy); increased marrow release (infection, drugs, inflam); demargination (drugs, stress, malign)
- elderly and immunocomp patients may not develop "elevated" WBC during infection; can make serious infections more difficult to recognize

Leukopenia: WBCs below normal range (4k - 10k/ul)
- concerns: susceptibility to bacterial and fungal infections
- causes: decreased production (drugs, malignancy); increased destruction (drugs, autoimmune disorders)
- Absolute Neutrophil Count (ANC): to determine absolute number of functional phagocytic cells present at any given WBC count; ability to resist infection
  ANC = [(%neutrophils) + (%bands)] x WBC
  Neutropenia: ANC <1000; greatly increases risk of bacterial and fungal infections
- patients who are leukopenic at baseline may elevate their WBC into normal range with infection; can make infection difficult to recognize
- neutrophils (bacterial), lymphocytes (viral), monocytes (chronic/TB), eosinophils (eating parasites), basophils (beestings/allergy)

Eosinophilia: eosinophils above normal range (0-5% of differential)
- concerns: clinically benign; concern above underlying cause
- drug or environmental, **allergies**, collagen-vascular disease, malignancy, parasitic infections

Recognize each type of common anemia by symptoms and laboratory findings
Understand, use, and explain the basic pathophysiology of each anemia
Understand treatment regimens, goals, and monitoring for each common anemia

Anemia: hemoglobin below normal range (M<13 F<12 g/dl)
- symptoms: dyspnea with exercise, fatigue, palpitations, angina (increased stroke volume)
- signs: tachycardia, wide pulse pressure (SBP-DBP), pallor, ejection murmurs

RBC Morphology: normocytic, macrocytic (megaloblastic), microcytic
Pathophysiology: excessive loss, excessive destruction, intra-RBC factors, decreased production

Excessive Blood Loss

Acute loss: trauma, GI bleed
Chronic loss: usually detected as iron deficiency anemia, develops over months to years; discussed below under 'iron deficiency anemia'

Excessive RBC Destruction

RBC antibodies (ITP/TTP, hemolysis, transfusion rxn), Drugs (hemolysis), Physical trauma (articial heart valve), Excessive RBC removal (hypersplenism)

Hemolysis: lysis (breakage) of erythrocytes; most common cause of RBC destruction
- causes: antibodies common (drug allergies, transfusion mismatch); also inherited hemoglobinopathies (sickle cell, thalassemia, porphyria, G6PD deficiency)
- recognition of hemolysis (if someone is hemolyzing, they're generally anemic)
  - decreased hematocrit
  - hemoglobinuria (dark urine)
  - reticulocytosis, if chronic (increase in reticulocytes, immature RBCs; bent and convoluted; reticulocytosis = bone marrow working overtime and effectively)
  - schistocytes on peripheral smear (fragmented RBCs, broken/divided, comma shaped edges; often microcytis with no central pallor)
  - haptoglobin decreased (lab test; is a protein produced by liver that body uses to clear free hemoglobin, found outside of RBC, from circulation)
    - binding to free hemoglobin causes serum (free) haptoglobin to decrease; lab test measures free, unbound haptoglobin (if bound, undetectable)
- Dx hemolytic anemia: someone is hemolyzing chronically, they should have schistocytosis; probably have reticulocytosis and low haptoglobin
- Tx: remove offending drug; supportive care, transfuse if Hb <8 g/dl; iron supplementation neither necessary nor useful (haptoglobin scavenges iron)
- drugs associated with immune-mediated hemolysis (test: can you recognize hemolysis and can you identify the last drug added and suspect it)
  - cephalosporins, levoflox, nitrofurantoin, penicillin, sulfonamides, NSAIDs, quinidine, levodopa, dapsone, phenazopyridine, methyldopa, others

Physical Trauma
- causes: usually artificial valve or hypersplenism
- recognition
  - decreasted hematocrit
  - reticulocytosis (more immature RBCs)
  - schistocytes on peripheral smear
  - hemoglobinuria
  - possibly low haptoglobin
- Tx: supportive care; transfuse if Hb <8 g/dl; iron suppl only if iron studies suggest deficiency and if not transfused
  - splenectomy: vaccines---Pneumococcal (PCV13/PPSV23), Meningococcal (MenACWY or MenB), Hib (Haemophilus influenzae type b)

Intra-RBC Factors

- causes: disorders of Hb synthesis (sickle cell, thalassemias, porphyrias), G6PD deficiency

Thalassemias
- autosomal recessive abnormal composition of either alpha or beta hemoglobin chains; inherited blood disorder causes body to have less Hb than normal
- abnormal RBCs subject lysis and/or premature destruction by reticuloendothelial system (REC); RBC production cannot balance destruction
- resulting microcytic anemia is chronic and can be mild, severe, lethal
- often confused with, and inappropriately treated as, iron deficiency
- *target cells of thalassemia (small, clear, irregularly and variably shaped RBCs)

G6PD Deficiency: RBCs vulnerable to lysis in presence of oxidizing drugs: *know: -quines, -azos, -nitros, systemic sulfonamides
- recessive, X-linked, genetic point mutation that render RBC membrane susceptible to oxidative stress
- abnormal RBCs subject lysis and/or premature destruction by reticuloendothelial system (REC); RBC production cannot balance destruction
- resulting normocytic anemia can be acute, chronic, mild, severe
- reticulocytosis should be present (why?)

Decreased RBC Production
- causes: deficiencies (iron, folate, B12), infiltration of marrow (malign), endocrine abnormalities (hypothyroid, hypoadrenal, hypopituitary), CKD, chronic disease

Mean Corpuscular Volume (MCV) = Hematocrit/RBC count
- describes mean size of a single RBC (normal 80-100 fl); RBCs that are abnormally large (macrocytic) or small (microcytic) suggest underlying pathologies
- possible to have a macrocytosis/microcytosis without being anemia

Iron stores: 3-4g total iron in body; 2.5g contained in Hb, remainder as ferritin, small amount free as serum iron
Iron deficiency caused by inadequate intake/absorption (gluten allergy) or by chronic blood loss
Recommended daily elemental iron intake: 14-18yo: 11M 15F mg/day 19-50yo: 8M 18F >51yo: 8mg/day [upper intake: 45mg/day]
Ferrous sulfate 325mg = 65mg elemental iron (20%) Ferrous gluconate 325mg = 36mg elemental iron (12%) Ferrous fumarate 325mg = 106mg iron (33%)
- GI intolerance, begin qday and escalate as tolerated; last resort take with food; high-iron foods/cereals
- iron best absorbed acidic environment (food/PPIs decreases F by 50%); empty stomach/OJ - IV risky but possible
- *200mg elemental iron per day for 3-6mo after Hb normalizes; qod dosing better absorption; DDIs iron binds levothyroxine
- iron is toxic: favors neoplastic cell growth; overdose causes impaired oxidative phosphorylation and mitochondrial dysfunction
- response: Hct should increase 1-2% weekly; reticulocytosis 3-4d

Iron Deficiency Anemia
- symptoms: generalized symptoms of anemia (pallor, dyspnea, fatigue, disproportionate tachycardia with exercise)
- if iron deficiency is severe: koilonchia (spoon fingernails), angular stomatitis (swollen, red corners of lips), glossitis (inflame tongue), pica (craving crunchy shit)
- chronic blood loss 1mg blood = 0.5mg iron (GI ulcers, NSAIDs, malignancies/colon cancer); menstrual losses
Labs: ↓MCV ↓Ferritin ↓Serum iron ↑Transferrin ↓Transferrin saturation% ↑TIBC
- transferrin (carrier protein); TIBC (total iron-binding capacity is ability of plasma to bind to iron in vitro)
- several microcytic anemias resemble iron-deficiency anemia (thalassesmia and chronic heavy metal exposure); ↓ferritin and ↑TIBC important discriminators

Cobalamin (B12) Deficiency ↓Hb ↓Hct ↑MCV ↓Cobalamin
- who's at risk: elderly (tea and toast); vegans, RA/Addison's, achlorhydric's; gastric bypass; longterm metformin
- ↓cobalamin, mild leukopenia and thrombocytopenia, ↓reticulocyte count
- neurologic or psychiatric abnormalities (cobalamin related to myelination and nervous transmission; if untreated, irreversible)
- Schilling test: 'pernicious anemia': autoimmune destruction of gastric parietal cells and subsequent loss of Intrinsic Factor
- treatment: if able to absorb: B12 250mcg daily until normalization; if unable to absorb: 100mcg IM daily x2-3wk then 100mcg IM weekly until normal
- can oral replace 1000mcg qday (even Roux-en-Y)
- response: reticulocytosis in 2-4d; Hb rise in 2wk and normal in 2mo; MCV normalize over 2mo

Folate Deficiency ↓Hb ↓Hct ↑MCV ↓Folate
- who's at risk: elderly, alcoholic, pregnant/lact - causes: dietary insuff, hemodialysis, drugs (pheny, rifampin, barbit, ethanol, sulfasalazine)
- mild leukopenia and thrombocytopenia; decreased reticulocyte count; no neurologic/psych abnormalities
- treatment: rule out B12 def; 1-5mg folic acid qday
- response: reticulocytosis 2-4d; Hb 2wk and normal 2mo; MCV normalize over 2mo

Heme half

Anemia of Chronic Kidney Disease

- may present when GFR <30-40 chronically; function of decreased erythropoietin production (function of reduced kidney mass)
- Labs: normocytic anemia with burr cells on peripheral smear; (can be macro/micro if deficiency in vitamin/iron with HD pts)
- Tx: erythropoietin; HD pt may require iron, B12, folate because of dialytic extraction

Anemia of Chronic Disease

- most common causes of anemia, chronic illness>2mo; strongly associated with chronic inflammatory* conditions
- pathophys: iron release from marrow stores blocked and erythropoietin production and marrow response are abnormal and RBC lifespan shortened
- Labs: normocytic anemia; ↓serum iron ↑ferritin ↓TIBC
- Tx: supportive, treat underlying, search for concurrent deficiencies, supplemental erythropoietin?

Anemia of chronic disease is immune driven; cytokines and cells of the reticuloendo-thelial system induce changes in iron homeostasis, the proliferation of erythroid pro-genitor cells, the production of erythropoietin, and the life span of red cells, all of whichcontribute to the pathogenesis of anemia
A hallmark of anemia of chronic disease is the development of disturbances of ironhomeostasis, with increased uptake and retention of iron within cells of the reticuloen-dothelial system. This leads to a diversion of iron from the circulation into storage sitesof the reticuloendothelial system, subsequent limitation of the availability of iron forerythroid progenitor cells, and iron-restricted erythropoiesis.
Thecytokines interleukin-1 and TNF-a directly inhibiterythropoietin expression
Anemia of chronic disease is a normochromic, nor-mocytic anemia that is characteristically mild (he-moglobin level, 9.5 g per deciliter) to moderate(hemoglobin level, 8 g per deciliter). Patients withthe condition have a low reticulocyte count, whichindicates underproduction of red cells
Iron is an essential nutrient for prolifer-ating microorganisms, and the sequestration of ironfrom microorganisms or tumor cells into the retic-uloendothelial system is believed to be a potential-ly effective defense strategy to inhibit the growth ofpathogens

Table 3. Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia.*

Variable	Anemia of Chronic Disease	Iron-Deficiency Anemia	Both Conditions†
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
Soluble transferrin receptor	Normal	Increased	Normal to increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)	High (>2)
Cytokine levels	Increased	Normal	Increased

* Relative changes are given in relation to the respective normal values.
† Patients with both conditions include those with anemia of chronic disease and true iron deficiency.

Pcol Cytotoxic

GG https://accessmedicine-mhmedical-com.proxy.lib.ohio-state.edu/book.aspx?bookid=2189
Dipiro https://accesspharmacy-mhmedical-com.proxy.lib.ohio-state.edu/book.aspx?bookid=2577
Katzung https://accesspharmacy-mhmedical-com.proxy.lib.ohio-state.edu/book.aspx?bookid=2249

Goodman Gilman Chart
Monitoring Anticancer Drugs
Pathway-Targeted Therapies

Exam 2

Chemo ADEs

General Modes of Anticancer Drug Therapies

I. Biochemical stress which impacts
  a. Signaling, or
  b. the ability to maintain cellular homeostasis (ie Some type of starvation, molecular damage)

II. Targeted disruption of normal signaling pathways that control cell growth and death
  a. Signal transduction
  b. Endocrine/steroid hormonal systems supporting cancer
    - Estrogens promote some Breast Cancer
    - Androgens promote Prostate Cancer
    Strategies
      - Decrease level of endogenous hormone
      - Attack hormones receptors

III. Immune Strategies
  a. Passive immunization with anti-cancer cell antibodies
  b. Immune system activation

pg7 figure

Carcinoma - epithelial cell cancer Sarcoma - mesodemal cancer Hemangiosarcoma - endothelial cell cancer Leukemia - White Blood Cell Cancer

Why is cancer bad?
- Solid tumors disorganize normal tissue in the area
- Some tumors even retain parental cell function; May secrete hormones or respond to drugs like the parental cell types
- Over-accumulation of cells can lead to resource consumption, waste production, or other disruptions of homeostasis

Significant Steps in the Overall Development and Growth of Cancer

I. Carcinogenesis- Produces Primary Tumor: A multistage process of transformation of a normal cell into a cancerous cell.
  - Cancer arises from normal cells: It is difficult to find selective targets for therapy

II. Metastasis – Produces Secondary Tumor: Migration of primary cancer cell into blood/lymph and distribution to other sites

III. Angiogenesis - Blood Vessel Formation: Primary and Secondary Metastatic Solid Tumors must recruit blood vessels so they can survive.
  - There is natural selection for tumors that can produce angiogenic factors.
  - Anti-vascular therapy seeks to block this.

Points to remember about metastasis
- Metastatic cancer is the usual cause of death.
- Although it is inefficient, there is a large number of metastatic cells

Cancer = an imbalance between Growth and Death of cells
  Normal Tissue → Growth = Death
  Neoplastic Tissue → Growth > Death

Therapeutic approaches:
  A. Reduce Growth
    - mitosis controlled by signaling pathways; disrupt signaling
    - disrupt enzymes/proteins needed for mitosis; disrupt normal biochem (DNA synth)
  B. Increase Death
    - death by apoptosis is controlled by signaling pathways; agents promote signaling
    - death by necrosis caused by disrupting normal biochem

Oncogenes → cancer caused when **activated**; normal versions are called proto-oncogenes
Tumor Suppressor Genes → cancer caused when **inactivated**; transcription factor p53 commonly found in lots of cancers

Role of signal transduction: most are critical points in carcinogenesis oncogenes or tumor suppressors

<u>Main Points</u>

Cyclin D starts the cell cycle
- Kicks off sequential increases in each subsequent cyclin protein

1. Cyclin D triggers mitosis, mediated by waves of Cyclin-CDK activities
2. CDKs are further regulated by CDKI proteins that can arrest mitosis when they are induced
3. a. A cancer could be treated by directly inhibiting CDK, or
  b. indirectly inducing levels of CDKI proteins; Tumor suppressor p53 induced by DNA damaging agents does this

pg19-32 exam2

- triggering cell cycle by raising level of Cyclin D
  - increase Cyclin D synthesis by increasing mRNA→protein: Ras- Mitogen Activated Protein Kinase (MAPK) Pathway
    - ie production of Cyclin D through the Ras/MAPK protein kinase cascade to activated transcription factors
  - stop degradation of Cyclin D protein after it is made: Phosphatidyl Inositol 3 (PIP3) kinase – Protein Kinase B (PKB) pathway
    - ie activation of PKB can stop degradation of Cyclin D

1:14:00 good info, https://echo360.org/media/2885d403-6695-46bd-99be-1e9ccdd69d8f/public?autoplay=false&automute=false&startTimeMillis=0

Phase 1: Signaling at cell membrane
- Receptor Tyrosine Kinases

Phase 2: Signals from membrane to cytoplasm
- Proteins in the Ras/MAPK path

Phase 3: Signals from cytoplasm to nucleus increase Cyclin D

pg33

P53 normally inhibits cell cycling and shuts down mitosis; most important tumor suppressor
- inactive mutants cannot slow down mitosis (leading to excess mitosis); it is mutated and inactivated in 50% of cancers
- MDM2 normally keeps P53 at low level, marks p53 for destruction
- one inducer of p53 is DNA damage
- DNA damaging anticancer drugs can induce and activate p53

1. P53 is increased by DNA damage
2. P53 is a transcription factor that induces production of regulatory proteins, like CDKI. This slows the cell cycle.
   (NOTE P53 also causes cell death – see later in notes)
3. P53 is a tumor suppressor that has been found to be mutated and inactivated in about 50% of all cancers.
4. DNA-damaging anticancer drugs can stop cancer cells from dividing by inducing p53.

pg38-40 know about cell death and PARP
- **necrosis**: cells lose homeostasis and eventually lyse; often due to **depletion of ATP**
  - affects tracts of contigious cell, cell volume ↑, organelles swell, **cell ruptures**, cell contents released, chromatin generally forms small aggregates
  - PARP (Poly[ADP-ribose] Polymerase): mediates necrosis
    - if you turn on PARP too much, lots of NAD/nicotinamide produced, excessive consumption of ATP = depletion and necrosis
- **apoptosis**: regulated Cell Death: cells engage a program of self-destruction; can be engaged by manipulating the death signal transduction systems
  - affects scattered individual cells, cell volume ↓, organelles retain integrity, cell breaks into fragments, phagocytized, chromatin clumps, DNA breaks
  - can be physiological (regulated by hormones and receptors), or stress activated (intracellular proteins sense DNA damage, others initiates death program)

pg41 know roles of Cytochrome C and Signaling Caspase (a protease) and Effector Caspase (a protease)
- apoptosis mediated by proteases called Caspases
- signaling caspses activate Effector Caspases, which destroy critical cell proteins

pg42-43 know red boxes about extrinsic and intrinsic paths of apoptosis

In the Extrinsic Pathway outside of the cell, hormones/ligands activate receptors that cause cleavage of the inactive form of a signaling caspase to its active form. Active signaling caspase then cleaves and activates an effector caspase, leading to apoptosis

In the Intrinsic Pathway inside of the cell, stimuli like DNA damage induce p53 to produce BAX with displaces Cytochrome C from mitochondria. Cytochrome C assembles a complex that activates a signaling caspase, which cleaves and activates an effector caspase, causing apoptosis

pg44 know how BAD, BAX and BCL2 function
- apoptosis is further regulated by a balance of death-promoting and death-inhibiting molecules inside cells
- pro-survival
  - BCL2 protein binds to BAX and inactivates it; BCL2 (B-cell Lymphoma-2) is an oncogene, it inhibits apoptosis caused by almost any stimulus
- pro-apoptosis
  - BAX protein elicits death by displacing Cyt C
    - BAX is a protein that can be induced by p53, BAX goes to mitochondria to release Cyt C which, which can activate Caspases, leading to cell death or apoptosis
  - BAD inactivates BCL2 by binding to it; therefore BCL2 unavailable to antagonize BAX

***OVERALL: BAX will kill cells (through Cyt C, Caspase activation, apoptosis); BAX can be blocked by BCL2; but BCL2 can be blocked by BAD**
  - therapeutic strategy: disrupt interaction of BCL2 with BAX

pg45 know drug venetoclax (Venclexta); peptidomimetic of BH3 protein interaction domain in BCL2
- MoA: binds to BCL2, prevents interaction with BAX, blocks pro-survival effect of antagonizing BAX, restores apoptosis to cancer cells
- Use: CLL and AML overexpressing BCL2 (as BCL2 is the critical oncogene causing these)
- Tox: myelosuppression: neutropenia (increases susc to inf), lymphocytopenia, thrombocytopenia, anemia; others: edema, GI, electrolytes, hepatic, skin rash

pg46-53 exam2

BAX = pro-death
BCL2 = pro-survival
BAD inactivates BCL2 = pro-death
JNK phosphorylates BCL2 and inactivates BCL2 = pro-death
PKB phosphorylates BAD and inactivates BAD = pro-survival

mTOR
- PI-3-Kinase/PKB activates mTOR
- mTOR promotes nutrient uptake and protein synthesis, and inhibits apoptosis

mTOR inhibitors
- Antagonize pro-survival actions of PI-3-Kinase/PKB
- might increase the sensitivity of cancer to other drugs

pg55 know (start of 3rd recording)
Carcinogenesis: multistage process of normal cell transformation into a cancerous cell
- Initiation
- Promotion
- Progression

pg56 understand each of the elements in the diagram on
exposure can lead to DNA damage to initiate, cell damage could change DNA sequence (mutation); repair systems limit consequences of damage
from mutation, activation of oncogene or inactivation of tumor suppressor gene

Be able to explain how each one may function in carcinogenesis and anticancer drug action

pg57 know
DNA damage has at least 2 outcomes:
1. carcinogenesis
2. cell dysfunction/death:
DNA repair activated in response to damage; resists carcinogenesis, resists gene inactivation, and reduces stress signaling; though errors may introduce mutations

pg59 Chemical Reactions with DNA. If presented with drug, be able to say if and what types of reaction it may exert on DNA
1. Deamination: loss of N from bases in DNA changes their base pairing properties
2. Covalent Modification: must be repaired; may alter base pairing with H-bonding
- many compounds react spontaneously with DNA; activated nonenzymatic hydrolysis or enzymiatically actiated to electrophilic species (N/O reaction with E+)
2a. Direct acting covalent mutagens or carcinogens: nitrosurea (carmustine), nitrogen mustards (nonenz intramol rxn)
2b. Promutagens/Procarcinogens: metabolically activated by enzymes to E+ cpds that attack EN attoms; CYP450 system; e- transfers, superoxide, tissue sensitiv
- **genetics and exposure to multiple drugs and environmental agents may affect metabolic consequences
pg65-66 know scheme of reactive oxygen species production
- activation of oxygen to indirectly damage DNA; reactive oxygen species; hydroxyl radical is most reactive; radiation produces it from water
- hydroxyl radical reacts with Carbon in DNA or abstract H from C causing strand scission; superoxide and peroxide can oxidize DNA
- oxidative damage to DNA may explain:
1. ionizing radiation does not damage anhydrous DNA well
2. basal, chemical and metabolism-stimulated DNA damage
3. DNA damage caused by active inflammatory cells
- activated oxygen species (superoxide, H2O2 and Hydroxyl radical) can add to carbon in DNA bases
- damaged bases are removed by DNA repair or they may pair incorrectly (similar to alkylation); example: cov mod of Guanine to 8-hydroxyguanine
3. Strand Scission: must be repaired; breaking phosphodiester backbone and may be clastogenic→DNA rearrangements may activate or inactivate genes
- single and double strand breakage, may lose sections of DNA
- causes: hydroxyl radical and bleomycin (anticancer drug)
- H extracted from C4 of deoxyribose resulting in strand scission
4. Intercalation: alters pairing of strands since double helix is abnormally expanded
- chemical inserts itself into the rungs of a double helix; ex proflavine, ethidium, anthracyclines (doxorubicin)
- effect of expansion of double helix by unwinding:
- mutagenic: distortion of helix may cause mispairing during replication—frameshift (highly mutagenic would be this unwinding due to intercalators)
- metabolic effect: distortion also inhibits DNA and RNA synthesis (since distorted helix of bases)
5. Incorporation of agents into DNA:
- abnormal bases may mispair, causing mutations during replication of DNA; nucleoside analog cancer drugs (purine and pyrimidine antagonists)
- analogs lacking 3'OH cause chain termination leaving a break that must be repaired or clastogenesis results (large scale chromosomal alterations)

pg69 know
DNA repair: major factor in net effect of drugs on DNA
1. repair usually restores the normal structure of the damaged genome
2. however, repair may actually generate mutations by making mistakes: *increasing demand for repair increases the frequency of errors
3. most mutations are detrimental to gene function: it may be possible to kill cancer cells by blocking inhibiting repair to increase gene inactivation
- this is a new anticancer strategy; might expect repair inhibitors to increase mutagenesis
Strategy to accomplish DNA repair
1. process damage caused by reactions with DNA
2. restore correct base sequence – usually requires a DNA polymerase
3. ligate breaks remaining after polymerization (3'OH ligated to 5'Phosphate of next base)

pg70 Single Strand Repair; know the names and roles of the proteins in repair of single strands of DNA
a. direct repair of damaged base:
- **Dealkylase**: transfers alkyl group from DNA to cysteine; must synth new protein to repair lesions; restores normal base structure; resistance to alkylating agents
b. base excision repair and nucleotide excision repair of single DNA strand
A. Base excision repair
- **DNA N-glycosylases** process damaged base
- **AP endonuclease** (Apurinic/Apyrimidinic Endonuclease): recognize site lacking base, cuts phosphoester backbone
B. Nucleotide excision repair
- **Endonucleases**: cut DNA on either side of damaged areas
C. **DNA polymerases**: for both excision repairs: used to copy bases from opposite strand and replace damaged area with correct sequences
D. **DNA ligases**: for both excision repairs: close last gap containing 3'OH left in DNA

pg73-74 know how cell generated DNA breaks are present in repair sequence and role of PARP
**Overactivation of PARP can deplete ATP
**PARP uses NAD to activate DNA ligation and can deplete ATP if overactivated
**Main Points to Know About Excision Repair of Single Strand Damage and PARP
Base and Nucleotide Excision Repair Systems are basically similar:
Step 1: remove damaged base
Step 2: Use a DNA polymerase to replace the correct base coded by the undamaged strand
Step 3: Use a DNA ligase to seal the gap left in the repaired strand after polymerase copying
Significance of PARP (important new drug target)
1. Ligation requires PARP
   - Aids DNA repair
   - Overactivation depletes ATP (and NAD)
2. Activated by DNA strand Breakage
   - Direct Action of Drugs on DNA
   - Cellular Reaction to Damage
   - DNA repair endonucleases
   - Topoisomerase inhibitor reaction

pg76 Double Strand Repair; know the types of double strand break repair; know point about non-homologous end joining (do not need know the specific proteins)
Double strand breaks and crosslinks
- May be more dangerous to a cell than single strand breaks; more difficult to repair correctly; lead to Mutagenesis and genetic instability; Therapeutic and Toxic
- May occur with high doses of agents or with bifunctional agents

Repair of Double Strand Breaks: Two Main Methods
A. Non-Homologous End Joining (NHEJ)
   - grabs ends of the broken DNA and pulls them together
   - appears to trim ragged ends
   - leading to a high error rate in repair - mutagenesis
B. Homologous Recombination
   - uses the homologous sister chromosome as a possibly undamaged template for reproducing the correct sequence as it trashes the damaged bases
   - has a low error rate
   - defects in BRCA 1 and 2 predispose to cancer
   - apparently these cancers survive using backup DNA repair systems involving PARP in some way
*NHEJ is Error Prone: double strand breaks repaired by NHEJ may contain errors/mutations
*PARP Inhibitors: generally kill BRCA defective cancers by stopping their repair of "last resort"

BRCA (Breast Cancer Susceptibility Genes 1 and 2)
- tumor suppressors: mutations that inactivate BRCA 1 or 2 increase risk of breast and ovarian cancer (up to 80%)
- BRCA mutant cells adapt to use alternate DNA repair systems to stay alive; PARP acts as backup repair system that BRCA deficient cells use to stay alive
- inhibiting these alternate systems can kill BRCA-deficient cancers
- synergy between a biological phenotype and drug action is termed "synthetic lethality"

pg79 know the PARP inhibitor drug olaparib (Lynparza) and that it can kill cancers with mutated BCRA proteins
PARP inhibitors: olaparib (Lynparza), talazoparib (Talzenna), rucaparib (Rubraca), niraparib (Zejula)
- MoA: antagonize PARP; reduce base excision repair; kills BRCA mutant cells, may kill other repair-deficient cancers
  - excess double strand breaks accumulate in BRCA deficient cells; probably activates p53-intrinsic apoptosis pathway
- Use: **cancers with mutated BRCA**; some breast, ovarian, pancreatic
- Tox: myelosupp, pulm tox (cough, dyspnea), NVD, constipation

pg81 know how repair of DNA crosslinks can be repaired and the differences between homologous recombination and repair using error prone DNA polymerases
Method 1: homologous recombination using BRCA1/2 system: destroy modified sequence then using sister chromosome to fill in good DNA with a lack of errors
Method 2: use of *error-prone DNA polymerase; will produce mutations at a higher frequency

pg82 know the *three types of mutation
1. Point Mutations: one base change
2. Frame Shift Mutations: changes all codons downstream; a second shift usually needed to restore frame so only small segment is affected
   - in other words, a single frame shift is almost always lethal; DNA intercalation causes this; anthracycline anticancer drugs do this
3. Clastogenesis: large scale gene rearrangements

pg83 know redbox about mechanism of mutation due to chemical reactions with DNA
**A. Mutations may initiate carcinogenesis
**B. Mutations may disable genes to kill cancer and normal cells

pg84 know points about intercalation
- mutations due to intercalation results in *Frame Shift mutations; mech: DNA helix unwound and expanded, bases may add/delete during replication

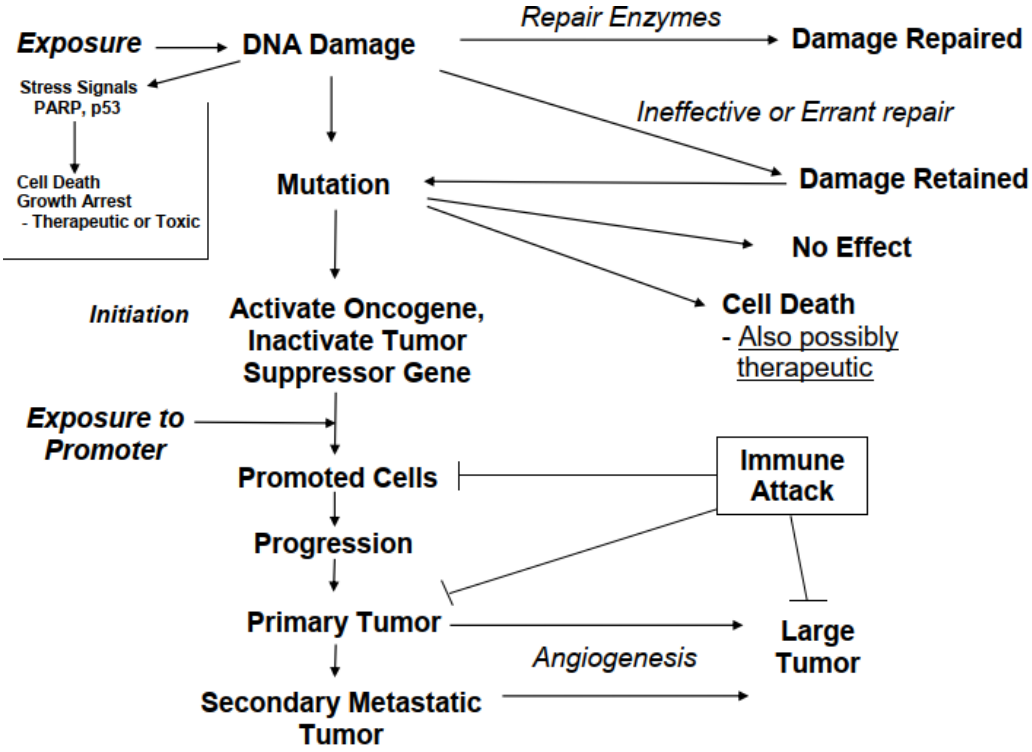
pg84 know info about effects of DNA damaging anticancer drugs
- base analogs (purine/pyrimidine antagonists) may be incorporated into DNA; may incorporate as one base but pair as a different one
- if agent terminates the DNA chain, repair must deal with the break-like end; excess repair activity increases chances for mistake

pg87 know consequences of DNA damage

1. Cell death: Extensive damage or mutation of genes so that they are useless
   - activation of PARP and p53: Necrosis. Apoptosis.
     - may be a way to kill cancer cells; toxicity if the wrong tissue is affected
2. Growth Arrest: Damage response induces p53 and slows mitosis; a way to stop cancer growth; toxicity in rapidly growing normal tissues
3. Genetic Diseases and Teratogenesis (birth defects; occurs only if damage during a critical stage of development. if not at critical stage, no effect or death results)
4. Cancer: see earlier – Mutations

*Protein Kinase C (PKC) activation or other promoters may change the behavior of normal signaling resulting in cancer

pg90 Overall Process of Damage Response and Carcinogenesis



To wrap up the whole idea about carcinogenesis, and even its role in anti cancer drug actions, both therapeutic and side effect in terms of carcinogenesis, again, are that you have to be exposed to something that causes DNA damage, which can lead to base changes, or could be repaired effectively with no consequences, or could be attempted to be repaired with different mistakes. We've seen systems that are mistake-prone, or mistake- free. You can have changes in base sequence due to activities of our own cells, essentially, but mutations might have no effect at all on a cell. Maybe not changing the coding of a sequence or resulting the same amino acid being produced despite a base change or being involved in some unexpressed region of the genome. Or accessibly, could disable the proteins that might be produced leading to destabilization of the cells with death. There might even be a therapeutic modality. Of course, you have mutagenesis to initiate cells to activate oncogenes or turn off tumor suppressors. Then, as we just saw, exposure to some kind of promotional agent, which is essentially a, usually, a reversible event - that's kind of a biochemical or signaling activity that makes those cells rely extensively on the effects of their altered genes to give a promoted cell, that could evolve over time in the stage of progression, to give you a successful tumor that might further evolve to leave the tumor and become metastatic that might further evolve in a solid tumor to recruit a circulatory system by the process of angiogenesis, all the while from the tumor's point of view, trying to avoid our own immune attack on the system. And finally, damage - it may be as a part of eliciting repair reflexes, damage being able to turn on stress signaling, that role of PARP which can respond to DNA breaks and maybe excessively consume NAD and ATP, the role of p53 that could be induced by DNA strand breaks, and p53 being able to elicit the intrinsic path of apoptosis by causing the production of BAX protein, which displaces cytochrome C from mitochondria, activating the protease cascade of the caspases, and also p53 inducing cyclin-dependent kinase inhibitors that might stop the process of mitosis by blocking cyclin-dependent kinases.

pg91

Cancer Therapy

I. Oxygen Activating Therapies – drugs, radiation (DNA damage contributes to action)

II. Chemotherapy

A. Cytotoxic

DNA Damaging: activate PARP, induce p53, growth arrest, cell death by necrosis/apoptosis

1. Covalent Modifiers of DNA
2. Topoisomerase Inhibitors: cannot unwind DNA for repl/transcr, causes DNA breaks; activate PARP, induce p53, growth arrest, cell death by necrosis/apopt
3. Mutagenic Antibiotics

Block Mitosis

4. Microtubule Inhibitors: chromosomes cannot segregrate, cells cannot divide

Disrupt Metabolism

5. Antimetabolites (DNA damage response may contribute to action)
6. Ribonucleotide Reductase
7. Protein Synthesis Inhibitor
8. Proteasome Inhibitor

Other

9. Thalidomide Derivatives

B. Targeted Therapy

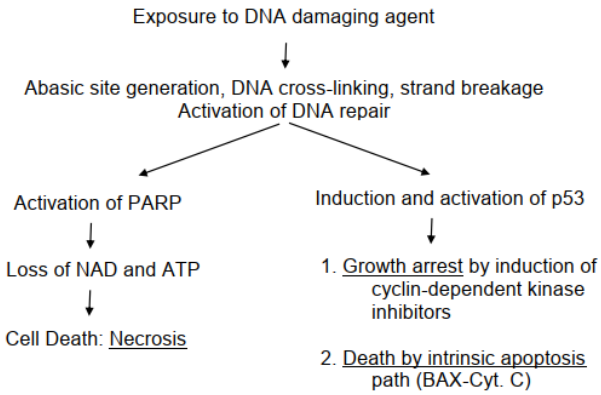
Signaling and Hormonal

III. Immunotherapy

IV. Surgery

DNA Damaging Therapies

1. induce cell death by necrosis and apoptosis
2. block mitosis by induction of endogenous CDK inhibitor proteins



pg96-97 know the considerations about cytotoxic chemotherapy

- selective toxicity is the goal
  - normal cells: small fraction of cells in cell cycle
  - cancer cells: larger fraction of cells are cycling in G1-S-G2-M; unreg growth, utilize lots of resources
- combination therapy (rarely use single drug)

pg98 know the definition of cell cycle specific and cell cycle non-specific agents

- cell cycle specific agents: EC50 may be lowest in one phase of the cycle; good for leukemias and rapidly proliferating tumors
- cell cycle nonspecific agents: EC50 less variable over cell cycle; good for slow and fast growing tumors
- agents of any type may cause growth arrest and cell death
- only need to know that microtubule inhibitors are M-phase specific

pg99-100 be able to contrast the idea of high intensity chemotherapy and metronomic chemotherapy

- high intensity chemotherapy: kill as many cells asap so resistance is limited; high-dose therapy side effects of myelosupp
- metronomic (antivascular) therapy: reduced periods of intense treatment and more continuous admin of agents used to suppress angiogenesis with toler doses

Common Toxicities of Cytotoxic Chemotherapeutic Drugs

A. Myelosuppression: leukopenia → infections thrombocytopenia → bleeding immunosupression → infections & cancer

B. Other adverse consequences: mucositis, cancer, genetic diseases, teratogenesis, infertility

C. Acute-subacute symptoms of chemo: hair loss, NV, loss of appetite

p104 Main point: Most of the agents cause myelosuppression

Those that cause less myelosuppression are unusual and fewer in number; These might be used in combinations to limit myelosuppression by a drug cocktail

Main examples that you need to know:

- streptozotocin at doses that kill pancreatic cancer
- cisplatin
- bleomycin

p109: 5. Antimetabolites 6. Ribonucleotide Reductase 7. Protein Synthesis Inhibition
Know the names, classification, mechanism and possible resistance for the drugs marked with an asterisk in the list

5. Antimetabolites

5A: Folic acid antagonists (analogs)

methotrexate

pemetrexed

5B: Purine antagonists (analogs)

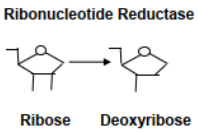
6-mercaptopurine: after activation, metabolites inhibit purine/DNA/RNA/PS synth; allopurinol use inhibit xanthine oxidase and decr uric acid may require dose red
fludarabine: after dephos and rephos to triphos: inhibits DNA pol, DNA ligase, ribnucleotide reductase; incorp DNA blocking further polymerization
pentostatin: adenosine analog directly inhibits adenosine deaminase: ↑adenosine, deoxyA, inhibits ribo reductase, ↓deoxynucleotide levels, ↓DNA synth

5C: Pyrmidine antagonists (analogs)

5-fluorouracil: metabolized to 5dUMP, inhibits thymidylate synthase, ↓TMP, ↓DNA synth; incorp metabolites into RNA, inhibit RNA synthesis
- phosphorylation of fdU by thymidine kinase, or add ribose to 5FU by PRPP transferase or uridine phosphorylase = 5-fluorodeoxyuridine monophosphate (5dUMP)
capecitabine: 5-FU prodrug via hepatic esterase, cytidine deaminase, thymidine phosphorylase
cytarabine: phosphorylated to ara-CTP, inhibits DNA polymerase; incorp DNA inhib chain elong; terminated DNA may resemble damaged DNA
gemcitabine: phosphorylated to di-tri forms competes with dCTP, incorp DNA inhib chain elong; terminated DNA may resemble damaged DNA
5-azacytidine: monophosphate inhibits pyrimidine synthesis; triphos incorp DNA/RNA = inhib of DNA/RNA/PS; also incorp base inhibits DNA methyltransferase
decitabine (deoxy-azacytidine)

6. Ribonucleotide Reductase

hydroxyurea
MoA: inhibit ribonucleotide reductase; decreases DNA synthesis; S-phase selective
- ribonucleotide reductase converts ribose → deoxyribose



7. Protein Synthesis Inhibitor

pegaspargase
- polyetheylene glycol-conjugated Asparaginase enzyme from E. coli (less allergenic)
MoA: inhibit protein synthesis via L-asparaginase deamination of asparagine [L-asparagine → L-aspartic acid + NH3]
- normal cells synthesize L-Asparagine; lymphoblastic leukemia (childhood) cells cannot synthesize; depletion of circulating Asparagine stops protein synthesis
- when used in combination with other agents, usually must be given later. Inhibition of protein synthesis decreases level of enzymes and proteins that are targets of other chemotherapeutic agents, lessening their effect.
Resistance: cells acquire ability to synthesize asparagine
Tox: hypersens and anaphylaxis

Toxicology

Alkylating Agents

busulfan: seizures (must use prophylaxis AED); sinusoidal obstruction syndrome: life-threatening liver toxicity, prevent using ursodiol
cyclophosphamide: hemorrhagic cystitis (doses >1000mg/m2 require mesna); SIADH, cardiac toxicity high doses
ifosfamide: hemorrhagic cystitis (always require mesna); neurological toxicity
melphalan: mucositis
bendamustine: rash, requires antiviral and PJP prophylaxis
dacarbazine: flu-like syndrome
procarbazine: Antabuse-like reaction, MAOI intx
carboplatin: thrombocytopenia, Calvert equation
cisplatin: nephrotoxicity, electrolyte abnormalities, NV, ototoxicities
oxaliplatin: cold-induced neuropathy

Antimetabolites: S-phase specific

azacytidine: myelosuppression, NV
decitabine: myelosuppression, NV
cytarabine myelosuppression, rash, HA, fever; high dose (>1g/m2): conjunctivitis, cerebellar toxicity
gemcitabine: myelosuppression, rash, flu-like syndrome
methotrexate: nephrotoxicity, mucositis, hepatotoxicity; high dose MTX requires leucovorin rescue and urinary alkalization (pH>7 to promote renal elim)
- avoid aspirin, penicillin, Bactrim, probenecid, NSAIDs, PPIs with HD MTX
pemetrexed: myelosuppression, erythematous and pruritic rash; requires premed with folic acid and B12 to decrease myelosupp
fluorouracil: Bolus: mucositits/diarrhea, dermatitis, nail changes, hyperpig, myelosupp; Continuous infusion: hand-foot syndrome, EKG changes/MI
capecitabine: dose-limiting hand-foot syndrome, diarrhea, NV
hydroxyurea: myelosuppression, diarrhea, rash, mucositits, hyperpigmentation
fludarabine, pentostatin, cladribine: myelosuppression/immunosuppression (requires viral and PCP prophylaxis); mild NV, flu-like sx; neurotox in older/renal (flud)

Antimetabolites: Plant Alkaloids

docetaxel: fluid retention, hypersensitivity reaction, peripheral neuropathy, alopecia, myelosuppression
paclitaxel: hypersensitivity reactions (can use abraxane), peripheral neuropathy, myelosuppression, alopecia
etoposide: myelosuppression, mucositits, alopecia
irinotecan: diarrhea: early <24hrs treat with anticholinergics, late >24hrs treat with antidiarrheals
vinblastine: myelosuppression, HTN, less neuropathy tthan other vinca alkaloids
vincristine: peripheral neuropathy, constipation, paralytic ileus, minimal myelosuppression
vinorelbine: myelosuppression, neuropathy

Antitumor Antibiotics

Anthracyclines: cardiotox (acute/subacute/chronic), myelosupp (highest with daunorubicin), NV, vesicant, alopecia, radiation recall, mucositis, diarrhea
- daunorubicin: stain tears/contact lenses/urine orange-red for 1-2 days
- doxorubicin: stain tears/contact lenses/urine orange-red for 1-2 days
- idarubicin:
- mitoxantrone: less cardiomyopathy, less NV, less alopecia; more mucositis; blue-green secretions (urine, sclera, fingernails)

bleomycin: pulmonary fibrosis (test pulm function prior); hypersensitivity, fever/chills, mucositis, skin rash

Miscellaneous

bortezomib: peripheral neuropathy (SC preferred), diarrhea, NV, fever
pegaspargase: hypersensitivity rxn, thrombosis, pancreatitis, elevated LFTs, hyperbili, hypofibrinogenemia, increased INR/PT
all trans retinoic acid (ATRA): differentiation syndrome, pseudotumor cerebri, LEFT elevations
arsenic trioxide: myelosupp, QTc, monitor Mg/K

MC
Covalent modifiers of DNA: mechlorethamine, melphalan, bendamustine, cyclophosphamide, ifosfamide, busulfan, dacarbazine, cisplatin, carboplatin, oxaliplatin
Antitumor antibiotics: bleomycin, doxorubicin, daunorubicin, idarubacin
Topoisomerase inhibitors: doxorubicin, daunorubicin, idarubacin, mitoxantrone, etoposide, topotecan, irinotecan
Microtubule inhibitors: vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, eribulin, ixabepilone
Antimetabolites: methotrexate, pemetrexed, 5-fluorouracil, capecitabine

Exam 2

Exam 2 will cover notes pages 132-178, plus some of the introductory information in Part I, pages 11-32 and 46-53.

pg19-22 know
pg25-26 show where SH2 and SH3 domains function.
pg26, p29 include a map of all the events after GTP-Ras activates RAF
pg30 know the function of phosphatidyl inositol-3 kinase and phosphatidyl inositol triphosphate and Protein kinase B outlined on
pg31 know the red box
- PI-3-kinase makes PIP3, which can recruit and activate PKB
- PKB (AKT) phosphorylates and inactivates Glycogen Synthase Kinase-3β
  - flags, stabilizes and prevents Cyclin D degradation, which ↑Cyclin D levels, triggering mitosis and stimulates cell cycle
  - other targets of PKB stimulate translation of proteins and inhibit cell death

pg32 know overall effect on Cyclin D in the red boxes

A. Receptor Tyrosine Kinase Inhibitors: 1. Antibodies to Growth Factor Receptor 2. Small Molecules
B. PI-3 Kinase Inhibitors
C. Serine/Threonine Kinase Inhibitors: RAF Kinase Inhibitors, MEK Inhibitors, Cyclin Dependent Kinase Inhibitors, mTOR Inhibitors
D. Multi-kinase Inhibitors – inhibit Serine/Threonine and Tyrosine Kinases
E. Non-receptor tyrosine Kinase Inhibitors: BCR-ABL Tyrosine Kinase Inhibitors; FYI: Janus Kinase (a tyrosine kinase)
F. FYI Other: Hedgehog pathway; Immune activation by blocking Programmed Cell Death Receptor-1

A1. Receptor Tyrosine Kinase Inhibitors

trastuzumab (Herceptin)

- ERB2 antibody
- bind to extracellular portion of receptor; inhibition should stop downstream signaling for mitosis and cell survival
- antibody to Her2/neu receptor tyrosine kinase (ErbB2) - binds and inhibits activity - overexpressed in up to 30% of breast cancers

Use: Metastatic breast cancer expressing Her2 (ErbB2) protein; Metastatic gastric cancer and gastroesophageal cancers expressing Her2
Tox: Severe adverse reactions in about 5-20%: Cardiomyopathy can lead to heart failure, Infusion reactions that can be fatal, Pulmonary toxicity: acute respiratory distress that can be fatal

pertuzumab (Perjeta)

- antibody to Her2/neu receptor tyrosine kinase (ErbB2) - inhibits receptor dimerization by binding to a different site than herceptin

USE: treatment of HER2-positive breast cancer TOX: Severe adverse: Heart failure, Fetotoxicity, Neutropenia (50%), Diarrhea (8%)

p144 While I will not ask about specific small molecule receptor tyrosine kinase inhibitors, must know the background information on p144, except for the details about types I-IV. However, remember that there are competitive and non-competitive, allosteric and irreversible inhibitors as summarized under point A on p160

A2. Small Molecules that can inhibit Receptor Tyrosine Kinases
a. Many are reversible: Competitive and non-competitive/allosteric
b. Several are irreversible: Covalent modifiers of the kinases

idelalisib (Zydelig)
Mechanism: - inhibits the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ); This can cause apoptosis in cancerous B-Cells
- Also inhibits several signaling pathways, including B-cell receptor, CXCR4/CXCR5 GPCR signaling which may play important roles in chronic lymphocytic leukemia

p164-167 Know the target and consequences based on signaling maps for dabrafenib, trametinib, palbociclib
C. Serine/Threonine Kinase Inhibitors
1. RAF – dabrafenib (Tafinlar), vemurafenib (Zelboraf), encorafenib (Braftovi)
   - Raf currently used in melanomas containing oncogenically transformed RAF = BRAF; can be activated by mutation Val (V) to Glu (E), in 50% of melanomas
2. MAPKK: Mitogen-activated extracellular kinase (MEK) inhibitors where MEK is a MAPKK – trametinib (Mekinist), cobimetinib (Cotellic)
   - MEK inhibitors also used in melanomas with oncogenic Ref
3. Cyclin Dependent Kinase (CDK) inhibitors: palbociclib (Ibrance), ribococlib (Kisqali), abemaciclib (Verzenio)
4. mTOR inhibitors: everolimus (Afinitor), temsirolimus (Torisel)
   - mTOR is a serine/threonine kinase that has pro-survival activity

dabrafenib (Tafinlar)
- BRAF inhibitor; inhibits mutated forms of BRAF Use: melanoma, metastatic or unresectable with BRAF-V600E mutation

trametinib (Mekinist)
- MEK inhibitor; inhibit mitogen-activated extracellular kinase (MEK) 1+2; oncogenic BRAF mutations overactivate downstream MEK
   - MEKs normally activated by RAF - reduces proliferation and induces apoptosis - Used in cancers having oncogenically mutated RA

palbociclib (Ibrance)
- CDK inhibitor; inhibit CDK4 and 6 which are activated by Cyclin D
- decreases retinoblastoma protein (Rb) phosphorylation resulting in reduced E2F levels and signaling

everolimus (Afinitor)
- mTOR inhibitor; limits effects of upstream stimuli (Receptor Tyrosine Kinase/PI3K/PKB)
- binds to the FK binding protein-12 (FKBP-12), inhibiting mTOR kinase activity

D. Multi-kinase Inhibitors: Inhibit Serine/Threonine and Tyrosine Kinase
sorafenib (Nexavar)
- inhibits Raf serine/threonine kinase and several Receptor Tyrosine Kinases

E. Non-receptor tyrosine Kinase Inhibitors
- regulate cell growth and death; in addition to MAPK and PKB/AKT pathways, there are Non-Receptor Kinases that dock on pY of receptor tyrosine kinases via SH2 domains

imatinib (STI-571, Gleevec)
- BCR-ABL Tyrosine Kinase inhibitor
- *can be used for cancers containing oncogenic fusion protein
- Developed as a selective inhibitor of BCR-ABL tyrosine kinase
- Also inhibits KIT and platelet derived growth factor (PDGF) receptor tyrosine kinases
- Much higher EC50 for inhibition of other serine/threonine kinases
Mutations and fusions of ABL, KIT and PDGF receptor tyrosine kinases to other proteins are examples of oncogenes:
   - BCR-ABL, described earlier is a hyperactive kinase: Associated with chronic myelogenous leukemia (**CML**)
   - Mutant KIT receptor tyrosine kinase is found in some gastrointestinal stromal tumors.
   - PDGF Receptor fusions to other sequences, producing PDGF independent receptor kinase activity occur in some chronic myelomonocytic leukemia (**CMML**) and in hypereosinophilic syndrome (HES)

MoA: inhibits several tyrosine kinases (see above), reducing cell proliferation and increasing death of susceptible cells
Resistance: predominantly results from mutations in the kinase domain

Chemotherapy Adverse Effects and Clinical Pearls

Identify commonly used chemotherapy agents and their general drug classes
Predict the most significant toxicities associated with common chemotherapy agents
Recognize appropriate supportive care agents and mitigation strategies
Review clinical pearls for commonly used chemotherapy agents

Cancer: Exam 2

Solid Tumors

Describe the elements contributing to overall prognosis (tumor biology, tumor grade, stage, performance status) for a patient with cancer
Explain the general principles of when to apply the three major treatment modalities in treatment of solid tumors
Review how efficacy of cancer therapies are assessed discussed in the medical literature

Melanoma

- Describe the epidemiology, risk factors, presentation, and prevention strategies of melanoma
- Develop melanoma treatment plans
- Explain the mechanisms of action, monitoring parameters, and common side effects for melanoma therapies
- Identify immunotherapy-related adverse events and develop management strategies

Epidemiology

100k dx in 2020; men increasing more rapidly (5th, 7% of cancers); women (6th, 4% of cancers); median age at diagnosis 65yo; 6850 deaths last year (decreasing)
Localized: confined to primary site (83%, 99%-5yrsurv) - Regional: spread to regional lymph nodes (9%, 66%-5yrsurv) - Distant: metastasis (4%, 27%-5yrsurv)

Pathogenesis

- cancerous growth of melanocytes (pigment cells)
- benign nevus, dysplastic nevus, radial growth phase, vertical growth phase, metastatic melanoma
Cutaneous: chronic sun damage (CSD), nonchronic sun damage (non-CSD), acral (soles/palms/nailbeds)
Non-cutaneous (outside of skin): mucosal (sinuses, oral cavity, anorectum, vulva, vagina, GI, etc); uveal (eye)

Risk Factors

M >60yo, whites, hx blistering sunburns, multiple dysplastic nevi or atypical moles, sun/UV tanning, intermittent intense/chronic sun; immunosupp, FH, genmut

Prevention

- avoid UV exposure; sunlight 10a-2p; wear protective clothing, use sunscreen appropriately
  - chemical sunscreen: absorb UV radiation (avobenzone, octocrytene, oxybenzone); some blood conc
  - physical sunscreen: reflect UV radiation (zinc/titanium oxide-based products); difficult to rub into skin
- SPF 30+, apply chemical 15min prior to going outside, reapply q2h (more often if water/sweat)

Presentation: itching, scaling, oozing, bleeding, redness, swelling, tenderness
Asymmetry (drawing a line through middle, size of halves won't match)
Border (edges uneven, crusty, notched)
Color (variety of colors, especially white/blue is bad)
Diameter (usually larger in diameter than pencil eraser)
Evolving (mole changes in size, shape, color or begins to bleed/scab)

Diagnosis

- total skin exam, assess melanoma-related risk factors
- biopsy of suspicious lesion: depth, ulceration status, rate of growth, margin status, microsatellitosis, pure desmoplasia, lymph invasion
Stage III (node positive) and Stage IV (metastatic) disease: LDH; CT/PET/MRI/CT; genetic mutations (BRAF, KIT, +/- NRAS)

Treatment Modalities

immunotherapy: stimulates immune system to target the cancer
small molecule drugs: interfers with specific cancer cell targets; in melanoma, tumor testing required for genetic mutations
chemotherapy: targets (non-specific) rapidly dividing cells
oncolytic virus: replicates in and lyses tumor cells

neoadjuvant therapy: treatment given prior to primary treatment (**before surgery**), to shrink the tumor; has a defined course
treatment: treatment of active disease; may or may not have a defined course (until progression/intolerance)
adjuvant therapy: treatment that is given after the primary treatment (**after surgery**), to prevent disease recurrence; has a defined course

Treatment

Treatment Overview

Node Negative	Stage 0	in situ disease	wide excision	common follow up
	Stage IA	<0.8mm, no ulceration	wide excision	common follow up
	Stage IB	<0.8-1mm or <0.8+ulc	wide excision +/- consider sentinel node biopsy	common follow up (sentinel node negative)
	Stage IB/II	>1mm thick	wide excision +/- offer sentinel node biopsy	common follow up (sentinel node negative)
Node Positive	Stage IIIA-D	sentinel node positive	nodal ultrasound or complete lymph node dissection → adjuvant therapy or observation	
	Stage III	clinically positive node	core biopsy or fine needle aspiration → wide excision and therapeutic lymph node dissection → consider radiation and/or adjuvant therapy or observation	
	Stage IV	metastas/progress on adjuv	resection, primary RT, systemic therapy, intralesional T-VEC, observation	

Treatment Regimens

Adjuvant Therapy: Stage III (node positive)

Preferred Regimens
- Nivolumab
- Pembrolizumab
- Dabrafenib + Trametinib [if BRAF V600-activating mutation positive]

- Other BRAF/MEK combinations can be considered if toxicity occurs
- Duration of Therapy: 1 year

Metastatic Systemic Treatment: First Line

Preferred Regimens (Category 1)
- Anti PD-1 Monotherapy
  - Nivolumab
  - Pembrolizumab
- Combined Anti-PD-1 + Anti-CTLA-4
  - Nivolumab + Ipilimumab
- Combined BRAF + MEK Inhibitors [if BRAF V600-activating mutation positive]
  - Dabrafenib + Trametinib
  - Vemurafenib + Cobimetinib
  - Encorafenib + Binimetinib

Other Recommended Regimens
- Combined Anti-PD-1 + Anti-CTLA-4
  - Pembrolizumab + Ipilimumab
- Combined BRAF + MEK Inhibitors + Anti-PD-L1 [if BRAF V600-activating mutation positive]
  - Vemurafenib + Cobimetinib + Atezolizumab

Metastatic Systemic Treatment: Second Line

Preferred Regimens
- Anti PD-1 Monotherapy
  - Nivolumab
  - Pembrolizumab
- Combined Anti-PD-1 + Anti-CTLA-4
  - Nivolumab + Ipilimumab
  - Pembrolizumab + Ipilimumab (if progressed after prior anti-PD-1 therapy)
- Combined BRAF + MEK Inhibitors [if BRAF V600-activating mutation positive]
  - Dabrafenib + Trametinib
  - Vemurafenib + Cobimetinib
  - Encorafenib + Binimetinib

Other Regimens
- Ipilimumab
- High-dose IL-2

Useful in Certain Circumstances
- Ipilimumab/Intralesional T-VEC (Category 2B)
- Cytotoxic Agents
  - Dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin + paclitaxel
- Imatinib if KIT mutation positive
- Larotrectinib or entrectinib for NTRK gene fusion positive tumors
- Binimetinib for NRAS mutated tumors that have progressed after prior immune checkpoint inhibitors

Chemotherapy

- not as effective as immunotherapy/targeted; considered if above options are exhausted
- regimens: dacarbazine (only FDA-approved chemo regimen), temozolomide, paclitaxel, nab-paclitaxel, carboplatin/paclitaxel, cisplatin/vinblastine/dacarbazine

Programmed Cell Death-1 (PD-1), Programmed Cell Death-1 Ligand (PD-L1), Cytotoxic T-lymphocyte Associated Antigen 4 (CTLA-4), B-raf (BRAF), mitogen-activated protein kinase (MAPK), extracellular signal-related kinase (ERK)

Medications

PD-1 inhibitor
nivolumab (Opdivo)
pembrolizumab (Keytruda)
inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding; the negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune and antitumor response. Anti-PD-1 antibodies reverse T-cell suppression and induce antitumor responses.

PD-L1 inhibitor
atezolizumab (Tecentriq)

CLTA-4 inhibitor
ipilimumab (Yervoy)
a recombinant human IgG1 mab that binds to CTLA-4, a down-regulator of T-cell activation pathways, allows for enhanced T-cell activation and proliferation.
In melanoma, ipilimumab may indirectly mediate T-cell immune responses against tumors. Combining ipilimumab (anti-CTLA-4) with nivolumab (anti-PD-1) results in enhanced T-cell function that is greater than that of either antibody alone, resulting in improved antitumor responses in metastatic melanoma and advanced renal cell carcinoma.

BRAF Kinase inhibitor
vemurafenib (Zelboraf)
dabrafenib (Tafinlar)
encorafenib (Braftovi)
selectively inhibits kinase activity of certain mutated forms of BRAF (V600), which suppresses the MAPK pathway, thereby blocking cellular proliferation, resulting in cell death
- when V600 mutations results in constitutive activation of BRAF pathway and uncontrolled proliferation; V600E~80%, V600K~15%, V600R/M/D/G~5%(limited benefit)

MEK inhibitor
cobimetinib (Cotellic)
trametinib (Mekinist)
binimetinib (Mektovi)
selectively reversibly inhibits MEK1/2, a downstream effector of BRAF and upstream regulators of the ERK pathway; decreased cellular proliferation, cell cycle arrest, incr apoptosis

Combinations
BRAF/MEK
vemurafenib-cobimetinib
dabrafenib-trametinib
encorafenib-binimetinib

PD-1/CLTA-4
nivolumab-ipilimumab

Oncolytic Virus
talimogene laherparepvec (T-VEC, Imlygic)
Indication: local treatment of unresectable, cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
MoA: genetically modified attenuated herpes simplex virus 1 (HSV) oncolytic virus which selectively replicates in and lyses tumor cells
- virally derived granulocyte-macrophage colony stimulating factor (GM-CSF) recruits and activates antigen-presenting cells, leading to an antitumor immune response
Avoid concurrent use of anti-HSV agents (acyclovir/valacyclovir)

Conclusion
- Primary treatment strategy for melanoma is surgical resection. Adjuvant therapy is considered for patients who have stage III disease.
- Most effective treatment options for melanoma include immunotherapy agents and BRAF/MEK inhibitors, if BRAF positive.
- Immunotherapy-related adverse events are inflammatory in nature. Steroids are the backbone of their management strategies.

Lung Cancer

List common risk factors for lung cancer
Discuss treatment of non-small cell lung cancer based on staging, goals of care, histology, and mutational status
Review common toxicities of oral targeted therapies for lung cancer
Discuss treatment of small cell lung cancer based on staging and goals of care

Risk factors

Smoking (>85% lung cancers); first/second hand; exposure impacts risk (dur/intensity); quitting reduces risk
Radon, chest radiation, asbestos, coal dust, diesel exhaust, chem, +/-FH

Clinical Presentation

Primary tumor: SOB, cough, chest pain, hemoptysis Local spread: SVC syndrome, pain Metastatic: Bone (pain/fract), Brain (neuro, HA, NV), Liver (jaundice)
Dx: Imaging (CT MRI PET); Pathology (tissue is the issue, staging, cell histo, mutational analysis)
  NSCLC: (Adenocarcinoma 50%; Squamous 30%, Large/Other 5%) SCLC: 15%

Treatment

Non-Small Cell Lung Cancer (NSCLC): surgery, radiation, chemotherapy, targeted therapy, immunotherapy
Small Cell Lung Cancer (SCLC): radiation, chemotherapy, immunotherapy

DNA-binding agents •Cisplatin •Carboplatin •Lurbinectedin
Topoisomerase inhibitors •Etoposide •Irinotecan •Topotecan
Microtubule inhibitors •Paclitaxel •nab-paclitaxel •Docetaxel •Vinorelbine
Antimetabolites •Gemcitabine •Pemetrexed
Monoclonal antibodies •Bevacizumab •Ramucirumab •PD-1/PD-L1 inhibitors
Tyrosine kinase inhibitors •Osimertinib •Alectinib, Lorlatinib •Entrectinib •Capmatinib •Selpercatinib, Pralsetinib •Dabrafenib, Trametinib

NSCLC

TNM Staging System - Tumor: Size, Location - Nodes: Regional vs distant - Metastases: Present vs not
Stage I refers to tumors confined to the lung without lymphatic spread (limited/localized)
Stage II refers to large tumors with ipsilateral peribronchial or hilar lymph node involvement
Stage III includes other lymph node and regional involvement that may or may not involve both lungs
Stage IV includes tumor with distant metastases

Limited, Resectable NSCLC
Stage I-IIIA; goal CURE; (only 20-30% of pt will be surgically resectable)
Surgical resection: wedge, segmental, lobectomy, pneumonectomy
Adjuvant chemotherapy (not for IA, only for IB >4cm tumors) started 6-12wk after surgery
- cisplatin + vinorelbine x4 cycles

Limited, Unresectable NSCLC
Stage I-IIIC; goal CURE; (unable to perform/tolerate resection)
Chemoradiation: radiation + concomitant chemotherapy
- cisplatin + etoposide
- carboplatin + paclitaxel

Stage IIIA-IIIC: maintenance therapy
- durvalumab x1yr following chemoradiation

Advanced/Metastatic NSCLC
Stage IV; goal prolong life, palliation, QoL; (>70% of pt with NSCLC at dx, without systemic therapy surv 4-5mo, with >12mo, better with targeted)
Treatment: chemotherapy, targeted therapy, immunotherapy
Considerations: Adenocarcinoma (mutations), Squamous, Other; (Tyrosine kinase inhibitor (TKI) preferred with selected mutation)
Mutations: Epidermal Growth Factor Receptor (EGFR+), Anaplastic Lymphoma Kinase (ALK+), ROS Proto-Oncogene 1 (ROS-1+), Mesenchymal-epithelial transition (MET) exon 14 skipping, Rearranged during transfection (RET) fusion, BRAF V600E

EGFR+	osimertinib		
ALK+	alectinib (lorlatinib 2nd option)		
ROS-1	entrectinib		
MET ex14	capmatinib		
RET fusion	selpercatinib OR pralsetinib		
BRAF V600E	dabrafenib AND trametinib		
No Mutation			
PD-L1 ≥50%	nonsquam	pembrolizumab alone → upon progression: carboplatin + pemetrexed	maintenance: pemetrexed
	squamous	pembrolizumab alone → upon progression: carboplatin + paclitaxel	maintenance: none
PD-L1 <50%	nonsquam	carboplatin + pemetrexed + pembrolizumab x4 cycles	maintenance: pemetrexed + pembrolizumab
	squamous	carboplatin + paclitaxel + pembrolizumab x4 cycles	maintenance: pembrolizumab
Progression	tyrosine kinase agent if mutation; otherwise, single-agent nonplatinum IV chemo - pemetrexed (nonsquam), paclitaxel, docetaxel, gemcitabine, vinorelbine		

pemetrexed
- for nonsquam only; folate inhibitor, ultimately inhibit purine/pyrimidine synthesis
SE: ↓blood cell counts, mucositis, rash
CI: CrCl <45 ml/min
Supportive care required: vit b12 1000mcg IM q9wk (start 1wk bf chemo); folic acid 1mg po daily (start 1wk bf chemo); dexameth 4mg po bid day before, of, after

SCLC

- rapid doubling time, very responsive to chemo and radiation

Limited Stage (ES): confined to single hemithorax, in single radiation port (30% of dx, 5yr survival 20%)

- goal CURE - response rate 70-90% - median OS 1.5-2yrs
- tx: chemo + radiation (daily mon-fri x6-7 weeks)
  - cisplatin + etoposide x4 cycles

Extensive Stage (ES): not LS (70% of dx, 5yr survival <5%)

- goal palliation - response rate 1st-line chemo 60-70% (2nd-line >3mo 40%, <3mo 10%) - median OS 9-11mo (2yr survival <5%)
- tx: chemo + atezolizumab without concurrent radiation (radiation can play palliative role)
  - carboplatin + etoposide + atezolizumab x4 cycles → maintenance atezolizumab alone
  - 2nd-line and beyond: depends on duration of completion of carbo+etop
    >6mo repeat again without atezo
    <6mo single agent (lurbinectedin, topotecan, irinotecan, paclitaxel, etc)

Summary

<u>NSCLC Limited</u>

- Surgery is goal if limited/localized stage
- Adjuvant cisplatin-based chemotherapy x 4 cycles
  - Cisplatin+vinorelbine preferred, except stage IA, stage IB (< 4 cm) as no survival benefit in these stages
- Concurrent chemotherapy + radiation if limited disease, but surgery is not an option

<u>NSCLC Metastatic/Unresectable</u>

- Check mutation status in nonsquamous histology: Targeted tyrosine kinase therapy first, if positive EGFR/ALK/ROS-1/MET exon 14 skipping/RET/BRAF V600E
- Immunotherapy
  - Pembrolizumab alone prior to IV chemo if PD-L1 ≥ 50%
  - Pembrolizumab given in combination with platinum-based IV chemo if PD-L1 < 50%
- IV Chemotherapy +/- Pembrolizumab; platinum doublet x 4 cycles
  - NON-SQUAMOUS: Carboplatin + pemetrexed +/- pembro
  - SQUAMOUS: Carboplatin + paclitaxel +/- pembro
- Non-platinum agents in recurrent setting

<u>SCLC Limited</u>

- Concurrent chemotherapy + radiation
  - Cisplatin + etoposide x 4 cycles

<u>SCLC Extensive</u>

- Chemotherapy + Atezolizumab (without radiation)
  - Carboplatin + etoposide + atezolizumab
  - Therapy at progression dependent on duration of response

Breast Cancer

Risk factors
can't control: age>50, FH, genetics, personal hx
can control: hormone replacement therapy, alcohol, post-menopausal obesity/BMI, late 1st preg, nulliparous, oral contraceptives
protective: pregnancy, lactation, exercise, BMI

Pathology
Non-Invasive: Lobular Carcinoma in situ (LCIS), Ductal Carcinoma in situ (DCIS)
Invasive: Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC) are most common

Tumor biology
Tumor size
Tumor grade (well differentiated=grade 1, still look like normal tissue; poorly differentiated=grade 3)
ER/PR (hormone receptor HR): ER+ slower growing
HER2 based on overexpression, more aggressive
Ki67 index: higher more aggressive (associated with tumor cell proliferation and growth); more responsive to treatment
Lymph node status: positive worse
Lymphovascular invasion

Staging
T – tumor size
N – nodal status
M – metastases to distant site (bone*, brain, lung, liver)
Now includes ER/PR, HER2, tumor grade
- "early stage" breast cancer (**ESBC**) tx goal: CURE - stage 0, I, II - stage III "locally advanced" (↑lymph node involvement)
- "metastatic" breast cancer (**MBC**) tx goal palliation - stage IV

ESBC "Better" Prognostic Factors
>50yo (post-menopausal)
nodes negative
small tumor (<1cm)
$ER^{(+)}$ or $PR^{(+)}$ (i.e. "hormone positive=$HR^{(+)}$"): slower growing tumor, provides target to treat with hormone therapy
$HER2^{(-)}$ less turnover
tumor grade 1 (well differentiated), better than grade 2 or 3
negative lymphovascular invasion (on biopsy)
lower Ki67 index

ESBC "Worse" Prognostic Factors
<50yo (pre-menopausal)
nodes positive: already spread to lymph nodes, has it spread further? increases recurrence
larger tumor (>3cm)
$ER^{(-)}$ or $PR^{(-)}$ (i.e. "hormone negative"): faster growing tumor
$HER2^{(+)}$ more aggressive
"Triple negative" $ER^{(-)}$ $PR^{(-)}$ $HER2^{(-)}$ – no targets for drugs, most aggressive
tumor grade 2/3 (poorly differentiated)
positive lymphovascular invasion (on biopsy)
higher Ki67 index

ESBC Systemic Treatment (subsets)
$ER/PR^{(+)}$, $HER2^{(-)}$ chemo or no? endocrine therapy always
$ER/PR^{(-)}$, $HER2^{(-)}$ chemotherapy
ER/PR, $HER2^{(+)}$ targeted therapy, chemotherapy, +/- endocrine therapy

ESBC – Why give chemotherapy? Can kill micrometastic tumors (cells left behind after local therapy); Chemo targets rapidly dividing cell lines
Outcomes: DFS (disease-free survival; 5yr still alive, no recurrence); OS (overall survival)
Neoadjuvant (chemo before surgery); Adjuvant (chemo after surgery)
Who gets chemotherapy? Highest risk of recurrence: $HER2^{(+)}$ $Node^{(+)}$ $ER^{(-)}/PR^{(-)}/HER2^{(-)}$ (Triple Negative)

The Oxford Overiew
35yr f/u 100 RTs (100k ESBC pts)
Adjuvant chemo ↓absolute risk recurrence 12% (<50yo) at 15yr; ↓absolute of death by 7% at 10yrs (older chemo)
Combo chemo better than no chemo; Anthra better than non; Additional taxane further reduces mortality
Duration 3-6mo of chemo as good as longer

ESBC

HR(+), HER2(-)

- 60% of all newly dx; slower growing tumors; all patients adjuvant endocrine therapy*

Node(+) or large tumor (>5cm)

AC-T: doxorubicin + cyclophosphamide q2-3wks x4 cycles followed by paclitaxel q2wk x4 cycles or q1wk x12 doses

TC: docetaxel + cyclophosphamide q3wk x4 cycles (Anthracycline sparing; cardiotoxicity (HF); maxed dose of Anthra from earlier cancer)

Node(-)

use genomic testing (Oncotype DX) get "Recurrence Score"; calculates risk reduction benefit from chemo

- low scores (0-25) no chemo: adjuvant endocrine therapy
- high score (>30) chemo
  - non-anthracycline preferred: TC x4 cycles
  - may use anthra-only regimen: AC x4 cycles

<u>ESBC Endocrine Therapy</u>

goal: further prevent risk of disease recurrence; primary tumor and any residual disease now eradicated via surgery +/- chemo +/- radiation;

Any ER/PR(+), regardless of HER2 or menopausal status get adjuvant endocrine therapy; don't give endocrine with chemotherapy

May give concurrently with trastuzumab +/- pertuzumab

- primary source of estrogen: pre-meno ovaries, post-meno aromatase

<u>ESBC Adjuvant Endrocrine Therapy: Post-menopausal</u>

Aromatase Inhibitors: anastrazole 1mg, letrozole 2.5mg, exemestane 25mg

- AI's vs. Tamoxifen no OS; ↑DFS vs Tam alone; reduces risk of recurrence 40-50%

Adverse effects:

- anthralgias/myalgias (AI>TAM)
- vaginal dryness, hotflashes/menopausal sx
- risk of osteoporosis/fractures (AI>TAM): calcium 1200-1800mg + vitd 800iu; preexisting osteoporosis, tamoxifen?
- no risk of thrombosis for AI (TAM); no effect on endometrium; adverse lipid profile unclear; cardiac events (AI=TAM)
- **don't** use in pre/peri-menomausal women; may induce increased estrogen production

Treatment:

- anastrazole or letrozole x5-10yrs
- tamoxifen x2-3yrs then anastrazole/exemestane; tamoxifen x5yrs then letrozole x5yrs (switch therapy; used in perimenopausal)
- tamoxifen x5-10yrs (if severe OP, hx fractures)

<u>ESBC Adjuvant Endrocrine Therapy: Pre-menopausal</u>

Tamoxifen 20mg qday x5-10yrs

- antagonist (breast, CNS); agonist (bone, endometrium)
- reduces risk of recurrence 40%; beneficial lipid profile; cheap; breast cancer prevention in high risk patients

SE: menopausal sx (**hot flashes**, mood swings, libido, depression); thrombosis, secondary endometrial cancer, vaginal bleed/discharge/irritation

- prodrug 3A4 2D6 active metabolite endoxifen; avoid strong 2D6 inhibitors
- DDIs: strong inh (paroxetine, fluoxetine, bupropion, quinidine); moderate (sertraline, duloxetine); weak (citalo/escitalo, venla/desvenla)

TEXT/SOFT trial: tamoxifen/AI + ovarian suppression (oophorectomy or LHRH agonist)

- goserelin/leuprolide for continuous stimulation of pituitary ↓FSH/LH, ↓estrogen from ovary; chemically make pre-meno woman post-menopausal (reversible)
- adding tamoxifen/AI + OS improved DFS compared to tam alone; largest benefit in "high risk" (chemo-requiring); low risk patients minimal benefit in OS

ESBC Endocrine Treatment Summary

Goal of adjuvant endocrine treatment: cure by preventing disease recurrence

Premenopausal women: source of estrogen ovaries; tamoxifen x5-10yrs; "High Risk" patients – Tam / AI + ovarian suppression

Postmenopausal women:source of estrogen aromatase; should receive an AI at some point; AI containing regimens: ↑DFS, no OS benefit yet; TAM regimen option

Triple Negative HR$^{(-)}$, HER2$^{(-)}$
- anthracycline based regimens preferred plus incorporate taxane (improves DFS and/or OS)
Treatment
AC→T: doxorubicin + cyclophosphamide q2-3wks x4 cycles followed by paclitaxel q2wk x4 cycles or q1wk x12 doses

ESBC-HER2$^{(+)}$ Regimens
HER2$^{(+)}$ regardless of size, node, ER/PR
- trastuzumab (Herceptin) added to chemotherapy (with taxane); given IV **q3wk** (requires LD) for total of **1 year** (neo/adjuvant)
- trastuzumab: inhibits HER2 dimerization with other HER3, activates antibody-dep cell-mediated cytotoxicity (ADCC), inhibits multiple HER-mediated signal paths

HER2$^{(+)}$ >2cm or node(+), regardless of ER/PR
- pertuzumab (Perjeta) added to chemotherapy (with taxane); given IV **q3wk** for total of **4-6 cycles or up to 1 year** (neo/adjuvant)
- pertuzumab prevents HER2 domain cleavage, activates ADCC, inhibits HER-mediated signaling pathways

trastuzumab/pertuzumab given concurrently with taxane (don't give with anthra cardiotox); trastuzumab+pertuzumab (Phesgo) combination available in SC

ESBC-HER2$^{(+)}$ Adjuvant/Neoadjuvant Chemotherapy
HER2$^{(+)}$ >2cm and/or node(+) = "high risk"
- PTP/PTD → AC/FEC → surgery → trastuzumab +/- pertuzumab
  - pertuzumab + trastuzumab + paclitaxel IV qwk/docetaxel IV q3wk x4 cycles then AC/FEC x4 cycles
- TCH + P → surgery → trastuzumab +/- pertuzumab
  - docetaxel + carboplatin + trastuzumab + pertuzumab q3wk x6 cycles

Other Adjuvant treatments "high risk"
- pathology from surgery determines adjuvant treatment
  - pCR (pathological complete response): continue trastuzumab +/- pertuzumab to complete 1 year of HER therapy
  - residual disease: ado-trastuzumab emtasine q3wk x14 cycles
  - neratinib oral HER2 targeted tyrosine kinase inhibitor: 240mg qd x1year after completion of trastuzumab; improved DFS (best in HR+ and/or node+); diarrhea*

Other Adjuvant treatments "low risk" <2cm and node negative
- paclitaxel + trastuzumab x12 doses → trastuzumab q3wk to complete 1 year (preferred)
- "TCH" IV q3wk x6 cycles → trastuzumab q3wk to complete 1 year

HER$^{(+)}$ Adjuvant Chemotherapy Summary
"High Risk" >2cm and/or node(+)
- PTP/PTD x4 → AC x4 → HER2 therapy x1yr
  - pertuzumab + trastuzumab + paclitaxel/docetaxel x4 cycles → doxorubicin + cyclophosphamide → trastuzumab +/- pertuzumab
- TCH-P x6 → HER2 therapy x1yr
  - docetaxel + carboplatin + trastuzumab + pertuzumab q3wk x6 cycles → trastuzumab +/- pertuzumab

"Low Risk" <2cm and node negative
- adjuvant paclitaxel + trastuzumab x4 → trastuzumab x1yr
- adjuvant TCH x6 → trastuzumab x1yr

Summary ESBC Chemotherapy
Goals of Neo- or Adjuvant chemotherapy: eradicate micrometastatic disease; prevent disease recurrence, i.e. cure
Chemotherapy - patient specific - when tumor displays poor prognostic features
Anthracycline regimens are generally preferred
Node(+), HER2(+) or Triple(-) pts - additional taxane chemotherapy
HER2(+) receive 1 year of trastuzumab +/- pertuzumab

MBC

- incurable; <10% MBC are new cancers; common metastasis (bone, liver, lung, brain); always biopsy, survival 2-5yrs, minimal role for surgery/radiation
- therapy goals: palliate symptoms (maintain QoL, prolong life); prevent disease progression (PFS-progression free survival)

Endocrine therapy "-static"

1st-line: premeno: ovarian suppression (to make them postmeno with LHRH agonists leuoprolide/goserelin), then treat as postmenopausal
postmeno: AI +/- CDK4/6 inhibitor: palbociclib (Ibrance), ribociclib (Kisqali), abemaciclib (Verzenio); all cause neutropenia, diarrhea, rash, mucositis
2nd-line: fulvestrant (Faslodex) 500mg IM q28d +/- CDK4/6 inhibitor if CDKi not previously used
3rd-line: everolimus (Afinitor) + exemestane
PFS interval will shorten each new regimen; "ride the endocrine therapy train"
PI3K inhibitor: apelisib (Piqray) can combine with fulvestrant in 1st or 2nd line patient has PIK3CA mutation; ADE hyperglyc, rash, diarrhea

Chemotherapy "-cidal"

- begin chemo when failure of multiple endocrine manipulations, or visceral crisis, or patient symptomatic, or patient decision-hope for complete response (CR)
- PFS interval will shorten each new regimen; good performance status tolerate best; single agent preferred over combo; CLINICAL TRIALS

<u>MBC-HER2(+)</u>

1st-line: PTD (pertuzumab + trastuzumab + docetaxel); continue until disease progression/good response/toxicity
2nd-line: ado-trastuzumab-emtansine (Kadcycla) or tucatinib+capecitabine+trastuzumab
3rd-line: lapatinib+capecitabine or lapatinib+trastuzumab or trastuzumab+salvage chemo or trastuzumab deruxtecan

<u>MBC-HER2(-)</u>

1st-line: - paclitaxel weekly 3wk on 1wk off - liposomal doxorubicin (Doxil) if anthra naïve - capecitabine (used after taxane and/or anthra)
Triple Negative *if tumor is PD-L1 positive 1st-line - nab-paclitaxel (Abraxane) + atezolizumab (Tecentriq) - pembrolizumab (Keytruda) + chemotherapy
3rd-line: eribulin or sacituzumab govitecan (Trodelvy)

"Salvage" regimens beyond 2nd progression: "dealers choice" based on expected toxicities
Taxanes, Anthracyclines, Eribulin, Capecitabine should have been used previously at some point
- CTs, gemcitabine, carboplatin/cisplatin, ixabepilone, liposomal doxorubicin, vinorelbine, olaparib/talazoparib (BRCA mut), paclitaxel albumin-bound, rechall endocrine therapy if ER+?

<u>Summary MBC Chemotherapy</u>

Begin chemotherapy when: failure of multiple endocrine manipulations, or visceral crisis, or pt is symptomatic, or pt decision, hope for complete response (CR)
Goal of chemotherapy is palliation, prolong life
HER2(+) - targeted therapy ± chemotherapy
HER2(-) - taxane, anthracycline, eribulin, capecitabine, based therapies before moving to salvage agents
PFS interval will shorten with each new regimen

<u>Quick Chemotherapy Cases</u>

ER/PR (+), HER2 (-), Node negative, 3 cm, grade 2, high oncotype
Chemo: TC x 4 cycles
ER/PR (+) HER2 (+) node positive, 2.6 cm, grade 3
Chemo: TCH-P x 6 cycles or PTD/PTP x4 + AC x4; all get 1 year of HER2 directed therapy
ER/PR (-), HER2 (-), node negative, 1.2 cm, grade 3
Chemo: AC-T (doxorubicin+cyclophosphamide->paclitaxel)
ER/PR (-) HER2 (+), node negative, 1.6 cm, grade 3
Chemo: paclitaxel + trastuzumab x 12 weeks then trastuzumab to complete 1 year

Colon Cancer

Describe goals of treatment when chemotherapy is offered to patients with colon cancer based on initial disease stage
Recommend chemotherapy for adjuvant treatment of a patient with a resected, early-stage colon cancer
Select an appropriate treatment regimen for a patient with previously untreated metastatic colorectal cancer using cancer biomarkers, chemotherapy SE profiles
Design a plan for monitoring, preventing, and treating adverse drug events when presented with a chemotherapy regimen for a patient with colon cancer

Stage I: Limited to mucosa/submucosa or invades muscularis propria. No lymph node involvement.
Stage II: Through muscle wall or into nearby tissue. No lymph node involvement.
Stage III: Regional lymph node involvement without distant metastasis.
Stage IV: Distant metastasis (including non regional lymph nodes).

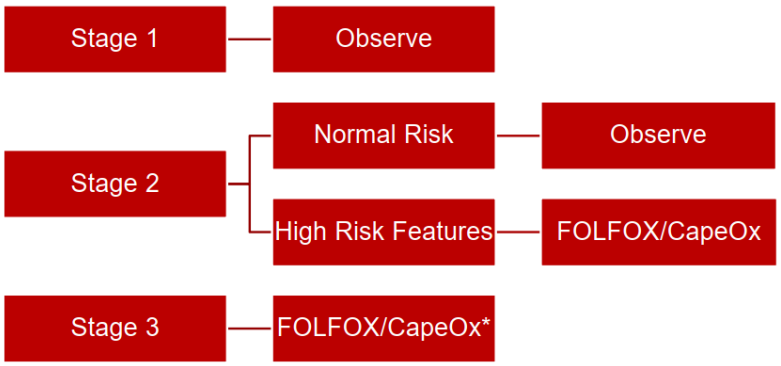
Stage 0-I: surgery alone
Stage II: surgery +/- adjuvant chemotherapy (high risk pt)
Stage III: surgery + adjuvant chemotherapy
Stage IV: chemotherapy +/- surgery

Treatment (*FOLFOX and CapeOX equally efficacious unless stated otherwise)
FOLFOX (repeat q2w) oxaliplatin 85 mg/m2 IVPB over 2h + leucovorin 200-400 mg/m2 IVPB over 2h + fluorouracil 400 mg/m2 IV PUSH plus fluorouracil 2400 mg/m2 CIV over 46h
FOLFIRI (repeat q2w) irinotecan 180 mg/m2 IVPB over 1.5h + leucovorin 200-400 mg/m2 IVPB over 2h + fluorouracil 400 mg/m2 IV PUSH plus fluorouracil 2400 mg/m2 CIV over 46h
CapeOX/XELOX (repeat q3w) oxaliplatin 130 mg/m2 IVPB over 2 hrs, Day 1; capecitabine 1000 mg/m2 (po) BID on days 1 thru 14

FOLFOX (q2w)	oxaliplatin IVPB + leucovorin IVPB + flurouracil IV PUSH + fluorouracil CIV over 46h
FOLFIRI (q2w)	irinotecan IVPB + leucovorin IVPB + flurouracil IV PUSH + fluorouracil CIV over 46h
CapeOX/XELOX (q3w)	oxaliplatin IVBP on day 1, then capecitabine po days 1-14

Low-risk Stage III (T1-3, N1)
High-risk Stage III (T4, N1-2 or any T, N2)

Decision Tree
Stage 1: observation after surgery
Stage 2 normal risk: observation after surgery
low-risk: 5FU alone or no chemo
high-risk: FOLFLOX/CapeOX
- T4, perforation/obstruction, lymph/vascular, poor diff, pos margin
- lymph <12 nodes examined
Stage 3: FOLFOX/CapeOX (consider 3mo for low-risk CapeOx —T1-3, N1)

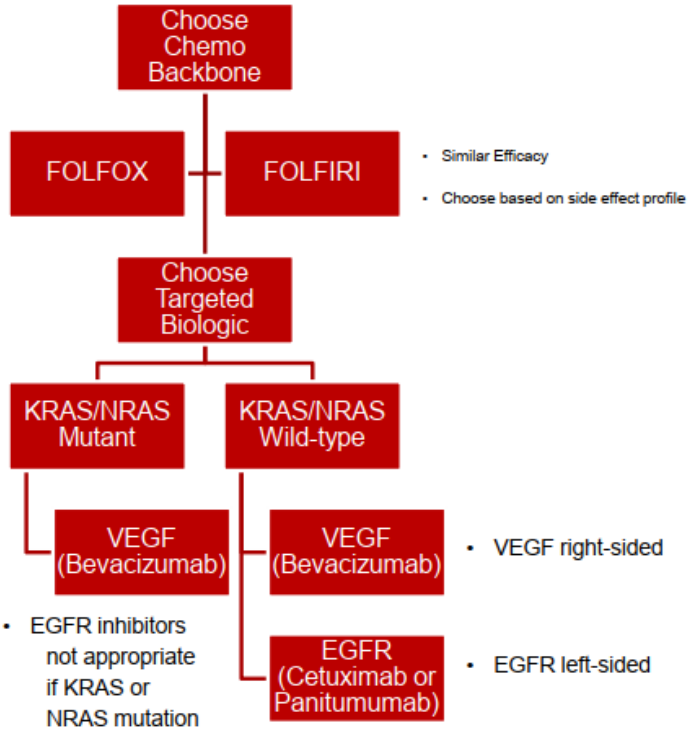


*Consider shorter duration (i.e., 3 months) for T1-3, N1; strong recommendation for CapeOx

Metastatic Treatment Regimen

5FU-based chemo is mainstay; usually FOLFOX or FOLFIRI

Targeted biological therapies should be added to chemo for
- Vascular Endothelial Growth Factor (VEGF)
- Epidermal Growth Factor Receptor (EGFR)



Chemo "Backbone": FOLFOX vs. FOLFIRI
- equally efficacious; decision based on side effects

fluorouracil/capecitabine
metabolized by DPD enzyme (dose red if hepatic dysf)
- neutropenia (bolus of FU)
- mucositis, mouth sores - diarrhea
- hand-foot syndrome (cape>fu)
- cardiac toxicity (vasospasms) rare

oxaliplatin
- nausea (moderately emetogenic)
- neuropathy (acute vs. cumulative)
  - acute exacerbated by cold; self-limiting
  - cumulative long-lasting, can be permanent
- myelosupp (thrombocytopenia>neutropenia)
- renal elimination; dose adj not necessary for mild-mod (d/t ppb)

irinotecan
- nausea (moderately emetogenic)
- diarrhea* (refractory, dose red also other antidiarrheals codeine, opium, octreotide)
  - acutely (<24hr): acute phase—cholinergic, use atropine/hyscyamine
  - chronically (5-7d post): delayed phase—use loperamide
- myleosupp (neutropenia>thrombocytopenia)
- metabolized 3A4 to active SN-38 cpd; consider DDIs
- SN-38 eliminated glucuronidation via UGT 1A1; dose adj liver dysf

Targeted Agents in the First Line
VEGF→antiangiogenesis = bevacizumab (Avastin)
EGFR→antiproliferation = cetuximab (Erbitux) chimeric mAb, panitumumab (Vectibix) human mAb
- used in NRAS/KRAS wild-type patients only (ie. if mutation no benefit and may be harmed); ~45% of patients are wild-type

bevacizumab - VEGF inhibitor
- dose limiting: HTN, impaired wound healing (hold at least 28 days prior to planned surgery*), fatigue, GI perforation, VTE/ATE
- hoarse voice, HA
- metabolized intracellularly (no ddis); proteinuria though

panitumumab/cetuximab - EGFR inhibitor
- rash (acneiform), paronychia, diarrhea, hypomagnesemia (hypocalc with prolonged hypomag); infusion rxns (more common/severe with cetuximab chimeric)
- rarely use cetuximab for colon cancer

Tumor Sidedness
Left-sided tumors (i.e., descending colon): VEGF preferred
Right-sided tumors (i.e., ascending or transverse colon): EGFR may be superior

Stage IV Drugs and Adverse Effects
5-fluorouracil Diarrhea, mucositis, myelosuppression, nausea and vomiting, HFS
capecitabine HFS, Diarrhea, myelosuppression, nausea and vomiting, abdominal pain, hyperbilirubinemia
irinotecan Diarrhea, myelosuppression, nausea and vomiting, mucositis
oxaliplatin Myelosuppression, nausea and vomiting, acute and cumulative neuropathies, some reports of extravasation injury
bevacizumab Hypertension, proteinuria, wound dehiscence, arterial thrombosis, hemorrhage, headache, voice hoarseness
cetuximab/panitumumab Skin rash, hypersensitivity reaction, electrolyte abnormalities

Cases

Case #1

MN is a 67-year-old male who was admitted to an outside hospital due to increasing shortness of breath which had worsened over the previous one to two weeks. A CT scan of the chest indicated multiple bilateral pulmonary nodules, and a PET scan showed a mass in the liver. A biopsy of the liver mass was performed, and while those results were pending, the patient was subsequently discharged from the hospital upon improvement in symptoms following medical management. Based on the presentation and location of masses, the patient was referred to thoracic oncology pending results of the biopsy.
PMH: Hypertension, diabetes mellitus
SH: Retired teacher with a 40 pack-year history of smoking
FH: Colon cancer (paternal grandfather), prostate cancer (father), and breast cancer (sister)
Ht: 5'10", Wt: 195 lb, SCr 0.9, Total bilirubin 0.8, AST/ALT are both normal

Question #1

The patient presents to clinic, and the liver biopsy is positive for small cell lung cancer (SCLC). Which of the following is most accurate in describing the stage of this patient's SCLC and the goal of treatment?

a. Limited stage; cure
b. Limited stage; palliation
c. Extensive stage; cure
d. **Extensive stage; palliation**

Rationale: The definition of limited stage SCLC is confined to a single hemithorax, in a single radiation port. Extensive stage is defined as anything that does not meet that definition of limited stage. Because MN has nodules in both lungs and biopsy-proven SCLC in the liver, the cancer is not confined to a single hemithorax that would fit in a single radiation port. Therefore, this is extensive stage. The treatment goal of limited stage SCLC is cure, and the treatment goal of extensive stage SCLC is palliation.

Question #2

Which of the following would be the most appropriate first-line treatment for this patient?

a. Cisplatin + etoposide plus concurrent radiation
b. Carboplatin + etoposide + atezolizumab plus concurrent radiation
c. **Carboplatin + etoposide + atezolizumab without radiation**
d. Cisplatin + etoposide without radiation

Rationale: A would only be the correct answer if the patient had limited stage SCLC. B is the appropriate systemic therapy regimen for extensive SCLC, but the answer is incorrect because concurrent radiation is not given for extensive stage. D is incorrect due to not being the optimal systemic therapy regimen for extensive stage.

Question #3

The patient completed 4 cycles of carboplatin + etoposide + atezolizumab (final dose of chemotherapy was on 1/31/20) and presented to clinic on 1/8/21 for cycle #14 of atezolizumab maintenance. His scans on 1/8/21 showed a new adrenal mass, and a biopsy of the new mass on 1/15/21 was positive for small cell lung cancer, confirming progression.

Which of the following would be the most appropriate next treatment for this patient?

a. **Stop atezolizumab and repeat carboplatin + etoposide**
b. Continue atezolizumab and add carboplatin + etoposide
c. Single-agent chemotherapy with lurbinectedin

Rationale: Because the patient has maintained a response for > 6 months following completion of platinum-containing chemotherapy, the patient has platinum-sensitive disease, so a platinum-containing chemotherapy regimen should be repeated. The patient is progressing while on atezolizumab, so it should not be continued. As such, A is correct and B is incorrect. C would only be a correct answer if the patient had progressive disease < 6 months following completion of platinum-containing chemotherapy (which would be called platinum-resistant disease).

CASE 2: RATIONALE AND ANSWERS:

JS is a 30-year-old male who has been treated by his primary care physician with multiple rounds of antibiotics over the past four months for presumed respiratory infections. Due to persistent respiratory symptoms, a chest X-ray and follow-up CT chest were performed, which indicated a mass in his left lung. A PET scan confirmed the left lung mass with additional avid lymph node involvement, but no distant masses were noted. A brain MRI shows no abnormal findings or masses. A biopsy of the lung mass is performed, which is positive for non-small cell lung cancer (adenocarcinoma). Based on scans and clinical presentation, the patient is diagnosed with stage IIIA disease.

- PMH: Seasonal allergies
- SH: Practicing attorney with no history of smoking
- FH: Bladder cancer (maternal grandfather)
- Ht: 6'0", Wt: 215 lb, SCr 0.7, Total bilirubin 0.6, AST/ALT are both normal

Question #4

The patient is seen by both thoracic surgery and thoracic oncology in clinic, and the thoracic surgeon decides that the patient is fit for a left upper lobectomy. If a successful left upper lobectomy is performed, and the stage is confirmed as IIIA, what is the most appropriate next step in treatment?

a. Radiation to the unresected part of the left lung
b. **IV chemotherapy x 4 cycles**
c. Surveillance with no further treatment at this time

Rationale: Adjuvant chemotherapy x 4 cycles is indicated following a lobectomy for stage II and stage III non-small cell lung cancer, and for stage IB non-small cell lung cancer if the tumor size is ≥ 4cm. This is done to reduce the risk of disease recurrence. This patient has stage IIIA, so adjuvant chemotherapy is indicated (the gold standard adjuvant chemotherapy regimen is cisplatin + vinorelbine), so B is the correct answer. Radiation to the unresected part of the lung is not done following resection, so A is wrong. If the patient had stage IA, or if he had stage IB with a tumor size < 4cm, then C would have been the correct answer.

Question #5

Prior to resection, the patient decides that he does not want to go through with surgery, but he still wants treatment for his cancer. Which of the following would be the most appropriate next step in treatment?

a. IV chemotherapy x 4 cycles without radiation
b. Radiation + concomitant chemotherapy, followed by surveillance
c. **Radiation + concomitant chemotherapy, followed by durvalumab for one year**
d. Surveillance with no further treatment at this time

Rationale: The patient declining surgery essentially causes us to treat him as if he is "unresectable". The goal of treatment for stage I-IIIB unresectable non-small cell lung cancer is still cure, and the curative intent treatment is concurrent chemoradiation. This means that A and D are incorrect. Because this patient has stage III disease, chemoradiation should be followed by durvalumab maintenance for one year, so C is correct. If the patient had stage I or II disease, B would have been correct.

Question #6

The patient completed carboplatin + paclitaxel + concomitant radiation and has received six months of durvalumab maintenance, and his scans show a new liver lesion. A biopsy of the liver lesion is positive for non-small cell lung cancer (adenocarcinoma, EGFR exon 19 deletion (-), EGFR exon 21 L858R mutation (-), ALK (-), ROS-1 (+), MET exon 14 skipping (-), RET fusion (-), BRAF V600E (-), PD-L1 70%).

Which of the following would be the most appropriate next treatment for this patient?

a. **Entrectinib**
b. Alectinib
c. Osimertinib
d. Pembrolizumab

Rationale: The patient now has metastatic disease. Because his pathology is positive for a ROS-1 mutation, A is the correct choice. The positive mutation trumps PD-L1 ≥ 50%, so the appropriate oral chemotherapy for the mutation should be given before pembrolizumab is considered. If ALK was positive instead of ROS-1, B would have been correct. If EGFR was positive instead of ROS-1, C would have been correct. If mutations were all negative, D would have been correct due to PD-L1 being ≥ 50%.

Question #7

Which of the following most accurately describes common side effects of the correct choice in the previous question?**Cardiomyopathy, cognitive effects, liver enzyme elevation, uric acid elevation**

CASE 3: Rationale and Answers

DV is a 64-year-old female who had an extensive workup at an outside thoracic oncologist's office and has been diagnosed with metastatic non-small cell lung cancer to the spine. She decided to move in with her daughter's family close to your clinic while undergoing treatment. A bone biopsy of the spine reveals: adenocarcinoma, mutation status negative, PD-L1 60%.

- PMH: Hypercholesterolemia
- SH: Retired nurse with a remote 10 pack-year history of smoking
- FH: Acute myeloid leukemia (sister), renal cell carcinoma (father)
- Ht: 5'6", Wt: 145 lb, SCr 0.8, Total bilirubin 0.9, AST/ALT are both normal

Question #8

Which of the following would be the most appropriate first-line treatment for this patient?

a. Osimertinib
b. **Pembrolizumab**
c. Carboplatin + paclitaxel + pembrolizumab
d. Carboplatin + pemetrexed + pembrolizumab

Rationale: B is the correct answer for first-line treatment of metastatic non-small cell lung cancer with mutations negative and PD-L1 ≥ 50% (regardless of histology). A would have been the correct answer if the patient had a positive EGFR mutation with metastatic non-small cell lung cancer with adenocarcinoma histology (regardless of PD-L1 status). C would have been the correct answer if the patient had metastatic non-small cell lung cancer with squamous histology and a PD-L1 < 50%. D would have been the correct answer if the patient had metastatic non-small cell lung cancer with adenocarcinoma histology with mutations negative and PD-L1 < 50%

Question #9

The patient has completed 24 cycles of the above treatment. Her scans show progression in the adrenal gland, which is confirmed by a biopsy.
Which of the following would be the most appropriate next treatment for this patient?

a. Carboplatin + paclitaxel
b. **Carboplatin + pemetrexed**
c. Alectinib
d. Dabrafenib + trametinib

Rationale: IV chemotherapy is the correct answer, and only A and B are IV chemotherapy regimens. A would have been correct if the patient had squamous histology. Because the actual histology is adenocarcinoma (nonsquamous), B is the correct answer. C would have been the correct first-line answer if there was a positive ALK mutation. D would have been the correct first-line answer if there was a positive BRAF V600E mutation.

Question #10

What of the following statements regarding pemetrexed is FALSE?

a. **Contraindicated if creatinine clearance < 60 mL/min**
b. Requires vitamin B12 supplementation to reduce the risk for decreased blood cell counts and mucositis
c. Requires dexamethasone the day before, day of, and day after chemotherapy to reduce the risk for rash
d. Requires folic acid supplementation to reduce the risk for decreased blood cell counts and mucositis

Rationale: A is false (and thus the correct answer) because pemetrexed is contraindicated if creatinine clearance is < 45 mL/min (not 60 mL/min). B, C, and D regarding vitamin B12, dexamethasone, and folic acid are accurate as written.

BREAST CANCER: CASE 1: Answers and Rationale

PR is a 40-year-old pre-menopausal female with no previous history of breast cancer. PR makes an appointment with her primary care physician due to recent onset rib pain. She is also complaining of increasing fatigue, weight loss, and "fullness" after eating small meals. Her physician discovers a small lump in her left breast, and her liver is slightly palpable on physical exam. Her physician orders an ultrasound of the breast and liver and discovers suspicious findings. She is referred to surgical oncology who orders CTs of her chest, abdomen and pelvis as well as a bone scan. The radiologist identified a series of osteolytic bone lesions in her rib and pelvis, as well as multiple liver lesions, including a large 3 cm x 3 cm lesion in her right lobe. A biopsy of her breast lump and liver both reveal ER/PR (-) HER2 (-), PD-L1 negative, poorly differentiated, invasive adenocarcinoma, consistent with metastatic breast cancer. All laboratory results, including liver function, are within normal limits. PR is referred to a medical oncologist to discuss treatment.

PMH: HTN, type II DM

- Current medications:
- Calcium 600 mg + vitamin D 400 IU daily
- Multivitamin daily
- Metformin 500 mg BID
- Lisinopril 10 mg daily
- Lorazepam 0.5-1 mg QHS PRN
- Allergies: sulfa (hives)
- Current Ht: 5'8" and wt: 215 lb

SH: She is a homemaker, married and lives with her husband and 2 children. She does not drink, smoke, or use illicit drugs. She has never used birth control or hormone replacement therapy. There is no history of breast cancer in her family. Last menstrual period was 2 weeks ago. Her performance status is normal (ECOG 0).

Question #1

At this time, it would be appropriate for PR and her oncologist to:

a. Discuss the role of aggressive chemotherapy and radiation to cure her disease
b. Discuss the need for trastuzumab based therapy
c. **Discuss the role of chemotherapy to palliate her symptoms, improve her quality of life and prolong her life**
d. Perform surgical resection of her large liver lesion

Question #2

List 2 potential treatment options for PR:

Rationale/Feedback – taxane (weekly paclitaxel) or anthracycline (Doxil) based therapy are reasonable first line options for metastatic triple negative breast cancer. Capecitabine is also a reasonable option but was mainly studied after taxane and anthracycline. Enrollment in a clinical trial is always an option for patients. Platinum regimen here would also be acceptable as the patient is triple negative, but generally not used in the first line setting. Eribulin, vinorelbine, ixabepilone, any HER2 targeted therapy or any endocrine therapy would be incorrect. Since the patient is PD-L1 negative, immunotherapy is not a reasonable option for the patient.

BREAST CANCER CASE 2: RATIONALE AND ANSWERS:

HH is a 32-year-old female who notices a small lump in her left breast during her routine self-breast exam. Her OB/GYN orders a mammogram which confirms a small, 0.7 cm area of suspicion. The area is biopsied and reveals a low grade, ER/PR (+), HER2 (-) invasive ductal carcinoma. The patient is taken to surgery for a lumpectomy and sentinel lymph node biopsy. Pathology reveals: grade 1, 0.8 cm invasive ductal carcinoma, ER 100%, PR 90%, HER2 (-), 0/2 lymph nodes positive. An Oncotype Dx was ordered revealing a low score of 7. The patient is meeting with the medical oncologist to discuss adjuvant therapy.

PMH: anxiety, insomnia

Current medications:

- Sertraline 100 mg daily
- Zolpidem 5 mg QHS PRN
- Multivitamin 1 PO daily

SH: She is a physical therapist at a local hospital. She is married with 1 child (age 3). She does not smoke or use illicit drugs. She drinks 3 glasses of wine per week. Her last menstrual period started ~1 week ago.

Question #1

Determine which of the following are true regarding adjuvant endocrine therapy for HH? (Multiple answers)

a. HH has a high risk of recurrence and requires ovarian suppression with goserelin
b. HH requires chemotherapy prior to starting her endocrine therapy
c. **HH should be started on tamoxifen for 5-10 years**
d. HH should be started on letrozole 2.5 mg daily for 5-10 years
e. **Sertraline interferes with tamoxifen metabolism and should be changed to citalopram**
f. HH should be started on fulvestrant IM monthly for 5-10 years

Feedback: HH has an early stage, low grade, hormone positive breast cancer. Her risk of recurrence is very low after surgery/radiation. The Oncotype score of 7 confirms this. She will not benefit from chemotherapy. Since she has low risk disease she does not require ovarian suppression with her endocrine therapy. Tamoxifen x 5-10 years is completely reasonable. She will want to switch her SSRI (sertraline is moderate 2D6 inhibitor) to a minor inhibitor (citalopram, escitalopram). She is pre-menopausal so letrozole or any AI is not an option. Fulvestrant is only approved in the metastatic setting.

Question #2

HH completes her adjuvant endocrine therapy and has been in surveillance for the past 2 years. She starts to notice more hip pain that is constant without relief from stretching or OTC anti-inflammatory medications. Her primary care physician orders an X-ray which shows suspicious lesions throughout her hip. HH is referred back to her medical oncologist. Staging scans reveal extensive osseous lesions throughout the whole skeleton but not visceral disease. Bone biopsy reveals the same pathology as her primary tumor years prior. Her PMH has not changed other than a TAH/BSO the previous year. Her current medications are buspirone twice daily and zolpidem PRN.

What options should be discussed with HH for the treatment of her newly diagnosed cancer:

a. Palbociclib + fulvestrant until disease progression or toxicity
b. HH does not require treatment at this point, as she has bone only disease
c. **Ribociclib + letrozole until disease progression or toxicity**
d. HH should have one course of chemotherapy then switch to endocrine therapy
e. Fulvestrant until disease progression or toxicity
f. Weekly paclitaxel until disease progression or toxicity

Feedback: first line metastatic hormone positive breast cancer. She is now postmenopausal (TAH/BSO) so the first line choice is a CDK4/6 inhibitor (any of the 3) + an AI (any of the 3). With metastatic cancer, therapy is required and HH is symptomatic from her disease. Palbociclib + fulvestrant is a 2nd line option for patient who have not been exposed to a CDK4/6 inhibitor previously. Fulvestrant monotherapy is also a 2nd line option. The patient should be started on a bone modifying agent (either IV bisphosphonate or denosumab) with her extensive skeletal disease. These patients should "ride the hormone train" as long as possible before chemotherapy. Hormone therapy comes with less toxicity, and actually provides better outcomes for ER/PR (+) patients compared to chemotherapy. The only caveat is if the patient needs a response (visceral crisis, onc emergency, ect) which is not the case with HH.

Cancer2: Exam 3

Intro to Hematologic Malignancies

Discuss the differences in pathogenesis/diagnosis/staging/prognosis of the various hematologic malignancies
Describe the potential treatment options and type of responses for the various hematologic malignancies
Understand the rationale for Hematopoietic Stem Cell transplantation (HSCT)
Compare different types of HSCT, including incidence and associated disease states
Review the pre- and post-HSCT process
Know the complications and important supportive care options for patients undergoing HSCT

Myeloid	AML APL	CML	MDS (precursor to AML)	Aplastic Anemia
Lymphoid	ALL	CLL	Lymphoma NHL HL HCL	MM

AML: myeloid blasts, subtypes
ALL: lymphoid blasts, B or T cells
CML: uncontrolled clonal proliferation and maturation
CLL: clonal proliferation and accumulation of mature B lymphocytes, resulting from inhibition of apoptosis
Lymphoma: monoclonal proliferation of malignant B or T lymphocytes
Myeloma: malignant neoplasm of plasma cells accum in bone marrow, leads to bone destruction/marrow failure; overprod of dysfunctional immunoglobulins

Classification by progression and treatment

Acute Leukemia: AML (APL, others) ALL (B-cell, T-cell)
Lymphoma: NHL (FL, DLBCL, etc) HL CLL (most place it here)
MDS (treated similar to AML)
Multiple Myeloma
Chronic Leukemia: CML CLL HCL
Other: aplastic anemia MPD/MF ET/PV

Diagnosis and staging tools

bone marrow biopsy (BmBx): acute leukemias, myeloma, chronic leukemias, lymphoma
excisional lymph node biopsy: lymphoma (gold std), ALL (rare)
skin biopsy: acute leukemia, lymphoma (cutaneous)

Tests conducted on BmBx, lymph node biopsy, peripheral blood
- cytochemical stains: leukemia, lymphoma
- flow cytometry: all malignancies
- cytogeneic/mutational analysis: all malignancies
- PCR: CML, AML, ALL

immunofixiation/serum/urine analysis (monoclonal protein): myeloma
scans: PET (lymphoma, potentially CLL); CT (lymphoma); bone survey (myeloma)
lumbar puncture (look for CNS disease): ALL, AML (if sx), lymphoma (if sx or after PET)

Staging systems

Acute Leukemias: none, can state level of proliferation; can state if CNS, skin, other organs
CML: phases (chronic, accelerated, blastic) based on s/s, blood counts, percent blasts
CLL: RAI stage 0-IV (based on lymphocytes, lymphadenopathy, sx, Hb, plts); Binet (based on lymphoid areas, Hb, plts)
Lymphoma: Ann Arbor (based on number and regions of lymph nodes involved, evaluate progression to bone marrow or CNS)
Myeloma: ISS, rervised-ISS incorporate cytogenetics; not widely used

Treatment options

no role for surgery, unless aids in palliation/pain
radiation: lymphoma, bone mets/palliation, pain
chemotherapy: mainstay, typically in combinations
immunotherapy: added to chemotherapy or monotherapy
  monoclonal antibodies: lymphoma, CLL, acute leukemias, myeloma
  PD-1 inhibitors: lymphoma
  angiogenesis inhibitors (lenalidomide): myeloma, FL, MDS
targeted therapies added to chemotherapy or monotherapy: mainstay in AML, CML, CLL

Response criteria

Acute Leukemias: morphological (peripheral blood/bone marrow blood counts and percent plasts); CR PR Cri PD; cytogenetic CR; molecular CR and MRD
CML: hematologic, cytogenetic, molecular (CR PR SD NR PD)
Lymphoma: CR PR PD SD based on sx, counts, bone marrow, CNS involvement
CLL: CR PR PD SD based on sx, counts, bone marrow involvement
Myeloma: stringent CR PR very good PR minimal response SD PD based on plasma cells percentage in bone marrow, M-protein serum/urine; MRD

Hematopoietic Stem-Cell Transplant (HSCT)

IV infusion of hematopoietic stem cells into a recipient after administration of high-dose chemotherapy
Goal of Transplant: re-establish marrow in the recipient capable of differentiating into blood cells of all lineages
Myelosuppression is the dose-limiting toxicity (DLT) for many chemotherapy agents

Indications for transplant

- malignant disease: rescue the marrow from toxic effects of chemotherapy
  - Auto or alloHSCT: Leukemia, Lymphoma, Multiple myeloma, Myelodysplastic syndrome (MDS)
- non-malignant disease: replace the non-functional marrow
  - AlloHSCT only, Hematologic, Immunodeficiency, Genetic Examples: Sickle cell anemia, Aplastic anemia, Autoimmune disorders

Types of HSCT

- autologous: high dose chemo, reinfuse their own cells; dose escalate CT to overcome resistance, rescue pt from myelosupp effects of HD CT; dose-lim organ tox
- allogenic: high dose chemo, infuse donor cells; replace missing/abnormal hematopoietic/lymphoid, rescue recipient from myeloablative therapy, GVT/GVL effect
  - related: mismatched related, matched related (MRD), syngeneic (identical twins, based on HLA: human leukocyte antigen)
  - unrelated: mismatched unrelated, matched unrelated (MUD)
  - haploidentical: half matched (more capability of donors)

	Autologous	Allogenic
Definition	high dose chemo, reinfuse their own cells; dose escalate CT to overcome resistance, rescue pt from myelosupp effects of HD CT; dose-lim organ tox (auto grafts faster)	high dose chemo, infuse donor cells; replace missing/abnormal hematopoietic/lymphoid, rescue recipient from myeloablative therapy, GVT/GVL effect
Advantage	no HLA matching no GVHD no immune suppression lower risk for transplant-related complications	GVT/GVL activity lower risk of relapse stem cells not exposed to chemotherapy stem cells free of tumor
Disadvantage	no GVT/GVL effect higher risk of relapse stem cells damaged from prior chemo possible contamination with tumor	donor availability GVHD (graft-versus-host-disease) requires immune suppression higher risk for transplant related complications

Human Leukocyte Antigen (HLA) matching

Major Histocompatibility Complex (MHC): HLA codes for cell surface proteins
class I antigens: HLA-A -B -C class II antigens: HLA-DR -DP -DQ -DP class I/II antigens function as major transplantation antigens (two alleles)
Donor: depends on HLA-A -B -C -DR -DP two phenotypes for each locus (one from each parent) ideal match = 10/10 now can do 12/12 (-DQ)
Cord HSCT less stringent match HLA-A -B -DR (6/6) Options: siblings 25% chance for identical match; unrelated 70% do not have MRD

HSCT Process

stem cell collect/mobilization (outp) → condition regimen (inpat), (Day -7 to -1) → stem cell transplant (Day 0) → post-transplant (Day +1 +2 etc) → recovery (outp)
- system of counting days of transplant enables the team to target risks, side effects, and complications based on where a person is along this timeline

pg 39-47

Conditioning regimens: combo chemo and/or total body irradiation (TBI): goal to treat residual disease and make room for new stem cells
- three types: myeloablative, reducing intensity conditioning (RIC), nonmyeloablative

Complications from HSCT

- conditioning regimen toxicities, infection, graft-versus-host-disease (GVHD), sinusoidal obstructive syndrome (SOS), graft failure

RF for poor outcomes: old age, decr performance, comorbid, advanced disease, unrelated donor, greater HLA mismatch, gender mismatch, CMV+ recipient

Conditioning Regimen dose-limiting toxicities (DLTS)

bisulfan (hepatotox, GI, pulm, neurotox) carboplatin (nephrotox, ototox, hepatotox) carmustine (pulm, hepatotox, neurotox) cyclophosphamide (cardiotox) TBI (pulm, GI, hepato) cytarabine (neurotox) fludarabine (neurotox) etoposide (mucositis, GI) ifosfamide (bladdertox, neurotox, nephrotox) melphalan (mucositis, GI) thiotepa (mucositis, neuroto)

Supportive Care

Mucositis: topical anesthetics (lidocaine, magic mouthwash), opioids, Caphasol (prevention), palifermin (prevention)
Diarrhea: loperamide, diphenoxylate/atropine (Lomotil), octreotide, opium tincture
NV: aprepitant (prevention only), 5-HT3 antagonists (ondansetron), prochloperazine, metoclopramide, haloperidol, olanzapine, lorazepam, corticosteroids
Gastritis: PPI (esomeprazole), H2RA (famotidine) Pain: opioids Menorrhagia: leuprolide, oral contraceptives, progestins

Infection Prophylaxis

Bacterial (gm+ gm-): no prophylaxis
Fungal candida: fluconazole (alt echinocandins); duration: engraftment or off immunosupp therapy
Fungal aspergillus: posaconazole (alt vori, isa, echninochandins); duration: engraftment or off immunosupp therapy
Viral (herpes, varicella, CMV): acyclovir (alt valacyc, letermovir); duration: HSV engraftment; VZV day +180 or off immunosupp therapy
Opportunistic (pneumocytis jiroveci): Bactrim (alt dapson, atovaquone, pentamidine); duration: day +180 or off immunosupp therapy

GVHD background

frequent and serious complication following alloHSCT; donor T-cells attack tissues of immunocomp foreign/host/recipient
acute GVHD: 10-80% (unrelated>related), occurs before day +100; targets skin, liver, GI tract
chronic GVHD: 15-65%, occurs after day +100; multiorgan involvement (mouth, eyes, lungs)
long-term complications: secondary malignancy, late infections, organ dysf, changes infertility/sexually, QoL

Summary

Each malignancy is derived from a specific type of cell with a distinct pathogenesis pathway and therefore staged based on its progression
Staging assists with determining treatment options and prognosis
HSCT is an option for treatment and cure for many types of cancer; the two types of HSCT are autologous and allogenic
There are many complications with HSCT and GVHD remains a major cause of morbidity and mortality after transplant
HSCT pharmacists can greatly assist with immunosuppression, infection, and supportive care management!

Chronic Myeloid Leukemia (CML)

Provide an overview of chronic myeloid leukemia (CML) and multiple myeloma (MM) including definition, incidence and prognosis, epidemiology, and risk factors
Understand the pathogenesis, presentation, and signs/symptoms of CML and MM
Describe the staging process for CML and MM
Provide appropriate treatment options for CML and MM
Discuss appropriate use, MOAs and adverse effects of chemotherapy and targeted drugs

Chronic leukemia: malignant clonal expansion of hematopoietic progenitor cells; may affect myeloid, erythroid, megakaryocytic, B-cell and T-cell lymphoid lineages
- types: chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), prolymphocytic leukemia, hairy cell leukemia (HCL)

CML Epidemiology: 15-20% of all leukemias, median age dx 67yo, M (ratio of cases:deaths declining); almost 100% survival (like DM/HTN)
Patho: myeloproliferative disease; clonal expansion of hematopoietic progenitor cells—pluripotent stem cells focal point (myeloid, erythroid, magakar, lymphoid)
- presence of Philadelphia chromosome (Ph) in 95% of patients: t(9;22) translocation shortened chromosome 22 (BCR-ABL fusion gene), elongated chrom9
- ABL gene normally encodes tyrosine kinase, which is highly regulated
- BCR-ABL fusion gene (active tyrosine kinase) removes control of cell division, leads to uncontrolled proliferation, lacks differentiation and mutation

Dx: physical, CBC w diff, chem with LDL, peripheral blood smear FISH PCR, bone marrow biopsy (flow cytometry, cytogenetics, cytochem, FISH/PCR)
Sx: fatigue/pallor, wt loss/anorexia, fever, sternal tender, abd pain, decr exercise, splenomeg, hepatomeg, early satiety, night sweats, heat intol, bone pain, priapism, tinnitus, LUQ
Signs: hallmark sign leukocytosis (usually >25,000, upwards 300k); thrombocytopenia/cytosis, megakaryocytosis, baso/eosinophilia, hyperkal, hyperuriciema, ↑LDL aPTT serB12

<u>Staging</u>
chronic phase: ↑WBC, maybe increased plt, blasts <10%; splenomegaly, 50% asymptomatic, median survival 3-5yr
acclerated phase: recurrence of sx, 10-19% blasts in blood/marrow; thrombocytopenia/cytosis (<100k), increased WBC and spleen size; surv 6-9mo
blastic phase: transformation to acute leukemia, >20% blasts in blood/marrow; extramedullary disease; survival 3mo

Sokal risk stratification (low, int, high): based on age, spleen size, platelet count, percentage of blasts in peripheral blood; used in CTs

<u>Response</u>
hematologic: complete: WBC <10 $x10^9$/L, platelets <450k, no immature cells, normal spleen size
cytogenetic: complete 0 Ph+ cells, partial 1-35% Ph+ cells, major CR+PR (for CTs), minor 35-90% Ph+ cells
molecular: complete: negativity by RT-PCR assay sens; early molecular response: BCR-ABL (IS) ≤10% at 3 and 6mo; major: BCR-ABL <0.1% or >3log reduction base

Allogeneic hematopoietic stem cell transplant (HSCT) is the only known curative treatment option for CML and is reserved for patients with a suitable donor and progression after treatment with tyrosine kinase-based therapy.

Treatment

Treatment Overview

hydroxyurea, busulfan, interferon alfa (hx); TKIs: initial (imatinib, dasatinib, nilotinib); others (bosutinib, ponatinib); omacetaxine, induction chemo, alloHSCT, CTs

Chronic Phase

First Line Therapy

hydroxurea and busulfan: palliation (decreases WBC), hematologic remission 70-80% (decr blood clot), no effect on cytogenetic response or disease progression
interferon alfa (historical use): single agent or in combo with cytarabine (more cytogenetic response)

imatinib mesylate (Gleevec): TKI for Ph+ CML (all phases); IRIS trial huge results; 7yr f/u: major molecular response (MMR) 86%, no new safety issues
- inhibits BCR-ABL TK created by Ph+ abnormality, competes with ATP, inhibits prolif induces apoptosis; $66.5k/yr
dosing: chronic: 400mg qday, may increase 600mg qday accelerated/blastic: 600mg qday, may increase to 400mg bid

dasatinib (Sprycel): second-gen TKI, initially approved for Ph+ CML refractory or intolerant to imatinib (all phases), now first-line CML chronic
- dual BCR-ABL and SRC inhibitor, 2log potency to imat, activity against imatinib-resistant BCR-ABL mutants; no activity T315I mutant; $102k/yr
dosing: chronic/accelerated: 100mg qday blastic: 100-140mg qday if no response: may increase chronic 90mg bid, accel/blastic to 100mg bid or 140mg qday

nilotinib (Tasigna): second-gen TKI initially approved for Ph+ CML refractory or intolerant to imatinib (chronic/accel pahses), now first-line CML chronic
- inhibits BCR-ABL, binds more tightly than imatinib, better topological, 20x potent, activity against overexpressed/resistant, not T315I mutants; $118k/yr
dosing: chronic: 300mg bid, may increase to 400mg bid accelerated: 400mg bid

Choosing?
imatinib: long track record safety/durability, high effective salvage therapy, no evidence of improved survival with MMR or CMR, lower cost
2nd-gen TKI: no clear superior agent, lower risk of suboptimal response/progression; improved intolerance (GI effects)
  - faster rate to CCR/MMR 12mo; if "quicker" MMR translates to more frequent durable CMR in future, greater potential for discontinuation of therapy

imatinib resistance:
  - overexpression of BCR-ABL tyrosine kinase: dose esc 800mg, nilotinib, bosutinib, alloHSCT (unlikely)
  - mutations of ATP-binding site: dose esc 800mg; dasatinib, bosutinib, ponatinib (T315I mutation)

bosutinib: TKI approved for Ph+ chronic, accelerated, or blastic phase resistant or intolerant to prior TKI
  - inhibits BCR-ABL and SCR (inhbits imat, dasat, nilot resistant mutations); 3A4 substrate
dosing: 500mg qday, may increase to 600mg if response not achieved by week 8; may reduce for ADEs

ponatinib: TKI approved for Ph+ chronic, accelerated, or blastic phase resistant or intolerant to prior TKI
  - inhibits BCR-ABL and SCR (inhbits imat, dasat, nilot resistant mutations); **inhibits T315I mutation; also VEGFR, PDGFR, SRC, KIT, FLT3; 3A4 substrate
dosing: 45mg qday, but due to ADEs/DDIs usually 30mg qday

progression on imatinib: probably not escalating dose, pick a different TKI
progression on TKIs: omacetaxine, alloHSCT, CTs

omacetaxine: approved for Ph+ chronic and accelerated phase resistant or intolerant to 2 TKIs
  - protein synthesis inhibitor, reduced levelsof BCR-ABL and MCL-1; **inhibits T315I
dosing: induction 1.25mg/m2 SC bid x14 days q28 days until hematologic response; maintenance 1.25mg/m2 SC qday

CML: First-Line Therapies	^off-label	
Chronic Phase	**Accelerated Phase**	**Blastic Phase**
imatinib 400mg	imatinib 600mg	imatinib 600mg
dasatinib 100mg	dasatinib 100mg^	dasatinib 140mg^
nilotinib 300mg bid	nilotinib 300mg bid^	nilotinib 300mg bid^
		induction chemotherapy
	allogenic transplant	allogenic transplant
clinical trial	clinical trial	clinical trial
CML: 2nd, 3rd, 4th -Line Therapies	*T135I coverage	†must fail 2 TKIs
dasatinib 100mg	dasatinib 100mg	dasatinib 140mg
nilotinib 300mg bid	nilotinib 400mg bid	
bosutinib		bosutinib
ponatinib*	ponatinib*	ponatinib*
omacetaxine*† (3rd)	omacetaxine*† (3rd)	omacetaxine*† (3rd)
		induction chemo
allogenic transplant (3rd/4th)	allogenic transplant (3rd/4th)	allogenic transplant
clinical trial	clinical trial	clinical trial

TKIs SE: myleosuppression, rash, edema, fatigue, NV, diarrhea/constipation, muscle cramps, bleeding/bruising, increase in LFTs
- imatinib: higher incidence of GI
- dasatinb: pleural effusions, QT prolongation
- nilotinib: QT prolongation
- bosutinib: higher incidence of GI
- ponatinib: arterial thrombosis, hepatotoxicity, pancreatitis (dirty drug)

dasatinib: ↑[dasatinib] by 3A4 inhibitors; ↓[dasatinib] by 3A4 inducers, antacids (give 2hr prior/after), H2RAs/PPIs
- dasatinib alters others drugs of 3A4 substrates (narrow therapeutic index: cyclosporine, fentanyl, quinidine, sirolimus, tacrolimus)

ADEs: myelosupp (thrombocytopenia, neutropenia, anemia, leukopenia); GI, dyspnea, pleural effusions, cardio (dysrhyth, edema); rash/pruritus; athralgia/myalgia, musculoskel pain; dizziness HA, neuropathy; fatigue, fever, shivering

nilotinib: ↑[nilotinib] by 3A4 inhibitors; ↓[nilotinib] by 3A4 inducers
- nilotinib alters other drugs of 3A4 substrates (narrow therapeutic index)

ADEs: rash/pruritis, GI, HA, fever, fatigue, myelosupp (thrombocytopenia, neutropenia, leukopenia); electrolyte abnormalities, hepatotox, intracranial hemorrhage,
BBW: QTc prolongation and sudden deaths

omacetaxine SE: myelosupp, thrombocytopenia, anemia, neutropenia, lymphopenia; GI (diarrhea, N); fatigue, injection site rxn, pyrexia

Summary
CML is one of the most common types of chronic leukemias
First/second gen TKIs are first-line therapy for chronic and accelerated phases; evaluate patient and clinical situation to determine which agent should be chosen
Bosutinib and ponatinib (T315I) used as second/third-line therapies
Omacetaxine may be used after failure of 2 TKIs; covers T315I
Blastic phase should be treated as acute leukemia (ALL dasatinib crosses BBB for CNS; AML dasatinib has data)

CAR-T Therapy and Toxcities

Understand the mechanism of action and indications for Chimeric Antigen Receptor T-cells (CAR-T) Therapy
Identify signs and symptoms of cytokine release syndrome (CRS) and neurotoxicity following CAR-T therapy
Review appropriate management of CRS and neurotoxicity associated with CAR-T therapy
Briefly discuss other CAR-T toxicities
Understand the pharmacy role in management of CAR-T toxicities

axicabtagene ciloleucel (Yescarta): relapsed/refractory DLBCL
ZUMA-1: treated patients with refractory disease had high levels of durable response, with a safety profile that included myelosuppression, CRS, and neurologic events
tisagenlecleucel (Kymriah): relapsed/refractory ALL; relapsed/refractory DLBCL
JULIET: CTL019 produced high response rates with durable response (heavily pretreated population); high rates of serious, but manageable adverse events
brexucabtagene autoleucel (Tecartus); relapsed/refractory mantel cell lymphoma
ZUMA-2: CTL019 induced durable remissions in a majority of pts with relapsed or refractory (MCL); high rates of serious, but manageable ADEs; consistent with prev CAR results

Production: remove blood from patient to get T cells → make CAR-T cells in lab → grow cells → lymphodepleting chemo (fludarabine+cyclophos Days -5 -4 -3) → → infuse CAR-T cells into patient on Day 0 → CAR-T cells bind to cancer cells and kill them
MoA: chimeric antigen receptors allow T-cell to attack malignant cells CD19; receptor binding promotes T-cell expansion+activation, target cell death; unique tox target binding domain recognizes CD19 antigen on B-cells → hinge/transmembrane domain → co-stimulatory CD28 or 4-1BB domain enhances cytolytic function of T-cells (difference between products) → CD3 zeta signaling domain induces T-cell activation

CAR-T toxicity timeline
Day -5: lymphodeplet chemo NV Day 0: CAR-T cell infusion, NV Day 2-14: CRS, neurotoxicity, NV Day 21-28: delayed onset neurotox Day >30: infection, cytopenias, B cell aplasia

<u>Cytokine Release Syndrome (CRS)</u>
axicabtagene: 93% pts (13% ≥grade 3), onset 2d (1-12), resolution 8d (2-58); tisagenlecleucel: 58% pts (23% ≥grade 3), onset 3d (1-51), resolution 8d (1-36)
Pathophys: expansion of T-cells, characterized by immune activation and release of inflammatory cytokines; sx may occur hours to 2 weeks post-infusion
- result of high-level immune activation with T-cell infusion; increase in serum cytokines including IL-6, INF-γ and TNF-α
ADEs: constitutional (fever, rigor, malaise, fatigue, anorexia, arthralgias); cardio (tachy, hypo, arrhythm, ↓LVEF, troponinemia, QTc); pulm (tachypnea, hypoxia) organ: liver (hepatic dysf ↑AST ALT hyperbili), renal insuff, resp failure/edema, cardiac insuff/arrhythm; cytopenias >28d (avoid myeloid growth factor GM-CSF)

High-dose vasopressors for hypotension: norepinephrine mono or phenylephrine mono; alt epi mono, vaso+norepi, dopa mono
Grades for CRS and associated with immune effector cells (IEC): fever with either hypotension and/or hypoxia

tocilizumab reversal of CRS symptoms (give with dex); recomb humanized mAb against IL-6; blocks IL-6 from binding without inhibiting CAR-T cells
dosing 8mg/kg IV q8h (max 800mg, max 2doses/24h), 45% received after Yescarta
- reversal of HR RR C-reactive protein (inflam); CRS markers (IL-6, IFN-γ, CRP); if no response 24-48h, consider second dose or steroid initation

siltuximab for refractory CRS; chimeric anti-IL-6 mAb; binds IL-6 with higher affinity, less likely to compete bc tocil binds IL-6R; might be more effective CRS
dosing 11mg/kg IV, can be repeated in 10 days

<u>CAR-T related encephalopathy syndrome (CRES)</u>: referred to as neurotoxicity; s/s HA sed, confusion, delirium; severe: inability to write/communicate, seizures
Onset: biphasic, acute (<5d), late (begins after CRS sx resolved); delayed (3-4wks post); pathophys: not well understood; similar incidence between products
Risk factors: disease burden, cell dose, rapid CART cell expansion, Cy/Flu lymphodepl (IL-15 elev cerebral edema); early sys inflam, early CNS, MFR CD4:CD8 ratio
Sx/Grading: CARTOX10 (year, season, day, month, president) 10=normal; CTCAE neurological toxicity grading; ASTCT grading

Corticosteroids and CAR-T cells: previously avoid admin unless necessary; now degree of interfering with effectiveness less; still be aware of use/limit
ICANS consensus: Disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.

IEC-associated Encephalopathy (ICE) Score (no president): score 10 normal, score 7-9 G1, score 3-6 G2, score 0-2 G3 *combine with other ICANS assessments for final
- grade 3 get the seizures coming in, focal/generalized; grade 4 unarousable/coma

Neurotoxicity management
grade 1: levetiracetam prophylaxis, consider neuro consult
grade 2: leve prophylaxis; imaging; consult; steroid therapy*: dex x1 dose, if persists then q6h and taper
grade 3: leve prophylaxis; imaging, consult; lumbar puncture, steroid therapy*: dex 10mg q6h then taper
grade 4: leve prophylaxis; imaging, consult, lumbar, MICU, steroid: methylprednisolone 1g IV qday x3 days at least* until G1, then taper
- if >72h, IT triple therapy (MTX+cytarabine+hydrocort), siltuximab, anakinra, ATG

Steroids for neurotox: continue until ≤grade 1; taper by 25% to q8h x1-3d, q12h x1-3d, q24 x1-3d; if toxicity worsens, return to prev dose and taper slower

<u>Neurotoxicity: Summary of Management</u>
Grade 1: levetiracetam prophylaxis
Grade 2: dexamethasone + levetiracetam: work up other causes and consider neuro consult
Grade 3: dexamethasone + levetiracetam: neuro consult, consider ICU if patient worsens; for non-responders, may to treat according to grade 4
Grade 4: methylprednisolone + levetiracetam; ICU, may need respiratory and hemodynamic support; may need to consider refractory management

Additional toxicities associated with CAR-T
B-cell aplasia and hypogammaglobulinemia (on target, off tumor); infections (opport), prolonged cytopenias, tumor lysis syndrome TLS, infusion-related
- prolonged cytopenias: myeloid growth factors (GM-CSF) not rec'd for first 3 weeks following tisagenlecleucel

Premed and Prophylaxis
cell-infusion premed: APAP + DPH (no steroids); no steroids from start of lymphodepleting chemotherapy
infection prophylaxis: antivral, antifungal+FQ during neutropenia period, PJP prophyalxis
seizure prophylaxis: levetiracetam starting day -1 or 0 to day 30

REMS considerations: cert site; on-site access to tocilizumab ensuring 2 doses for each patient*; multidisciplinary approach
RPh role: REMS training, tocilizumab, corticosteroids (review prog notes, dose titration up/down); appropriate antimicrobial prophylaxis and use of IVIG labels

Summary
CAR-T: engineered T-lymphocytes programmed to attack malignant cells; high rates of response and survival in heavily pretreated patients
CRS: common AE in majority of patients receiving CAR-T products; typically occurs within 2-3 days and resolves within 1 week
Neurotoxicity: can occur within days to weeks following CAR-T infusion; prompt recognition and management is essential

Adult Lymphomas

Provide an overview of the pathogenesis, diagnosis, and prognosis of common lymphomas (pre-class reading)
Discuss treatment goals and preferred chemotherapy regimens for selected lymphomas
Describe side effects associated with chemotherapy and targeted agents used to treat lymphomas

Follicular Lymphoma (FL)

indolent, can transform to aggressive
initial stage may not have any symptoms at all

Advanced Stage Treatment

- **treatment not required until symptomatic**: nodal disease, compromised organ function, B symptoms, cytopenias, steady progression, clinical trial

Preferred:
- rituximab or obinutuzumab + bendamustine or CHOP or CVP
- rituximab + lenalidomide

Other:
- obinutuzumab + lenalidomide
- rituximab weekly x4 doses (low tumor burden)

For elderly/infirm:
- rituximab weekly x4 doses
- single agent alkylators (chlorambucil, cyclophosphamide) +/- rituximab
- radioimmunotherapy

R/O-CHOP = rituximab/obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Maintenance/Consolidation Therapy
- rituximab 375mg/m2 day 1 every 2 months x 2yr
- obinutuzumab 1000mg day 1 every 2 months x 2yr

Relapsed/Refractory Treatment

- most patients will relapse, treat when indicated as with initial therapy; first-line agents preferred depending on what was given prior and time to relapse

Preferred:
- rituximab or obinutuzumab + bendamustine or CHOP or CVP
- rituximab + lenalidomide
- lenalidomide +/- obinutuzumab
- rituximab or obinutuzumab monotherapy

Relapsed/Refractory to 2+ prior therapies:
- idelalisib
- copanlisib
- duvelisib
- tazemetostat (oral EZH2 inhibitor)

For elderly/infirm:
- rituximab weekly x4 doses
- single agent alkylators (chlorambucil, cyclophosphamide) +/- rituximab
- radioimmunotherapy

For elderly/infirm 2nd-line maintenance/consolidation:
- rituximab 375mg/m2 day 1 every 2 months x 2yr
- obinutuzumab 1000mg day 1 every 2 months x 2yr
- high dose therapy with autologous stem cell rescue
- allogenic cell transplant for highly selected patients

Diffuse Large B Cell Lymphoma (DLBCL)

more aggressive than FL
most common lymphoid malignancy (37% NHL)
etiology: pesticides/fertilizers, alkylating agents, immune def, viruses
path: malignant germinal center or activated B cells;
sx: rapidly enlarging masses, B symptoms (fever, weight loss, sweats)
prognosis: IPI index; 1 pt for each age >60yo, serum LDL>ULN, performance 2-4, stage III-IV, extranodal >1 site; more factors worse 4yr PFS/OS

Initial Treatment

Stage I/II
- nonbulky (<7.5cm): RCHOP x 3 + radiation or RCHOP x6 +/- radiation
- bulky (LN≥7.5cm): RCHOP x6 +/- radiation

Stage III/IV:
- RCHOP x6
- restaging scans after 2-4 cycles (responding disease complete 6 cycles, no response/progressive choose alternative therapy)

supportive RCHOP: antiemetics, +/- viral proph, laxatives, infusion reaction meds, +/- growth factor

CNS prophylaxis: high risk score 4-6 (>60yo, LDL>, performance >1, SIII-IV, nodal sites)
- IT chemo x4 doses (1 per cycle)
- HD-methotrexate x3 doses (1 per cycle)

Relapsed/Refractory Treatment

goal of therapy is still cure for most patients
Transplant eligible:
- salvage chemo RDHAP, RGDP, RICE, etc.; after ≥2 therapies: bendamustine + rituximab + polatuzumab (CD79b)
  - complete response: autologous stem cell transplant
  - partial response: CAR-T therapy (axicabtagene/tisagenlecleucel)
  - no response: alternate regimen/hospice

Transplant ineligible: palliative chemo RGemOX, RGDP, lenalidomide + rituximab/tafasitamab (CD19), bendamustine + rituximab, etc.

RDHAP = rituximab, dexamethasone, cytarabine, cisplatin
RGDP = rituximab, gemcitabine, dexamethasone, cisplatin
RICE = rituximab, ifosfamide, carboplatin, etoposide
RGemOx = rituximab, gemcitabine, oxaliplatin

Hodgkin Lymphoma (HL)

Curable in 80% patients
Risk factors: serum albumin <4, Hb <10.5, M, stage IV, age ≥45yo, WBC ≥15k, lymphocytopenia <600 or <8%WBC - more factors, less 5yr PFS/OS

ABVD given 28 days x2-6 cycles; supportive: antiemetics, laxatives, growth factor NOT rec'd
brentuximab+AVD 28d x6 cycles; supportive: antiemetics, laxatives, growth factor required

HL—initial

Stage I/II fav
- ABVD x2-4 cycles +/- radiation
  doxorubicin, bleomycin, vinblastine, dacarbazine

Stage I/II unfav (B sx, ESR≥50, >3 sites of disease)
- ABVD x4-6 cycles +/- radiation

BEACOPP considered if bad response on PET after 2 cycles
bleomyc, etoposide, doxorubicin, cyclophos, vincristine, procarbazine, prednisone

Stage II/IV
- ABVD x 2 cycles → PET
  CR: remove bleomycin, complete 6 cycles
  PR: change to escalated BEACOPP x 3 cycles, repeat PET
    CR: continue BEACOPP, complete 6 cycles
    PR: refractory disease, 2nd-line therapy
- brentuximab + AVD x6 cycles (for pt w/ no neuropathy, IPS≥4, or bleo CI'd)
- escalated BEACOPP x4-6 cycles (for pt IPS≥4, <60yo)

HL—R/R

Transplant eligible:
- salvage chemo

GVD, ICE, DHAP, gemcit+bend+vinorelb+bretunx
  CR/PR: auto stem cell → brentuximab maintenance (high risk)
  NR: alternate regimen/hospice

consider pembrolizumab or nivolumab in progress post-transplant

Transplant ineligible:
- palliative chemo

consider pembrolizumab or nivolumab

Other Lymphomas

mantle cell lymphoma: acalabrutinib, zanubrutinib
cutaneous T-cell lymphomas: belinostat, bexarotene, mogamulizumab, romidepsin, vorinostat
T-cell lymphomas: pralatrexate, romidepsin
Burkitt's lymphoma: treated similar to ALL
Castleman's disease: siltuximab

Chronic Lymphocytic Leukemia (CLL)

Review pathogenesis, diagnosis, and staging of chronic lymphocytic leukemia (pre-class reading)
Describe appropriate treatment options for CLL based on indications to treat, cytogenetics, and patient fitness
Discuss side effects associated with CLL treatments

Prognostic factors

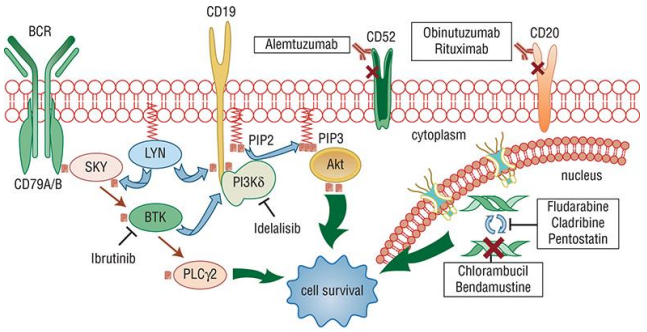
Rai staging for CLL		
Risk	**Stage**	**Description**
Low	0	Lymphocytosis only
Intermediate	I	Lymphadenopathy
	II	Hepato- or splenomegaly ± lymphadenopathy
High	III	Hemoglobin (Hg) <11g/dL
	IV	Plts <100,000/mm^3

Binet staging for CLL	
Stage	**Description** *Five lymphoid bearing areas are possible: cervical, axillary, inguino-femoral, spleen, and liver.
A	Two or less lymphoid bearing areas enlarged*
B	Three or more lymphoid bearing areas enlarged*
C	Presence of anemia (hemoglobin <10 g/dL) or thrombocytopenia (Plts <100,000/microL)

Indications for treatment

Initial Treatment

ibrutinib
acalabrutinib +/- obinutuzumab
venetoclax + obinutuzumab



CD20 mAbs

obinutuzumab, rituximab, ofatumumab
ADEs: infusion reactions (cytokine release vs. hypersensitivity): obin > ofat > ritu onset delayed >1hr into infusion; typically with first inf, likelihood with subseq
- arthralgia/myalgia, bronchospasm, cough, dizziness, fever, dyspnea, fatigue, headache, hypo/hypertension, nausea, vomiting, pruritus, rash, rigors, sweating, tachycardia, pain

Supportive: premed APAP, AH, dexa (obin ofat only); rescue AH, steroid, epi

Grade 1: Mild, infusion interruption not indicated
Grade 2: Infusion interruption, responds promptly to treatment
Grade 3: Prolonged, not rapidly responsive to interruption or treatment, recurrence of symptoms after initial resolution
Grade 4: Life threatening, pressor or ventilator support indicated
Grade 5: Death

Infusion Rxn treatment
slow rate/hold, administer H1/H2 antag (DPH+famot), CS (hydrocort or methylpred)
restart infusion at 50% rate and titrate to tolerance; rechallenge discouraged with recurrent G3-G4
--rigors (meperidine, hydromorph), fevers (apap, CS), bronchospasm (albuterol, montelukast)

BCR inhibitor

ibrutinib, acalabrutinib
MoA: irreversible inhibitor of Bruton's tyrosine kinase (BTK), an integral component of the B-cell receptor (BCR) and cytokine receptor pathways. Constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells; BTK inhibition results in decreased malignant B-cell proliferation and survival.

ibrutinib

ADE: **bleeding, Afib, HTN**, diarrhea, rash, GI, infection, fatigue; serious: cardiac arrythmias, invasive infections
3A4 ddi, **antiplatelets, anticoagulants** (warfarin is contraindicated); bleeding hold 3 days before after minor surgery, 7 days major
420mg qday, wowfood; caps/tabs

acalabrutinib

ADE: **HA** (resolves 1-2mo), myelosupp, infection, diarrhea, ms pain; serious: afib, bleeding
3A4, anttiplatelets, anticoagulants, **gastric acid-reducing agents**
100mg bid wowfood; caps

BCL-2 inhibitor

venetoclax
MoA: cytotoxic activity in tumor cells which overexpress BCL-2. Venetoclax selectively inhibits the anti-apoptotic protein BCL-2, which is overexpressed in chronic lymphocytic leukemia (CLL) cells and acute myeloid leukemia (AML) cells. BCL-2 mediates tumor cell survival and has been associated with chemotherapy resistance. Venetoclax binds directly to the BCL-2 protein, displacing pro-apoptotic proteins and restoring the apoptotic process.
ADEs: **myelosuppression** (WBC/neutrophil), diarrhea, N, infection, cough, ms pain, fatigue, edema; serious: **tumor lysis syndrome (TLS)**, febrile neutronpenia
3A4, oral chemo compliance; titrations 20, 50, 100, 200, 400 over 5 weeks
titrate 400mg qday **with food**

Relapsed/Refractory Treatment

acalabrutinib
ibrutinib
venetoclax +/- rituximab
duvelisib
idelalisib + rituximab

PI3K inhibitor

idelalisib

MoA: Idelalisib is a potent small molecule inhibitor of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ), which is highly expressed in malignant lymphoid B-cells. PI3Kδ inhibition results in apoptosis of malignant tumor cells. In addition, idelalisib inhibits several signaling pathways, including B-cell receptor, CXCR4 and CXCR5 signaling which may play important roles in CLL pathophysiology (Furman 2014). In lymphoma cells, idelalisib treatment inhibited chemotaxis and adhesion, and reduced cell viability.

ADE: **diarrhea**, cytopenias, rash, fatigue; BBW: **colitis**, **pneumonitis**, infections, intestinal perforation, fatal/serious hepatotox; warnings: myelosupp, skin tox
3A4; supportive: viral prophylaxis, PJP prophylaxis, monitor CMV
idelalisib 150mg bid wowfood + rituximab 375mg/m2 IV day 1,15; q28d

duvelisib

MoA: Duvelisib is an oral PI3K inhibitor with dual inhibitory activity primarily against PI3K-δ and PI3K-γ which are expressed in hematologic malignancies. Inhibition of PI3K-δ reduced tumor cell proliferation while allowing survival of normal cells. Inhibition of PI3K-γ reduces differentiation and migration of tumor microenvironment support cells (Flinn 2018). Duvelisib resulted in reduced viability of cell lines derived from malignant B-cells and CLL cells. Additionally, duvelisib inhibits B-cell receptor signaling pathways and CXCR12-mediated chemotaxis of malignant B-cells as well as CXCL12-induced T cell migration and M-CSF and IL-4 driven M2 macrophage polarization.

ADE: **diarrhea**, neutropenia, rash, fatigue, pyrexia, cough, N, resp inf, myalgia, anemia; BBW: **diarrhea/colitis, pneumonitis**, cutan rxns; Warn: hepatox, fetaltox
3A4 (substrate, moderate inhibitor); supportive: viral prophylaxis, PJP prophylaxis, monitor CMV
duvelisib 25mg bid wowfood

Acute Lymphoblastic Leukemia (ALL)

Briefly review the epidemiology, etiology, & pathology of acute lymphomblastic leukemia (ALL)
Describe the clinical presentation of ALL
Understand the prognostic factors & disease classifications for ALL
Review the current treatment strategies, including monitoring of common drug adverse event

Epidemiology: "pediatric dx"; most common <20yo (55%, median 15yo); accounts of 75% childhood leukemias (6.1k new cases, 0.3% cancers)
Mortality: 5yOS 69%, <1yo 56%, children 86%; adults-older 17-24%
Pathophysiology: blood stem cell → lymphoid stem cell → lymphoblast → early B-cell 80%, T-cell 10-15%, mature B-cell <5%
- see ↑lymphoblast ↑B/T lymphocytes; but ↓RBC, platelets, neutrophils/granulocytes - malignant transformation of progeniator cells
Cytogenetics: Philadelphia chromosome, Hyperdiploidy
Risk factors: few known for pediatric ALL (down syndrome); older age >70yo; exposure to chemo/radiation
S/sx: weakness/fatigue, fever/nightsweats, bruise/bleed, SOB, wt loss, bone/joint pain, swollen lymph nodes (neck, armpit, groin), swelling abd, freq inf
Workup: CBC w diff, Chem panel, Fibrogen/coags (PT PTT INR etc), evaluate inf/tumor lysis, bone marrow biopsy and aspirate, lumbar puncture with IT CT, CNS
Dx: bone marrow biopsy (morphology/immunopheno, cell surface markers differentiate CDs)
- acute lymphoblastic leukemia: bone marrow >20% lymphoblasts
- acute lymphoblastic lymphoma: bone marrow <20% lymphoblasts (and maybe extramedullary involvement)
Prognostic factors
- response to induction: goal is to eliminate disease at end of induction
- CNS disease
- cytogenetics: poor Ph+, t(4;11), low hypodiploidy better: delp, hyperdiploidy
- WBC count: T worse than B; B cell >30k is poor T cell >100k is poor
- age >35yo poor (1-10yo have best response)
Risk stratification
pediatric
- standard risk: age 1-9yo, WBC <50k
- high risk: age <1 or >10yo, WBC >50k, any T-cell ALL
- very high risk: age <1yo, BCR-ABL or Ph-like, hypodiploidy, failure to achieve remission with induction therapy
adult
- standard risk: no high risk features
- high risk: age >35yo AND elevated WBC, PH+, minimal residual disease at end of induction, poor risk cytogenetics
Response
- complete response: no circ blasts, bone marrow <5% blasts, ANC >1000 and platelets >100, no recurrence for >4wk
- complete response with incomplete count recovery: same ANC<1000 or platelets <100
- progressive disease: increase in circ blasts, increase in bone marrow by >25%, develop extramedullary disease
- refractory disease: failure to achieve CR at end of induction
- relapse: reaches CR but reappearance of blasts in blood or bone >5%, any extramedullary site after achievement of CR
Treatment: cure

Treatment

CNS prophylaxis: goal to prevent CNS disease or relapse; occurs in 50% w/o prophylaxis; continues throughout the therapy
Induction: goal to eradicate of majority of blasts; 1-2mo
Intensification/Consolidation: goal to eliminate any leukemic cells potentially remaining after induction; may be 6-12mo
Maintenance: goal to prevent relapse; continues 2-3years

Drugs: vincristine, steroids, asparaginase, anthracyclines, cyclophosphamide, mercaptopurine, methotrexate, cytarabine, IT chemo, thioguanine, TKIs (Ph+), mabs
- newer: inotuzumab, blinatumomab, nelarabine, tisagenlecleucel

vincristine
- treatment and maintenance
ADEs:
Safety: fatal if given intrathecally

steroids
- treatment, usually in bursts
dexamethasone: better CNS penetration, decreased risk of CNS relapse, improved event free survival; increased rate of myopathy, osteonecr, neuropsych SE
prednisone: no difference in overall survival/relapse; few side effects
SE: hyperglycemia, hypertension, psychosis, osteoporosis, osteonecrosis, infection risk

asparaginase
MoA: hydrolyzes and depletes asparagine (normal cells synth asp, leukemia cells require exogenous asparagine); inhibits PS leading to apoptosis
- admin IV/IM; given tiw (pegasparagase lasts 2 weeks); delayed hypersensitivity rxn possible, no cross-reactivity
ADEs: worse in adults than children: thrombosis (clotting), pancreatitis, elevated liver enzymes and hyperbili hypofibrino
- thrombosis: hold until s/s resolve and anticoag stable, dc for CNS thrombosis unless fully resolved, monitor antithrombin levels as secondary prophylaxis
- pancreatitis: perm dc for symptomatic pancreatits

TKIs
imatinib, dasatinib, nilotinib, bosutinib, ponatinib
- treatment for Philadelphia chromosome positive ALL
- in combo with multiagents, alone or combo with steroids for older/intolerable; dasatinib preferred (only TKI with CNS pen); resistance possible, maint transplant?

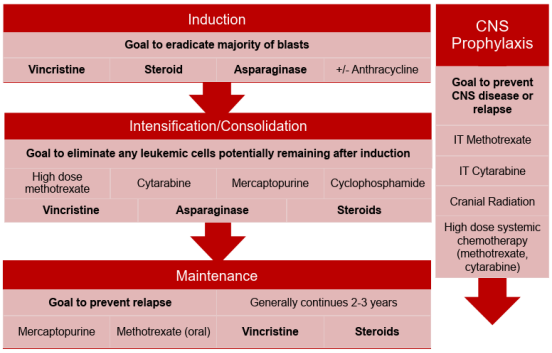
purine antagonists
mercaptopurine, thioguanine
- dosing is very complicated; take on empty stomach (space 2hrs milk/citrus)

<u>First Line Regimens</u>
HyperCVAD (adult)

Part A
- hyperfractionated cyclophosphamide bid days 1-3
- vincristine days 1+7
- adriamycin (doxorubicin) day 4
- dexamethasone days 1-4 and 11-14
- IT chemo days 1+8

Part B
- HD methotrexate
- HD cytarabine
- IT chemo

Add TKI on days 1-14 if Ph+
Alternate 28 day cycles x8 cycles Part A (induction) Part B (consolidation)



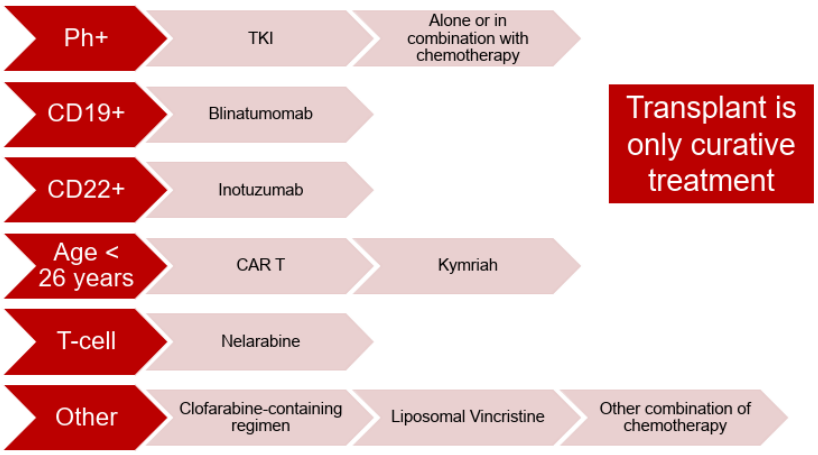
Infusion Visit, RPh responsibilities

Relapsed/Refractory (R/R) Treatment

blinatumomab
- R/R ALL (Ph+ or Ph-); ALL with minimal residual disease (MRD) after induction
MoA: BiTE therapy: Bispecific T-cell Engager, targets CD19
- 24hr CI x28d; 9mcg/day x7d then to 28mcg/d (hospital admit to ramp up)
SE: Cytokine Release Syndrome (CRS)* fever, hypotension, tachy
  - neurotoxicity*, LFT elevations, B cell depletion

inotuzumab
- R/R ALL, CD22+
MoA: antibody drug conjugate, targets CD22, calicheamicin released intracell
SE: fatigue, hepatic veno occlusive disease (VOD) risk increased after transplant
  - overall well tolerated since toxic component is released intracellulary

nelarabine
- R/R T-cell ALL
- 1500mg/m2 days 1,3,5
SE: myelosupp, diarrhea, LFTs, neurotoxicity



Supportive Care

Infection prophylaxis • Antibacterial: flouroquinolones • Antifungal: fluconazole • Antiviral: acyclovir or valacyclovir • PCP: Bactrim or dapsone
Febrile Neutropenia • Education on what constitutes a fever • Antibiotics
Tumor Lysis Syndrome • Monitor labs • IV fluids • Allopurinol • Rasburicase PRN
Steroid Management • Hyperglycemia • Steroid psychosis • Stress ulcer prophylaxis • Insomnia • Bone health
Nausea/Vomiting • Antiemetic prophylaxis and PRN

Summary
- ALL is the most common acute leukemia among children
- ALL is curable!
- Age, WBC count at diagnosis and cytogenetics are the most important prognostic factors
- Backbone of therapy: vincristine, steroids, asparaginase, anthracyclines (daunorubicin, doxorubicin)
- CNS prophylaxis is required throughout treatment
- Relapsed disease is associated with poor outcomes and stem cell transplant is the only curative option
- Recent approval of novel therapies has improved outcomes with fewer side effects than traditional chemotherapy

Acute Myeloid Leukemia (AML)

Briefly review the epidemiology, etiology, & pathology of acute myeloid leukemia (AML)
Describe the clinical presentation of acute myeloid leukemia (AML)
Understand the prognostic factors & disease classifications for AML
Review current treatment strategies, including monitoring of common drug adverse events
Discuss backbone of treatment and supportive care for acute promyelocytic leukemia (APL)

Epidemiology: disease of the elderly (median 68yo, new cases 19.9k, 11.2deaths); 28.7% 5yr survival (1.1% of cancers)
Pathophysiology: blood stem cell → myeloid stem cell → myeloblast
- see ↑myeloblast, ↓WBC RBC Plt

Cytogenetics: affects risk stratification; transloc/add/del; "core binding factor" inv(16), t(8;21) t(16;16) t(15;17) means good outcome; 11q23 prior tx caused AML
Presentation: leukocytosis, thrombocytopenia, anemia, elevated uric acid (tumor lysis TLS); sx: fatigue, leukemic infiltrate skin/spleen/liver; CNS involvement rare
Risk factors: prior chemotherapy like BC (alkylating agents, topoII inh); hx myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), CML
Dx: analysis of peripheral blood (presence of Auer rods); bone marrow biopsy >20% blasts; cytogenetics/immunopheno presence of t(8;21) or inv(16)
Classification (French-American-British; WHO classification)
M0-M1-<3 myeloblastic w/o-minimal-maturation M3 promyelocytic M4-M5 myelo/monocytic (CNS disease) M6 erythroleuk (bleed) M7 megakaryobl
Risk stratification: younger patients better prognosis; secondary AML always poor risk
favorable: "core binding factor" inv(16), t(8;21) t(16;16) t(15;17) NPM1 mutation w/o FLT3, isolated biallelic CEBPA mutation
intermed: normal cytogenetics, t(9;21), other mutation of KIT; NPM1 mutation with FLT3, NPM1-wt-FLT3
poor: complex cytogeny (>3abn), monosomal, 11q23, del5, del5q, del7, 7q-, inv(3), t(3;3), t(6;9), t(9;22) mutations: FLT3 TP53 RUNX1 ASXL NPM1-wt-FLT3
Treatment: cure

Treatment

Remission Induction: goal to get patient into remission; intensive vs. less intensive induction

Consolidation: goal to maintain remission by eliminating any residual disease; chemotherapy vs. stem cell transplant

Intensive Induction Chemotherapy

- goal to induce remission: eliminate circ blasts, clear blasts in marrow (<5%), restore hematopoiesis (WBC, Hgb, plt)

7+3 (cytarabine+daunorubicin)

7+3 with midostaurin if FLT3+

liposomal cytarabine+daunorubicin (Vyxeos) if therapy related or myelodysplastic changes

Response: goal to achieve CR after 1 cycle (<5% blasts, ANC>1000, plt>100k, no extramedullary disease)

7+3 (cytarabine+daunorubicin)

cytarabine 100mg/m2 CI over 7 days and daunorubicin 60-90mg/m2 IV qd for 3 days (max 60 older pt)

- always inpatient, stay until recover (28d); bone marrow biopsy on day 14 28 to assess response; may give re-induction therapy if residual on day 14

SE: tumor lysis TLS, myelosupp (need transf), inf risk/neutropen fever, NV, mucositis, hair loss, risk of extravas (need central line), cardiotox (ECHO prior), REDman

midostaurin

- indicated for FLT3 mutated AML; tyrosine kinase inhibitor targeting FLT3 (also targets KIT, PDGFR, VEGFR, PKC)
- given in combo 7+3, 50mg bid days 8-21

SE: NV, QTc, pulmonary (rare but serious interstitial lung disease, noninfectious pneumonitis)

liposomal cytarabine+daunorubicin (Vyxeos)

- approved for therapy-related AML or AML with myelodysplastic related changes; liposomal allows for taken up by leukemia cells more than normal bone

cytarabine 100mg/m2 and daunorubicin 44mg/m2 given on days 1 3 5; improve synergy/efficacy 1:5 molar ratio

SE: similar to 7+3 but better tolerated; prolonged cytopenias (up to 2 weeks longer than with 7+3) with older pt infection risk

Supportive Care During Induction

- high risk of tumor lysis syndrome (spont prior to tx init)
- leukostasis: high WBC decreased organ perfusion, often requires hydroxyurea prior to lower WBC; severe apheresis to lower WBC if sx (dyspnea, visual, stroke)
  - infections (require prophylactic abx/antiviral/antifungal; empiric abx for neutropenic fever) - transfusions

Less-Intensive Induction Chemotherapy

- goal: improve quality of life, restore normal hematopoeisis; used for older patients/comorbid

hypomethylating agents (decitabine, azacitadine)

venetoclax + hypomethylating agent or LD cytarabine (approved >75yo or comorbid)

IDH inhibitor (enasidenib, ivosidenib)

Response: generally takes >3-4 cycles before achieves remission; duration: continued until unacceptable toxicity or loss of response

hypomethylating agents

decitabine 20 mg/m2 daily on days 1-10 of 28 day cycle (5 days if remission); azacitadine 75 mg/m2 daily on days 1-7 of 28 day cycle

Fewer side effects than intensive chemotherapy: myelosuppression (less than 7+3); low-moderate emetic potential; no renal or hepatic adjustments

venetoclax

MoA: binds to anti-apoptotic protein BCL-2, restores normal apoptosis

Used in combo with hypomethylating agents or cytarabine

Risk for tumor lysis (requires ramp up to target 400mg qday; monitor labs 6-8hr after each dose escalation)

SE: myelosuppression 3A4, DDI requires dose adj (azoles- posa70mg, strong3A4inh/isuv 100mg, moderate3A4inh/fluc 200mg)

IDH inhibitors

MoA: oral small molecule that target mutant isocitrate dehydrogenase (IDH 1/2), leading to apoptosis

Time to response up to 6mo

ivosidenib: targets IDH1, 500mg qday wowfood; 3A4 (rec decr dose with strong 3A4i)

enasidenib: targets IDH2, 100mg qday wowfood, no DDI

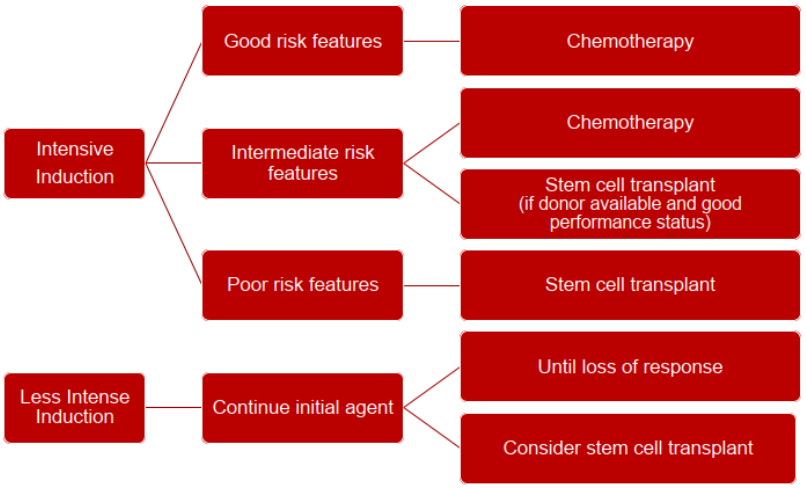
SE: QTc, hyperleukocytosis, differentiation syndrome, hyperbili (indirect);

IDH Differentiation Syndrome: occurs in 20%, rapid proliferation and differentiation of myeloid cells

- sx: elevated WBC, resp distress, pleural effusions, rapid wt gain/edema, fever, renal impair, bone pain
- tx: dexamethasone 10mg q12h PO/IV; continue until sx resolve then taper; continue IDH inh (unless pt severe pul sx requiring intubation or renal dysf>48h)

Consolidation Chemotherapy
- goal: eliminate residual disease; almost all will relapse without consolidation therapy; use chemo or stem cell transplant
  - dependent on factors: risk strat, performance status (tolerability to transplant), donor avail, caretaker avail

HIDAC: High Dose Ara-Cytarabine
  - 3g/m2 q12h day 1 3 5
IDAC: Intermediate Dose Ara-Cytarabine
  - 1g/m2 q12h day 1 3 5 (or 1g/m2 qd days 1-5)
  - pts >60yo or renal dysfunction
Complete 3-4 cycles, every 28 weeks



Relapsed/Refractory Targeted Therapy
- clinical trial preferred
Intensive chemo
  - reinduction with initial regimen (if late relapse)
  - MEC (mitoxantrone, etoposide, cytarabine)
  - FLAG +/- idarubicin (fludarabine, cytarabine, G-CSF)
  - CLAG +/- idarubicin, mitoxantrone (cladribine, cytarabine, G-CSF)
Less intensive regimens: hypomethylating agent (if prev not used)
Targeted therapy
  IDH1: ivosidenib
  IDH2: enasidenib
  FLT3: sorafenib, gilteritinib
  CD33: gemtuzumab

getmuzumab
MoA: mab targeting CD33 linked to cytotoxic calicheamicin, which is released inside of CD33+ cells, leading to apoptosis; cells must express CD33
- 3g/m2 on days 1, 4 and 7 of a single course (max 4.5 mg); no renal or hepatic dose adjustments
premedicate with APAP, diphenhydramine, steroids
SE: hepatotoxicity, veno-occlusive disease*; myelosuppression, prolonged thrombocytopenia; hypersensitivity; QTc prolongation

gilteritinib
MoA: tyrosine kinase inhibitor targeting FLT3 (2^{nd}-gen, more selective)
- 120 mg once daily; continue for at least 6 months to allow time for response; no renal or hepatic adjustments (not studied severe or <30)
substrate of CYP3A4, P-gp
SE: QTc prolongation, myalgias, arthralgias; LFT elevations

Acute Promyelocytic Leukemia (APL)

- Aggressive subtype of AML; accounts for ~10% of AML cases
- Characterized by t(15;17) chromosomal mutation; also known as PML-RARA
- Median age at diagnosis: 44 years
- Remission rate: 80%
- High risk for potentially fatal coagulopathies at diagnosis
- Risk stratification based on WBC count at diagnosis Low risk: WBC < 10,000 High risk: WBC > 10,000

Treatment

- ATRA (all trans retinoic acid) Vitamin A
  - Dosing: 45 mg/m2 PO divided twice daily
  - Taken continuously during induction
  - Taken 2 weeks on, 2 weeks off during consolidation
  - Side effects: differentiation syndrome, pseudotumor cerebri, LFT elevations
  - **Should be given ASAP if APL is suspected**
- Arsenic
  - Dosing: 0.15 mg/kg IV once daily
  - Given continuously during induction
  - Given 4 weeks on, 4 weeks off during consolidation
  - Side effects: myelosuppression
- Chemotherapy not required unless high risk*; most regimens add anthracycline if high risk

Supportive Care

- Coagulopathy: Maintain platelets > 50,000; Maintain fibrinogen > 150 mg/dL; Leukapheresis should be avoided
- QTc prolongation: Monitor EKG at least weekly during induction; Maintain K > 4 mEq/dLand Mg > 1.8 mg/dL
- Infection prophylaxis/management: G-CSF not recommended during induction

Differentiation Syndrome

- Mediated by cytokine release, leading to capillary leak syndrome
- May also be mediated by enhanced migration of maturing leukocytes, which infiltrate organs
- Often associated with WBC >10,000/mcL
- S/sx
- Fever
- Peripheral edema
- Pulmonary opacities
- Hypoxemia
- Respiratory distress
- Hypotension
- Renal/hepatic dysfunction
- Rash

Prevention and Treatment

- Dexamethasone 10 mg BID at the first suspicion of differentiation syndrome; Do not wait until diagnostic confirmation; Continue until resolution ofsx, then taper
- Typically recommended to continue ATRA and arsenic; Unless severe differentiation syndrome, then temporarily discontinue until symptoms resolve
- Prophylaxis: prednisone 0.5 mg/kg/day or dexa 10 mg BID, (steroid depends on regimen); continued at least 10-14 days and often until end of induction therapy

AML/APL Summary

- AML is a disease of the elderly
- Age, cytogenetics and molecular abnormalities are important prognostic factors
- Treatment consists of induction therapy followed by consolidation
- Recent approval of new targeted agents allows for treatment of older, more frail patients who cannot tolerate intensive chemotherapy
- APL is an aggressive subtype of AML, characterized by t(15;17).
- APL treatment consists of ATRA and arsenic, with the addition of chemotherapy for intermediate to high risk patients

	ALL	**AML**
Age affected	younger (median 15yo)	older (median 68yo)
Morphology	lymphoid (B cells, T cells)	myeloid (Auer rods present)
Symptoms	low counts more coagulopathies possible lymphadenopathy, night sweats/fever	low counts APL: highest risk of coagulopathies
CNS disease	common; must use prophylaxis	uncommon (except M5 subtype)
Treatment regimens	backbone: vincristine, steroids, pegaspargase, anthracyclines (cyclophosphamide, mercaptopurine, methotrexate)	intensive: 7+3 +/- midostaurin, Vyxeos less-intensive: hypomethylating agents, IDH inhibitors
Targeted agents	CD19: blinatumomab CD20: rituximab CD22: inotuzumab T-cell: nelarabine CAR-T (CD19): tisagenlecleucel	FLT3: midostaurin, gilteritinib IDH1: ivosidenib IDH2: enasidenib CD33: gemtuzumab APL: ATRA/arsenic

Multiple Myeloma (MM)

Review pathophysiology of Multiple Myeloma (MM)
Identify MM diagnostic criteria and myeloma defining events
Discuss MM treatment algorithm and various treatment options
Describe common toxicities and required supportive care of drugs used to treat MM

plasma cell

Epidem: 1% all cancers, 10% hemat cancers; median age 65yo M AA;

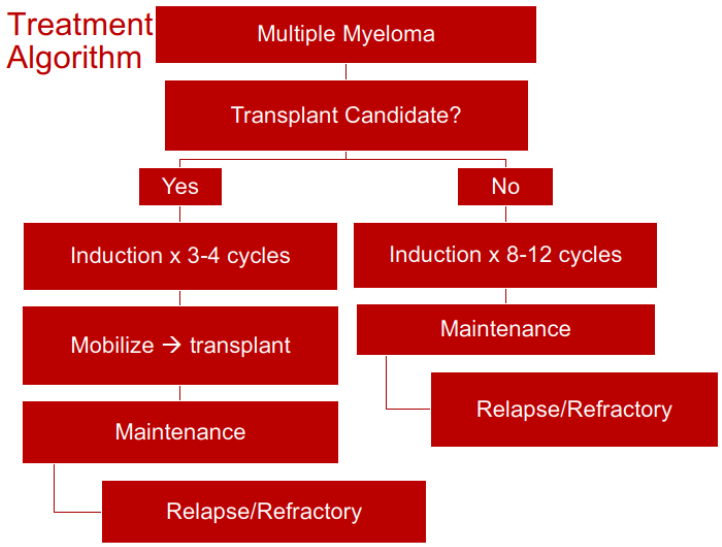
CRAB Criteria
hyperCalcemia: Ca >1 mg/dL ULN or >11 mg/dL
Renal insufficiency: SCr >2 mg/dL or CrCl <40 mL/min
Anemia: hemoglobin >2 g/dL below ULN or <10 g/dL
Bone lesions

Disease states
MGUS: noCRAB + <10% plasma cells in bone marrow; asymp, live 10yrs before dx; monoclonal gammopathy of undetermined significance (MGUS)
SMM: noCRAB + ≥10% plasma cells in bone marrow; smoldering multiple myeloma (SMM)
Multiple Myeloma: any CRAB (or MDE myeloma defining event) and ≥10% plasma cells in bone marrow

Principles of Therapy
- incurable

Treatment

Is transplant an option?



Induction Treatment Options
Anti-CD38 antibody: daratumumab
IMiD: lenalidomide (Revlimid)
Protease Inhibitor: bortezomib, carfilzomib
Alkylating Agent: cyclophosphamide
Steroid: dexamethasone

3 drugs > 2 drugs

<u>Induction – Transplant Eligible</u>
VRd gold standard: bortezomib + lenalidomide + dexamethasone
CyBord: cyclophosphamide + bortezomib + dexamethasone (preferred ESRD/renal)
KRd: carfilzomib + lenalidomide + dexamethasone (preferred high-risk MM)
DVRd: daratumumab + bortezomib + lenalidomide + dexamethasone (preferred high-risk MM)

<u>Induction – Transplant Ineligible</u>
VRd gold standard: bortezomib + lenalidomide + dexamethasone
CyBord: cyclophosphamide + bortezomib + dexamethasone (preferred ESRD/renal)
Vd: bortezomib + dexamethasone (renal dysfunction or intolerable to others)
Rd: lenalidomide + dexamethasone (option for older/unfit)
DRd: daratumumab + lenalidomide + dexamethasone (option for nontransplant candidate)

Assessing Response to Treatment
PR: partial response ≥50% reduction in M protein level
VGPR: very good partial response ≥90% in M protein level
CR: complete response no measureable M protein, <5% plasma cells in marrow
sCR: stringent complete response: no measureable M protein, no clonal cells in marrow

<u>Maintenance Post-Transplant</u>
standard: ixazomib or lendalidomide until progression
high-risk (del 17p or other): bortezomib until progression

<u>Maintenance Transplant Ineligible</u>
standard: lenalidomide +/- dexamethasone until progression
high: bortezomib based therapy until progression

<u>Relapsed/Refractory Treatment Regimens</u>: lots of regimens; salvage therapy, aim to get myeloma under control, minimize toxicities, improve QoL
Determine: what patient has tried, when relapse (maintenance or unmaintained), had transplant, comorbidities, tolerable side effects, QoL
e.g., bortezomib/carfilzomib/ixazomib + lenalidomide + dexamethasone darat + bort/carf + dex darat + lenal + dex

Toxicities

immunomodulators (IMiDs)- lenalidomide, pomalidomide, thalidomide; PO qday

BBW: embryo-fetal toxicity; neutropenia and thrombocytopenia, VTE SE: fatigue, diarrhea/constipation, rash, muscle cramps

Revlimid REMS to prevent embryotoxicity; weekly pregnancy tests 1st month, then every 4 weeks; only 28ds

protease inhibitors- bortezomib, carfilzomib, ixazomib

acyclovir for prophylaxis as ALL have risk of reactivating herpes; thrombocytopenia, neuropathy (bort>ixa>carf), neutropenia, edema, diarrhea/constipat, NV low

- bortezomib: neuropathy with IV; give SC qwk to reduce neuropathy* - carf: 10/30min IV infusion 1-2x/wk, risk of reversible LVEF HTN - ixa oral empty stomach

daratumumab anti-CD-38; IV infusion or SQ weeklyx8 then qow x8 then qmo; tox: 50% chance infusion rxn; fatigue, decreased WBC, HepB HSV reactivation

alkylating agents- cyclophosphamide IV/PO, diarrhea NV myelosupp; melphalan high-dose for transplant conditioning; diarrhea NV myelsupp

Supportive Care

infection: prophylaxis antibiotics-FQ or Bactrim for PJP; herpes zoster; recurrent infections consider IVIG admin

rash: topical corticosteroid or antihistamine diarrhea: colesevelam, loperamide

neuropathy

pain management

renal dysfunction

bisphosphonates: all patients should receive; prevent/reduce number of bone lesions; pamidronate, zoledronic acid, denosumab; hypercalc normalize in 24-72hrs

viral prophylaxis: fludarabine/pentostatin - acyclovir for bortezomib - CML, post-transplant
fungal prophylaxis: neutropenia like in acute leukemia during induction; not really in MM; maybe CML,
R=lenalidomide risk of thrombosis, at least asa81, maybe higher anticoag based on VTE risk factors

"I now have FL, is it early or advanced stage? young old? fit unfit? Don't worry about diagnosis, given dx"
know myeloid vs. lymphoid and drug classes on each side; toxicities and eliminating options based on given toxicity from prev medication
myeloid: no rituximab no CD20 inhibitors
lymphoid: btk

Cases

CASE 1: MM RATIONALE AND ANSWERS:

Questions

1. **What CRAB does TR have at diagnosis?**
    1. Hypercalcemia
    2. **Renal disease**
    3. **Anemia**
    4. **Bone disease**

Rationale: *TR has an elevated serum creatinine, her HgB is <10, and she has bone lesions. Her calcium currently is normal.*

2. **What would be an appropriate initial treatment for TR if transplant eligible?**
    1. Bortezomib, lenalidomide, dexamethasone (VRd)
    2. Lenalidomide, dexamethasone (Rd)
    3. Carfilzomib, lenalidomide, dexamethasone (KRd)
    4. **Cyclophosphamide, bortezomib, dexamethasone (CyBorD)**

Rationale: *This patient has standard-risk disease which would qualify her for VRd or CyBorD. Due to her current renal dysfunction, CyBorD is the most appropriate treatment option. Her CrCl is estimated to be 25 ml/min (AdjBW), and the IMiDs are not recommended in several renal dysfunction. KRd is recommended in patients who have high-risk disease and are transplant eligible. Rd may be recommended in frail, older transplant ineligible patients that have standard-risk disease and cannot tolerate a proteasome inhibitor.*

3. **What are some counseling points you would share with TR for the treatment that you selected in the previous question?**

Answer: *Discuss dosing regimen, routes of administration, side effects*

Cyclophosphamide: given orally, do not crush or chew capsules; nausea, diarrhea, stay hydrated to minimize risk of bladder toxicity; hazardous precautions

Bortezomib: peripheral neuropathy, subcutaneous injection (given SC instead of IV to decrease the risk of peripheral neuropathy); thrombocytopenia; risk of shingles reactivation

Dexamethasone: side effects of steroids (increased blood pressure, blood glucose, weight gain); take with food in the morning

4. **What supportive care medications does TR need?**
    1. Sulfamethoxazole-trimethoprim, acylovir
    2. Aacyclovir, isavuconazole
    3. **Acyclovir, pamidronate**
    4. Isavuconazole, acylovir, pamidronate

Rationale: *Patients on bortezomib should receive HSV prophylaxis. Bisphosphonates are recommended to prevent skeletal events in patients with one or more bone lesions present on imaging. Denosumab (Xgeva) is appropriate as well. Antifungal and PJP prophylaxis are not required.*

5. **Does TR need VTE primary prophylaxis at this time? If so, which agent? Defend your answer.**

Answer: *No, patient is not starting lenalidomide (IMiD). If patient was starting lenalidomide, she would need full anticoagulation as she has a history of a prior DVT.*

6. **TR will plan to proceed with transplant. What would you recommend for eventual maintenance therapy assuming her CHEM7 is now within normal limits?**
    1. Carfilzomib
    2. **Lenalidomide**
    3. Cyclophosphamide
    4. Daratumumab

Rationale: *Lenalidomide is the standard of care for maintenance therapy following an autologous transplant and should be continued until disease progression or unacceptable toxicity.*

CASE 2: AML Rationale and Answers

1. Prior to starting chemotherapy MP is found to be FLT3+. Which chemotherapeutic agent should be added to her 7+3 regimen?
    1. Venetoclax
    2. Enasidenib
    3. Mercaptopurine
    4. **Midostaurin**

Feedback: Midostaurin is tyrosine kinase inhibitor targeting FLT3. It is indicated for FLT3 mutated AML given in combination with 7+3. It is dosed 50mg BID on days 8-21. Side effects associated with midostaurin include N/V and QTc prolongation.

2. Which of the following side effects are associated with daunorubicin? (Circle all that apply)
    1. Red discoloration of urine and tears
    2. Peripheral neuropathy
    3. Hair loss
    4. Conjunctivitis
    5. Cardiotoxicity

Feedback: Daunorubicin can cause red discoloration of urine/tears, cardiotoxicity, and hair loss.

3. After completing induction therapy, MP undergoes a bone marrow biopsy that shows she is in complete remission (blasts 2%). The team would like to start her on consolidation therapy with high dose cytarabine (HIDAC). What side effects should you monitor for in patients receiving HIDAC? What supportive care medications should they receive?

Feedback:

1.
    - *Chemical conjunctivitis- eye drops should be used at the start of therapy and for at least 24 hours after the completion of therapy.*
    - *Cerebellar toxicity- no medications to prevent this toxicity. Patient's should be monitored for confusion/neurologic changes.*
    - *Rash- creams/lotions.*

- *Infections/FN- filgrastim or pegfilgrastim*

4. Unfortunately MP relapsed 8 months after completing consolidation therapy. Since she is FLT3+ and otherwise stable, the decision is made to start her on gilteritinib. MP had a difficult time tolerating 7+3+midostaurin and is apprehensive to start this targeted therapy. How would you counsel this patient on both the expected time to response with gilteritinib, as well as the side effects associated with this therapy?

Feedback: It may take up to 6 months to see a response with gilteritinib. The most common side effects associated with gilteritinib include QTc prolongation, myalgias/athralgias, and LFT elevations. Gilteritinib is dosed 120mg once daily and has not been studied in severe hepatic impairment or CrCl < 30.

ALL Case: Answers and Rationale

1. What signs and symptoms of B-cell ALL did SH exhibit on admission?

Feedback: SH is experiencing frequent nose bleeds (due to low platelets), shortness of breath with mild exertion (due to anemia), occasional night sweats (due to disease burden).Other signs and symptoms of B-cell ALL include weakness/fatigue, easy bleeding/bruising, unexpected weight loss, pain in bones/joints, swelling or discomfort in abdomen.

2. What is the goal of induction therapy for SH? Is SH done with treatment after induction? (If not, why and how long she should expect all courses of treatment to last?)

Feedback: The goal of induction therapy is to eradicate the majority of blasts. SH is not done with therapy after induction. Induction is then followed by intensification/consolidation therapy in order to eliminate any leukemic cells potentially remaining after induction. Maintenance therapy is used to prevent relapse. Treatment for ALL on the AYA regimen lasts 2-3 years.

3. Using the provided schema for the AYA regimen, list the days that SH will receive vincristine during course I. What are some major side effects associated with vincristine?

Feedback: She will receive vincristine on days 1, 8, 15 and 22. Major side effects associated with vincristine include constipation and neuropathy. Constipation can be managed by ensuring that the patient has an adequate bowel regimen (senna, docusate, miralax, etc). Neuropathy is something that will be assessed prior to each dose of vincristine. If a patient experiences neuropathy, vincristine doses may be held, dose reduced, or the patient may receive therapy to alleviate (gabapentin).

4. Which of the following are side effects associated with pegaspargase? (Circle all that apply)
    a. **Thrombosis**
    b. Pneumonitis
    c. **Pancreatitis**
    d. **Hypersensitivity reactions**
    e. **Hyperbilirubinemia**
    f. Heart failure

Feedback: Pegaspargase is associated with thrombosis, pancreatitis, hypersensitivity reactions, and hyperbilirubinemia. Other side effects associated with pegaspargase include bleeding, fatigue, N/V, hyperglycemia, neuropathy, hypofibrinogenemia, elevated liver enzymes, elevated PT/INR.

CLL CASE: Rationales and Answers

1. The team has decided that LP's CLL requires treatment. What first line treatment would you recommend for this patient and why?

Venetoclax + obinutuzumab – best option, the risks of bleeding and drug interactions with antiplatelet therapy is not present

Acalabrutinib ± obinutuzumab – although possible, there are drug interactions with antiplatelet therapy.

Ibrutinib – although possible, patient is going through a stent procedure and will be on DAPT therapy. Due to the drug interactions with antiplatelet therapy and inherent increased risk of bleeding, this option is not most appropriate.

2. Describe the mechanism of action and adverse effects associated with the treatment you chose above.

	MOA	*Adverse effects*
Venetoclax	*Selectively inhibits the anti-apoptotic protein BCL-2*	*Myelosuppression, diarrhea, tumor lysis syndrome*
Acalabrutinib	*Selective and irreversible BTK inhibitor*	*Headache*
Ibrutinib	*Potent and irreversible inhibitor of BTK*	*Bleeding, a fib, HTN*
Obinutuzumab	*CD20 monoclonal antibody*	*Infusion reactions, hepB reactivation*

3. The resident side bars you...

Rigors – Hydromorphone 0.5 mg IV, would NOT use meperidine because of Crcl of ~25 ml/min
H1/H2 antagonists: diphenhydramine 50 mg IV + famotidine 20 mg IV (renal dose adjustment)
Corticosteroids: hydrocortisone 50-100mg IV or methylprednisolone 1-2mg/kg IV every 6 hours
Acetaminophen 325-650 mg PO
If the patient responds to supportive care medications, restart then infusion at 50% rate and titrate to tolerance. If the patient does not respond to the supportive care medications, would not re-challenge.

FOLLICULAR CASE : Rationale and Answers

1. The resident on your team is asking for a first-line recommendation for JV. Based on his diagnosis, what would you recommend? Please include drug(s), and frequency.

Rituximab or obinutuzumab + bendamustine every 28 days for 6 cycles *– younger/fit so can tolerate a more aggressive regimen*

OR

Rituximab or obinutuzumab + CHOP for 6 cycles *- younger/fit so can tolerate a more aggressive regimen*
Rituximab or obinutuzumab + CVP – usually reserved for frail patients
Rituximab + lenalidomide – not usually used first line but an appropriate answer

2. JV is worried about the side effects associated with his chemotherapy. What side effects would you counsel him on based on your choice above? Are there any supportive care medications you would advise him to use if prescribed?

Rituximab/Obinutuzumab – infusion reactions, hepB reactivation
Bendamustine – nausea/vomiting (moderate), myelosuppression, rash, hair thinning, infection
CHOP – N/V, myelosuppression, red tinged body fluids, alopecia, neuropathy, constipation, hyperglycemia, insomnia, dyspepsia, jitteriness
CVP – N/V, myelosuppression, neuropathy, constipation, hyperglycemia, insomnia, dyspepsia, jitteriness
Supportive care – antiemetics, PCP and viral prophylaxis, rituximab pre-meds and rescue meds

3. The physician on your team is worried about recurrent disease and wants to be prepared with relapsed/refractory treatment. Which of the following would you recommend if JV relapses after his initial treatment (more than one answer possible)?
    c. **Rituximab**
    d. Idelalisib
    e. **Lenalidomide +/- rituximab**
    f. **Obinutuzumab + CVP**
    g. Bendamustine + CHOP
    h. Copanlisib

DLBCL CASE: Rationale and Answers

1. Even though the MRI came back negative, the hematologist is concerned about the location of her tumor for CNS extension or progression and wants to take preventative measures. What initial treatment would you recommend for MD? Please include drug(s), and frequency.

RMCHOP x 3 cycles and RCHOP x 3 cycles – include methotrexate for CNS prophylaxis

2. What common adverse effects do you counsel MD on based on your answer above?

Rituximab – Infusion reactions
Doxorubicin – Nausea/vomiting, myelosuppression, red tinged body fluids, alopecia
Prednisone – hyperglycemia, insomnia, dyspepsia, jitteriness
Cyclophosphamide – Nausea/vomiting, myelosuppression
Methotrexate – not mentioned in lecture but ulcerative stomatitis, leukopenia, nausea, and abdominal distress
Vincristine – neuropathy, constipation

Cancer3: Exam 4

Pharmaceutics of Cancer Therapies
Pharmacogenomics
VTE in Cancer
ESAs for Anemia and Cancer
Neutropenia and Thrombocytopenia Management of Neutropenic Fever Study Guide
Oncologic Emergencies Hypercalcemia
Nausea and Vomiting
Oral Chemotherapy Focus

Pharmaceutics of Cancer Therapies

- Obtain an understanding of how pharmaceutics concepts are used to facilitate optimal development and use of oncology drugs and drug formulations.
- Understand how variation in distribution of drugs can affect the therapeutic and/or toxic properties of oncology drugs.
- Discuss the main causes of inter-individual pharmacokinetic variation of oncology drugs, in particular DDIs.

Intro

Pharmaceutics is the discipline of pharmacy that deals with the process of turning a new chemical entity or old drug into a medication to be used safely and effectively by patients.
There are many chemicals with pharmacological properties, but need special measures to help them achieve therapeutically relevant amounts at their sites of action.
Pharmaceutics helps relate the formulation of drugs to their delivery and disposition in the body.
A key aspect of this is related to pharmacokinetic drug-drug interactions (DDIs), either those that are intentional or unintentional as a result of polypharmacy.

Intentional Drug-Drug Interactions: A Underexplored Area of Research?

Intentional biomodulation of oral oncology drugs (eg, docetaxel)

ibrutinib

BTKi; F 2.9%, %CV of ss AUC 70%, metabolized 3A4

1. What's cause of low F?
   3A4 deficiency increases ibrutinib pAUC by 9.7-fold compared to wt mice; Abcb1/g2 do not restrict ibrutinib F
   Admin of ibrutinib with ketoconazole (strong 3A4 inh) increases ibrutinib AUC by 24-fold and Cmax by 29-fold
2. Is 3A4-mediated route of metabolism via GI tract or liver or both?
   equal contributions of intestinal and hepatic CYP3A4
   Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine
   >99% of the ibrutinib dose is at least taken up into intestinal enterocytes and is broken down to metabolites
   Thus the low oral bioavailability is most probably due to very extensive first-pass metabolism
3. Is safety of ibrutinib compromised when given with grapefruit/apple juice?
   avoid grapefruit and orange during ibrutinib treatment as they can contain moderate inhibitors of intestinal 3A4, resulting diminished metabolism and higher Cp
   Grapefruit juice increases ibrutinib AUC by about 2-fold
4. Are food restrictions recommended when patients are receiving ibrutinib? (fasted AUC is only 60% when compared to high-fat meal)
   no prescribing info, but clinical trial most likely taken without food
   food effect with ibrutinib appears to be relatively modest compared to abiraterone (10-fold) so unlikely to be a clinical concern
5. Concomitant use of ibrutinib with carbazepine or phenytoin is discouraged, why?
   These agents are known to induce expression and function of CYP3A4; Compare with rifampin
   Prolonged use of such AEPs is expected to decrease ibrutinib concentration in the systemic circulation, and possible cause decreased efficacy (but less toxicity)

Because the main CYP3A4-mediated metabolite of ibrutinib retains BTK-inhibitory properties and circulates at higher levels than the parent drug, pharmacodynamics effects of CYP3A4 induction are difficult to predict and this requires further study.

ADME lesson's learned from ibrutinib

- Ibrutinib targets BTK, a kinase important for B-cell development, that has revolutionized lymphocytic leukemia (CLL/MCL) treatment; Global revenues ~$4b/year
- Ibrutinib has an unfavorable PK profile with an absolute bioavailability of 2.9% and %CV in steady state AUC of ~70%

– Improving bioavailability could decrease variability, adverse effects, and the development of resistance

Ibrutinib boosting with cobicistat, a 3A inhibitor = ↑Cp of ibrutinib and a proportional decrease in exposure to 3A4-mediated metabolite

Unintentional Drug-Drug Interactions: A Widely Neglected Problem?

Complexity of DDIs
1. Ethical considerations (drug dose, sample size)
2. Trial design considerations (steady-state vs first dose)
3. Clinical relevance
4. Endpoint considerations (importance of sample matrix)

Drug exposure-effect relationship
drug → PK (drug disposition and ADME; PGx/DDIs) → PD (drug effects and target organ/tissue effect: toxicity, efficacy, biological effect; inherited variability)

docetaxel exposure SE neutropenia; imatinib exposure SE myelosupp; irinotecan exposure SE diarrhea

Case 1: **docetaxel**-ketoconazole
PK/PD relationships: lower clearance associated with higher odds of [febrile] neutropenia; AUC only predictor of toxicity
3A4/5; if inhibitor: metabolism shutdown, dramatic increases in Cp, and subsequent increased exposure to injury sites that manifest as bone marrow suppression
e.g., ketoconazole coadmin results in 49% decrease in docetaxel clearance; 6.5-fold increased odds for febrile neutropenia

Case 2: **irinotecan**-SJW
metabolized via carboxyesterase conversion to SN-38 (active) and also 3A4 to inactive metabolites
3A4 inhibitor would increase irinotecan SN-38 active AUC; 3A4 inducer (anticonvulsants,dex) would lead to decreased exposure of active ingredient
3A4 inducer SJW resulted in decreased SN-38 exposure which inactivates irinotecan chemotherapy (contraindicated)

Case 3: **imatinib**-ritonavir
metabolized via 3A4, and SJW causes 30% decrease in imatinib AUC
ketoconazole increases in exposure via decreased clearance
ritonavir has no effect on imatinib AUC; at steady-state imatinib inhibits its own primary elimination primary; becomes dep on other enzymes not aff by ritonavir

Case 4: **sunitinib**-GFJ
3A4 inhibitor ketoconazole results in increase AUC of sunitinib
GFJ 3A4 intestinal inhibition does not affect sunitinib PK
Worried about DDIs with imatinib-GFJ? says to avoid grapefruit juice, but can be dissolved in apple juice (not studied though other OATP studied show this PK intx)

Case 5: **irinotecan**-milk thistle
milk thistle 3A4 UGT1A↓
no effect of milk thistle on irinotecan PK; "recommended" doses resulted in exposure that's too low to affect the clearance of irinotecan/SN-38

Case 6: **docetaxel**-garlic
garlic 2E1↓, 2B/3A↑
no change in docetaxel Cmax and AUC with garlic coadmin

Case 7: **cisplatin**-cimetidine
cisplatin accumulates in and affects kidney (proximal tubule S3 segment)
cisplatin causes renal injury which is dependent on OCT2 proximal tubular secretion
Oct1/2(-/-) mouse deficiency in it leads to decreased conc proximal tubules, leading to decreased urinary elim and also less damage to renal (less nephrotox)
but <u>unchanged</u> cisplatin plasma PK in Oct1/2(-/-) mice

Conclusion

- DDIs are difficult to study due to physician/IRB concerns regarding toxicity/lack of efficacy
- In vitro studies are not necessarily predictive for drugs with complex elimination pathways
- Important functional genotypes and appropriate biological matrices should be considered in DDI trial design
- Healthy subjects may not be appropriate for anticancer drugs, even "non-cytotoxic/targeted" agents
- Single dose vs multiple dose (steady-state) should be considered in DDI trial design
- Drug-CAM interactions are less likely than commonly held (except for SJW)

Elimination = excretion of unchanged drug + excretion of changed (metabolized) drug
Absorption Distribution Metabolism Excretion

Pharmacogenomics

Review of Genomic Principles

Review of: • Genomic Nomenclature • Central Dogma MolBio • -'Omic Variants • Traditional Methods Genome Analysis • Cutting-edge Techn • Challenges

Gene name vs. protein name: Breast Cancer Gene 2: **BRCA2 → BRCA2;** Epidermal Growth Factor Receptor 2: **ERBB2 → HER2**

Short Sequence Variants: Single Nucleotide Polymorphisms (SNPs): Variant at a single nucleotide
Large Sequence Variants: Copy number alterations (Duplication or deletion of an entire gene); Translocations/Fusions (Fused genes can alter oncogene expression or function)
Insertions/Deletions/Frame Shifts: Addition (insertion) or removal (deletion) of base pairs shifts the reading frame of the gene
Epigenetics: Alterations to DNA (methylation/acetylation); Does not affect genomic sequence; Changes regulation/expression of genes; Direct alteration of DNA strand or histones

DNA: PCR, Sanger Sequencing, Next-generation sequencing, FISH (fluorescence in situ hybridization detects DNA variants)
RNA: RT-PCR, RNA-Seq
Protein: IHC (immunohistochemistry detects protein variants), PPPA, ELISA

Micro Satellite Instability (MSI): Linked to genetic hypermutability and impaired DNA mismatch repair (MMR); Correlated to aberrant DNA repair and abnormal cell surface markers
Tumor Mutation Burden (TMB): Total number est. of variations in the genome; As variants per megabase (Mb); Correlated to aberrant DNA repair, abnormal cell surface markers
Loss of Heterozygosity (LOH) and Homologous Recombination Deficiency (HRD): Both measures of allellic imbalance; Correlated with poor double-stranded break DNA repair

Cutting-edge Technologies
Circulating tumor DNA (Tumor-derived DNA shed into bloodstream)
Circulating tumor cells (Solid tumors shed cells into the bloodstream)
Single cell genomics (Isolates genomic variants in individual cells; Provides insight into tumor heterogeneity)

Precision Oncology

BCR-ABL1: Ph+ chromosome 9/22
BRAF V600E: mutation in DNA sequence resulting in mutated protein V600E
EGFR: insertion/deletion exon 21; variants in the EGFR tyrosine kinase turn on function of EGFR
BRCA2: copy number alteration; BRCA2 responsible for repair of dsDNA; inhibit PARP1 therefore no repair and cell death
ERBB2: codes for HER2 protein, seen via FISH amplification
OncotypeDX: gene expression, breast cancer higher recurrence score use chemo
PD-1/PD-L1: IHC surface marker expressed
MGMT: epigenetics, MGMT DNA repair enzyme removes alkyl groups from O6 of guanine

Challenges: target validation, access to off-label therapy, number of trained professionals, lack of standardization
Molecular Tumor Board model a pharmacists role

VTE in Cancer

VTE Prophylaxis

VTE Risk factors: active cancer, chemo, radiation, age, prior VTE; smoking, obesity, immobility; ESAs, HRTs, OCs, megestrol
High-risk Outpatient on chemo: active cancers associated with VTE incidence (solid), prechemo plt >350k, prechemo WBC >11k, Hb <10, ESAs, BMI ≥35, prior VTE

Primary Prophylaxis indications
- hospitalized patients with active cancer
- ambulatory patients with cancer at increased risk: a) MM treatment with highly thrombogenic regimen; b) two or more individual or disease-related risk factors

LMWH Trials: incidence of VTE was lower with LMWH compared to placebo
DOACs Trials: rate of VTE lower with rivaroxaban/apixaban but rate of bleeding was higher compared to placebo
Aspirin may be an option in ambulatory patients with multiple myeloma with no more than one multiple myeloma-specific risk factor

ASCO Guidelines:
- pharmacologic prophylaxis is not routinely offered to all patients in the ambulatory setting with cancer
- high-risk patients with cancer may be offered prophylaxis with apixaban, rivaroxaban or LMWH
- patients with multiple myeloma receiving lenalidomide-based regimen and/or dexamethasone should be offered prophylaxis with aspirin (LMWH for higher-risk patients)

Key Points for Primary Prophylaxis
- Primary prophylaxis is recommended for all hospitalized patients with active cancer
- VTE prophylaxis is required for certain ambulatory patients with active cancer — High risk, multiple myeloma
- In the absence of contraindications, LMWH is generally the preferred agent, however DOACs are now supported as a reasonable option

VTE Pharmacologic Treatment

Initial Treatment
LMWH 1 mg/kg q12h
UFH 80u/kg x1 followed by 18u/kg/hr

CLOT Trial: dalteparin vs. warfarin — dalteparin more effective than warfarin for secondary prevention of VTE; no increase in bleeding risk.
Hokusai-VTE Trial: edoxaban vs. dalteparin — edoxaban was noninferior to dalteparin in the prevention of recurrent VTE and risk of major bleeding.
SELECT-D Trial: rivaroxaban vs. dalteparin — rivaroxaban lower risk of VTE recurrence; higher risk of clinically relevant nonmajor bleeding compared to dalteparin.
ADAM-VTE Trial: apixaban vs. dalteparin — apixaban lower incidence of major bleeding and VTE recurrence compared to dalteparin.

Guideline
ASCO/NCCN states all hospitalized and ambulatory patients with cancer should receive pharmacologic VTE prophylaxis.
Which agents should be used for long-term secondary prevention of VTE?
ASCO: LMWH, LMWH + edoxaban, rivaroxaban
NCCN: **DOACs** preferred **w/o GI lesions**—apixaban, heparin bridge + edoxaban, rivaroxaban **LMWH** preferred patients **with GI lesions**—dalteparin, enoxaparin

Key Points for VTE Initial and Long-term Treatment
- Historically, LMWH has been the preferred agent for long-term treatment/secondary prophylaxis in VTE
- DOACs are now being used more frequently for treatment within the cancer population
- It is important to consider patient-specific and drug-specific factors when selecting an agent

VTE Duration of Therapy
Primary prophylaxis: All hospitalized patients
Immediate treatment: Minimum 3-12 months
Secondary prophylaxis: Active cancer

Chronic VTE Treatment = secondary prophylaxis; LMWH or DOACs
- after no longer an active clot, the continuation of anticoag is considered secondary prophylaxis; duration of therapy for is warranted while the cancer is active

When to hold anticoagulation? enoxaparin dose modification in setting of thrombocytopenia (platelets down, bleed risk)
Plt >50k full-dose enoxaparin 1mg/kg bid (or 1mg/kg qday) Plt <50k half-dose enoxaparin 0.5mg/kg bid Plt <25k temporarily hold enoxaparin

Pharmacologic Options

UFH	prophylaxis: 5000 units SC q8h	no renal dosing	weight: 7500 units SC q8h in obese
	treatment: 80u/kg x1, then 18u/kg/hr		
LMWH	prophylaxis: 40mg SC qday	CrCl <30 30mg SC qday	weight: 40mg SC q12h in obese
	treatment: 1mg/kg q12h	CrCl <30: 1mg/kg qday	weight: 1.5mg/kg q24h in obese
warfarin	prophylaxis/treatment: INR goal to 2-3		
aspirin	prophylaxis: 81-325mg qday		
apixaban	treatment: 10mg bid x7d, then 5mg bid	CrCl <25 not recd	
rivaroxaban	treatment: 15mg bid x21d, then 20mg qday	CrCl <30 not recd	
edoxaban	treatment: 60mg qday (if >60kg)	CrCl >95 not recd	

ESAs for Anemia and Cancer; Chemotherapy Induced Anemia (CIA)

Identify the pathophysiology of anemia in cancer patients
Understand the risks/complications associated with treatment of anemia in cancer patients
Recommend initial dosing of erythropoietin-stimulating agents (ESAs) for CIA and know how to titrate dose based on product
Apply this to a patient case

Pathophysiology of Anemia

- Decreased Production of RBCs
  malignancy: - cancer cells - production of cytokines - specific diseases (MDS, AML, ALL)
  indirect: - nutritional deficiencies (appetite, impaired absorption) - renal insufficiency (Pt-containing)
- Increased Destruction of RBCs
  chemo/radiation: - directly impairs hematopoiesis - myelosupp (nadir 10-14d) - accum of toxicity
  secondary hypersplenism: - 10x normal size - spleen sequesters RBCs - caused by lympho/myeloproliferative disorders (CLL, NHL)
  hemolysis: - immune-mediated antibodies destroying RBCs (AIHA) - microangiopathic hemolysis
- Blood Loss
  - tumor growth - direct effects of malignancy/chemo/radiation - blood draws frequently for monitoring

Direct effect of cancer, An effect from product of the cancer, Effects of treatment directed against cancer

Assessing and Evaluating CIA

Anemia without cancer: M<13 F<12
Classification of anemia with cancer: **Hgb ≤11 g/dL or ≥2 g/dL below baseline**

Initial Assessment

HP (sx, FH, meds), Labs: CBC (severity), peripheral smear (hemolysis), reticulocyte count (BM producing?), MCV (type)
Correctable factors: hemorrhage, hemolysis, nutritional, inherited, renal/hormone dysfunction, chronic inflammation
if no cause identified, treat as CIA

Treatment of CIA

Packed RBC Transfusions (PRBCs): concentrated from whole blood donations or collected by apheresis; anticoagulated and contain preservatives
AABB: transfuse if Hgb <7 in hospitalized hemostable and Hgb <8 in orthoped/cardiac surgery or hx cardiovascular disease
NCCN: transfuse when high risk, *usually* when **Hgb <8**
transfuse: **high risk** (rapidly declining Hgb with recent intensive chemo/rad), **asymp with comorbidities** (COPD, hx MI/stroke, cardiac, CVA), **symptomatic**, **Hgb <8**
no transfusion: asymptomatic, no comorbidities, Hgb >7

Risks to Transfusions

- transfusion related reactions (immune-related or by blood itself):
  - acute: fever, chills, hives, itching—treat DPH+APAP, can be more severe resp distress, hypotension
  - delayed: presents days-weeks later as hemolysis
- transfusion-associated circulatory overload (TACO): fluid overload; 1 unit PRBC = 300mL; watch HF, chase with furosemide
- iron overload (after 10-20 transfus) when stores saturated, remain unbound; monitor serum ferritin, organ function; sx: fatigue, darkskin, anthralg, hepatomeg, cardiomyo, endocr
  - chelation therapy indicated when >20 RBC or ongoing transfusions, serum ferritin >2500 (target <1000) - deferoxamine SC, deferasirox PO qd, deferiperone

Benefits to Transfusions

- rapid increase in Hgb and Hct (1 unit PRBCs = ↑Hgb 1, Hct 3%)
- rapid improvement in symptoms; increased overall survival

Erythropoietin (EPO)

- **stimulates RBC production**; EPO hormone produced in kidney/liver, levels increase with decreased hemoglobin
- **indications**: **Hgb <10** (anemic), **dx cancer** (with CKD, or palliative, or myelosupp ct), **receiving chemo** for >2mo

epoetin alfa: HL 16-67h **darbepoetin alfa**: HL 74h (22-144h) - peak effect of Hgb increase 2-6 weeks

Principles of Dose Titrations

goal to maintain lowest level of Hgb to avoid RBC transfusions
- Hgb reaches level needed to avoid transfusion **OR** increases > 1g/dL in any 2 week period = reduce dose (dose reduction based on product used)
- Dc after 8 weeks if no response or transfusion dependent or 6 weeks after chemotherapy completed to ensure bone marrow recovery

Dosing guidelines for epoetin and darbepoetin in adults

	Three times weekly dosing	Weekly dosing
Epoetin alfa		
Starting dose (adults):	150 units/kg SC three times weekly	40,000 units SC
Reduce dose by 25% if:	Hemoglobin reaches a level needed to avoid transfusion or increases >1 g/dL in any two-week period.	
Withhold dose if:	Hemoglobin exceeds a level needed to avoid RBC transfusion; restart at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required.	
Increase dose:	To 300 units/kg SC three times weekly if response is not satisfactory (rise in hemoglobin <1 g/dL after four weeks of therapy and it remains below 10 g/dL) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion.	To 60,000 units SC weekly if response is not satisfactory (rise in hemoglobin <1 g/dL after four weeks of therapy and it remains below 10 g/dL) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion.
Discontinue if:	After completion of the chemotherapy course, or if after eight weeks of therapy, there is no response as measured by hemoglobin levels or transfusions are still required.	
	Weekly dosing	**Once every three weeks dosing**
Darbepoetin alfa		
Starting dose (adults):	2.25 microgram/kg SC once weekly	500 micrograms SC every three weeks
Reduce dose by 40% if:	Hemoglobin exceeds a level needed to avoid transfusion or increases >1 g/dL in any two-week period.	
Withhold dose if:	Hemoglobin exceeds a level needed to avoid RBC transfusion; restart at 40% below the previous dose when the hemoglobin approaches a level where transfusions may be required.	
Increase dose:	To 4.5 microgram/kg if response is not satisfactory (no reduction in transfusion requirements or rise in hemoglobin <1 g/dL after six weeks of therapy in the absence of RBC transfusion) to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for RBC transfusion.	N/A
Discontinue if:	After completion of the chemotherapy course, or if after eight weeks of therapy, there is no response as measured by hemoglobin levels or transfusions are still required.	

Titration for Response *exam

epoetin alfa

Hgb reaches level needed to avoid transfusion **OR** increases > 1g/dL in any 2 week period → **reduce dose by 25%**

Hgb does not increase by ≥ 1g/dL **AND** Hgb < 10g/dL after 4 weeks, follow dose titration increase

initial (Hgb <10):	150 units/kg TIW	40,000 units weekly
titration for NR:	300 units/kg TIW	60,000 units weekly

darbepoetin alfa

Hgb reaches level needed to avoid transfusion **OR** increases > 1g/dL in any 2 week period → **reduce dose by 40%**

Hgb does not increase by ≥ 1g/dL **AND** Hgb < 10g/dL after 6 weeks, follow dose titration increase

initial (Hgb <10):	2.25 mcg/kg weekly	500mcg q3wk
titration for NR:	4.5 mcg/kg weekly	N/A

No direct conversion ratio; data from anemia in CKD General: epoetin 2-3x/wk → darbepoetin qwk epoetin weekly → darepoetin q2wk

Transferrin saturation **TSAT** = (serum iron level) x100/TIBC

Iron Replacement with ESAs

absolute iron deficiency (depletion of total iron stores)
- Ferritin <30 AND TSAT <20% "low" → replace iron (PO/IV), reevaluate 4 weeks

functional iron deficiency (iron stores insuff, bioavail iron for erythroblast low)
- Ferritin 30-500 AND TSAT <50% → start ESAs, consider IV iron replacement

IV iron: many different products available on market; products are not interchangeable; not all approved for same indications; dosing variability between products can cause hypersensitivity, anaphylaxis or delayed reactions; evaluate need for test dose; monitor patients during and > 30 minutes post infusion

ESA Risks (BBWs): thromboembolism, increased mortality, tumor progression

ESA Benefits: transfusion avoidance, gradual improvement in anemia symptoms, effective (Hgb ↑≥1 in 65% cancer pt), maintenance of Hgb with repeat admin

VTE risk factors: hx prior VTE, heritable, hypercoagulability, elevated prechemo plt count, HTN, steroids, nonambulatory, recent surgery, lenalidomide, hormones

Increased Mortality/Tumor Progression: decreased OS but all trials used high target of Hgb >12
- still have these risks, but more benefit with lower Hgb targets

ESAs Final Recommendations

Discuss risks vs. benefits of ESAs over transfusions with patients

Initiate only if **Hbg ≤ 10g/dL** prior to therapy: studies showed fewer VTE and reduced morality; keep patients on lowest effective dose to avoid transfusions

Avoid in patients with high risk of VTE

Use only for recommended indications: patients receiving chemotherapy, palliative treatment

Decision to use for highly symptomatic anemia and Hbg 10-12 g/dL, based on clinical judgement, risk vs. benefits, patient preference

Myelodysplastic Syndrome (MDS)

- cancer caused by bone marrow making poorly formed blood cells (causes cytopenias Plt RBCs WBCs); can evolve to acute leukemias

causes: alkylating agents (cyclophos), etoposide, radiation; median dx 70-79yo, multicomorbid

goals: delay disease progression to acute leukemia, reduce RBC transfusions, improve qol

MDS treatment groups (risk strat)
- low-risk groups: transfusion support (PRBCs/platelets)
- low-int groups + sx anemia: **hematopoetic growth factor (ESA+/-GCSF)**; DNA hypomethylating, immunosupp/modulating
- mod-high groups: DNA hypometh, intensive chemo, alloHCT

ESAs **do not delay** progression to acute leukemia (only **help with sx anemia**, erythroid response rates of 40-60%)
- **best response seen with EPO level <500 units/L**; RBC transfusion requirement low (<2unit/mo)
- **goal to achieve Hgb 10-12**
- **less incidence of VTE, HTN, decreased survival than CIA**

Patients who refuse blood transfusions: reduce blood loss; consider daily folic/b12/iron; investigational blood substitutes IND-FDA

Biosimilars: only approved for same FDA indication as substitution; minor differences in inactive components (protein/aas), no diff efficacy, safety
- epoetin alfa-epbx (Retacrit) equivalent to epoetin alfa and darbepoetin alfa; however, not interchangeable

Summary

Anemia in cancer has a complex pathophysiology: malignancy, chemotherapy, other causes of anemia

Treatment of anemia is multifactorial

Weigh the risk vs. benefits of how and when to treat anemia: transfusion goals; use of ESAs

Future prospective trials needed to better evaluate risks associated with ESAs in cancer patients; overall survival and tumor progression

Consider: curative vs. non-curative (palliative), symptomatic anemia, PMH
- thresholds for starting (Hgb <10 ESA, Hgb <8 transfusion); may consider if highly symptomatic anemia Hgb 10-12
- get iron labs (ferritin <30 TSAT <20% replace iron; ferritin >30 TSAT <50% start ESA, consider IV iron)
- follow up: titration schedules for ESAs based on Hb rise in 2 weeks; iron continue if ferritin <500 and TSAT <50%

Management of Neutropenia and Thrombocytopenia

filgrastim (Neupogen)
G-CSF: stimulate the production, maturation, and activation of neutrophils to increase both their migration and cytotoxicity
- start 24-72hrs after the last dose of chemo - discontinue post-nadir, when ANC >500 and maintains; at least >14 days
5mcg/kg qday until ANC >500 (SC preferred, IV central line flush D5W) - if patient received pegfilgrastim, do not administer daily filgrastim
SE: ostealgia (bone pain long bones) treat with cetir/lorat, stop when ANC maxed; rotate injection site

pegfilgrastim (Neulasta)
G-CSF: stimulate the production, maturation, and activation of neutrophils to increase both their migration and cytotoxicity
- administered once per chemotherapy cycle until neutrophil recovery (ANC> 500); on-body injector
longer half-life compared to filgrastim secondary to its molecular size; serum concentration decreases as ANC increases maybe due to less renal elim
cannot repeat within 12 days of last dose; but >15 days can give chemo then next dose; wait 15 days for pegfilgrastim
SE: ostealgia (bone pain long bones) treat with cetir/lorat, stop when ANC maxed

sargramostim (Leukine)
GM-CSF: stimulates proliferation, differentiation, and functional activity of neutrophils, monocytes/macrophages, platelets, eosinophils, RBCs
250mcg/m2 qday (SC/IV flush NS)
SE: bone pain, fever, HA, muscle soreness

Neutropenia Management

Primary Prophylaxis
prior to **first** chemo cycle in patients with solid tumors and non-myeloid malignancies, risk assess chemo regimen
febrile neutropenia risk
- **high (>20%) → G-CSF prophylactically to prevent febrile neutropenia**
- int (10-20%) → G-CSF if ≥1 **risk factor** consider G-CSF
- low (<10%) → none

****risk factors** >65yo full chemo intensity, CrCl <50 (renal), Tbili>2 (liver), prior chemo/rad, persistent neutropenia, bone marrow involve, recent surgery/wounds

Secondary Prophylaxis
present with febrile neutropenia
- patients who received prophylactic daily filgrastim → continue G-CSF
- patients who received prophylactic long-lasting pegfilgrastim → no additional G-CSF
- patients who **did not** receive prophylaxis → consider therapeutic GM-CSFs if **risk factors** present for an infection-associated complication

****risk factors**: >65yo, sepsis syndrome, ANC <100, neutropenia expected >10days, pneumonia, invasive fungal, hospital at time of fever, prior FN episode, infect

Thrombocytopenia

due to radiation, cytotoxic agents
longer timeline than neutropenia: nadir 7-14 days after chemo, recovery over 14-28 days
Treatment: platelet transfusion as needed; delay admin of chemo
- platelets <10k risk of spontaneous bleeding, need platelet transfusion
- platelets >10k and active bleeding, need platelet transfusion

romiplostim (Nplate), eltrombopag (Promacta)
thrombopoietin peptide mimetic increases platelet counts in ITP by binding to and activating human TOP receptor (only FDA approved for non-cancer)

For your exam there will be one case to follow along to answer 9 questions.
Determining prophylactic CSF use 24hrs after chemo; the % will be given for low/int/high risk initial management
Determining whether a patient meets criteria to receive CSF now that are febrile neutropenic event, where they did not receive CSF after chemo

Memorize the patient risk factors needed (≥ 1 risk factor) to start CSF in a patient who received intermediate risk chemotherapy (slide 35).
Memorize slide 39 - know the risk factors for developing infection related complications. This will be needed in a patient case scenario where they did not receive CSF after their chemotherapy because either they received low risk (<10%) chemotherapy or intermediate risk (10-20%) chemotherapy with no risk factors and now have a neutropenic febrile event. Whether they can now receive CSF – (therapeutic use Slide 38) will depend on whether they have any of the risk factors listed on slide 39.

Management of Neutropenic Fever

Study Guide

Definition of

fever: single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period

neutropenia: ANC <500 ANC <1000 predicted to <500 over next 48hrs ANC <100 profound ANC <100 for 7 days prolonged (normal 2000-5000 cells/mm3)

Neutropenia timeline: **start** falls within 5-7 days of chemo **nadir** 7-10 days **recovery** 14-21 days

- duration of neutropenia lasts >14 days post-chemo for hematoloic malignancy (leukemia/lymphoma/BMT); lasts <7 days for solid tumors (lower incidence)

Given a patient case be able to:

Calculate the ANC, formula given.

ANC= [WBC (K/mm3) x (% segs + % bands) x 1000]/100 = [0.8x(5%+5%)x1000]/100 = 80

Determine the **MASCC** score, table given. **≥21 low risk** **<20 high risk**

Burden of febrile neutropenia (look for no/mild/moderate symptoms, hemodynamic stability)
No hypotension (SBP >90)
No active COPD
Solid tumor or no previous fungal infection (either one)
No dehydration requiring parenteral fluids (look for IV 0.9% NaCl bolus)
Outpatient status (where being treated? ED admitted to ICU)
Age <60yo (look for age)

TABLE 1. The Multinational Association for Supportive Care in Cancer (MASCC) Score

Characteristic	Weight
Burden of febrile neutropenia	
No or mild symptoms	5
Moderate symptoms	3
No hypotension (SBP > 90 mm Hg)	5
No active COPD	4
Solid tumor or no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age < 60 years	2

Outpatient vs. inpatient risk factors:

Low risk (outpatient): MASCC ≥21, solid tumor, anticipated neutropenia <7 days, no hemodynamic instability
High risk (inpatient): MASCC <21, hematologic malignancy or HCT, anticipated neutropenia ≥7 days

Empiric antimicrobials Low risk (outpatient): MASCC ≥21, solid tumor, anticipated neutropenia <7 days, no hemodynamic instability

amox-clav MSSA, CoNS, S. pneum, E. coli, S. pyog
levoflox MSSA, CoNS, S. pneum, E. coli, Pseudomonas
moxiflox MSSA, CoNS, S. pneum, E. coli
ciproflox CoNS, E. coli, Pseudomonas (good for renal failure) amox-clav + cipro combo covers gram negatives

Empiric antimicrobials High risk (inpatient): MASCC <21, hematologic malignancy or HCT, anticipated neutropenia ≥7 days

cefepime gram positive, gram negative, Pseudomonas (no anaerobic coverage, could add metronidazole; no CoNS)
pip-tazo gram positive, gram negative, Pseudomonas + ANAEROBIC COVERAGE (for anaerobic coverage, needed if a GI component-severe mucositis, abdom pain)
meropenem gram positive, gram negative, Pseudomonas + ANAEROBIC COVERAGE (reserved if history ESBL or MDR gram negative organisms)
vancomycin added if:

- CVC infection at site
- hemodynamically unstable (hypotensive, tachycardia, poor capillary refill time = peripheral vasoconstriction = septic shock)
- MRSA suspected bacteremia/pneumonia or fulminant severe pneumonia
- gram positive blood culture while waiting for susceptibility test
- cellulitis

metronidazole: DOC anaerobic coverage
vancomycin: DOC for MRSA, resistant CoNS, virdians, enterococcus linezolid: vanco-resistant VRE
gentamicin: hx MDRO, amikacin if genta-resistant

Duration
skin and soft tissue at least 5-14 days gram positive bacteremia 7-14 days (S. aureus 4 weeks from first negative culture) gram negative bacteremia 10-14 days bacterial pneumonia 5-14 days
consider removing central venous access device (if S. aureus, P aeruginosa, Corynebacterium, Acinetobacter, Bacillus, VRE, MDRO, fungi) bacterial sinusitis 7-14 days
Dur no mem: Until ANC >500, Resolution of signs and symptoms, Negative blood cultures, At least 7-14 days of anti-biotic therapy from first negative culture

Add empiric **antifungal** agent when neutropenic and febrile **≥4 days** from first fever

- need antifungal agent with excellent mold coverage (aspergillus)–voriconazole, posaconazole, isavuconazole, amphotericin B
- fluconazole good candida, but no mold - micafungin primarily for candida if suspected resistance to azole - amphoB usually avoid due to toxicity profile

Oncologic Emergencies

Tumor Lysis Syndrome

Who's at risk: ALL, NHL-Burkitt, SCLC; risk factors large tumor burden, high sensitivity to chemo, high proliferation rate

Pathophys:

Abnormality	**Onset**	**Symptoms**
↑K hypercalcemia >5.5	6-72h	lethargy, muscle weakness, paresthesia, bradycardia, EKG lethal cardiac arrhythmias, syncope, sudden death
↑PO4 hyperphos >4.5	24-48h	NVD, lethargy, seizure activity, oliguria, anuria, azotemia, ARF, exacerbation of renal compromise
↓Ca hypocalcemia <8.6	24-48h	muscle cramps, tetany, paresthesias, arrhythmias, syncope, sudden death, seizures
↑UA hyperuricemia >7.0	24-48h	NV, lethargy, acute uric acid nephropathy, sudden death, seizures
↑SCr/BUN renal failure	48-72h	oliguria, NV, lethargy, fluid overload, edema, CHF, seizures

Diagnosis: Cairo-Bishop Criteria (UA ≥8, K ≥6, P ≥4.5, Ca ≤7 or a 25% change from baseline)

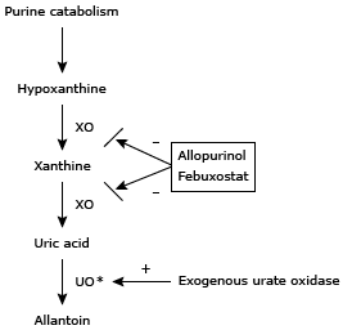
Grade	0	1	**2**	3	4	5
SCr	≤1.5x ULN	1.5x ULN	**>1.5-3.0x ULN**	>3.0-6.0x ULN	>6.0x ULN	Death
Arrhythmia	None	No intervention	**Nonurgent intervention**	Symptomatic uncontrolled	Life-threatening	Death
Seizure	None	-	**brief, generalized; controlled with meds**	altered conscious; poorly controlled	prolonged, repetitive difficult to control	Death

Risk Stratification

	Low Risk	**Intermediate Risk**	**High Risk**
Factor	<1% develop TLS	1-5% develop TLS	>5% develop TLS
Malignancy	most solid tumors, myeloma, indolent lymphomas, CML	DLBCL, SCLC	Burkitt's lymphoma, lymphoblastic lymphoma, most acute leukemias ALL
Baseline UA	<7.5	<7.5	>7.5
Baseline WBC	<25k	25-100k	>100k or bulky tumor
Baseline LDH	<2x ULN	>2x ULN	>2x ULN
Prophylaxis	monitoring hydration +/- allopurinol	monitoring hydration + allopurinol	monitoring hydration + rasburicase

Treatment: **hydration**, electrolyte management, allopurinol, rasburicase, dialysis
- fluids and hydration: improves intravasc volume, renal perfusion, glomular filtration; decrease risk of hyperkal arrythmias, may require diuretics
- **maintain urine output 80-100ml/m2/hr**; IV 5%dex/0.45%NS or NS; may require diuretics; always consider cardiac function

Hyperuricemia



allopurinol

use: intermediate risk of TLS; reduces obstructive uropathy incidence, ↓UA levels 90%
dose: starting 12-24h prior to chemo; 300mg qday or bid (high risk); renal adjust CrCl <20
duration: until normalization of uric acid and other labs; tumor burden decreases to low criteria
limitations: does not reduce already-formed uric acid (may take several days)
- increases conc of xanthine and xanthine oxidase metabolites (can precipitate)
- decreases clearance of certain chemo (mercapto, azathioprine, HD-MTX)

rasburicase

use: decreases uric acid levels, including those already formed, within 4hrs; use in pt not candidates for allopurinol, high risk
- recomb urate oxidase catalyzes oxidation of UA into soluble metabolite allantoin

dose: 0.2mg/kg/day IV staring day before or on chemo; but clinically see 3-6mg IV (no difference in normalization at 24-48hrs compared to wt-based)
duration: depends on efficacy of uric acid reduction; may require repeat daily dosing until uric acid normalizes
prophylaxis: prevention in high-risk (ALL, high tumor burden, elevated baseline labs); give 4hrs prior to chemo; shown effective at maintaining normal UA
limitations: G6PDH-deficiency (risk hemolysis; nonwhites); contraindicated preg/bf; risk of hypersens with each use; degrades uric acid in blood samples; $cost

Alkanize Urine? Not recommended to use for prophylaxis or treatment; risks metabolic alkalosis, Ca-Phos precipitation

Electrolyte Management
- treat each metabolic abnormality as it is identified; may require intensive care setting

HyperUA: IV fluids and Loop diuretics prn + allopurinol +/- rasburicase
Hyperkal: IV fluids and Loop diuretics prn mild <6: SPS severe ≥6: SPS, IV calc gluc, dextrose/insulin, sodium bicarb, dialysis
Hyperphos: oral phosphate binders (aluminum hydroxide, calcium acetate, sevelamer, lanthanum); restrict dietary phos 800-1000mg/day
Hypocalc: usually after hyperphos corrected; for sx pt only (IV calc gluconate if tetany, arrhyth, delium, seizures)

TLS Monitoring
- prior to chemo (baseline): UA Phos K Ca LDH SCr urine output
- first 72hrs after chemo: UA Phos K Ca SCr q6h; rasburicase UA 4hrs after dose
- goals: avoid need for dialysis, minimize morbidity/mortality

Hypercalcemia

epidemiology: 20-30% cancers (decreasing d/t bisphos use; lung, breast, heme); nonmalig causes: primary hyperthy, med, renal
pathophys: ↑calcitriol, ↑bone resorption, ↑PTHrP, ↓renal Ca elimination, bone metastases (BLT kosher pickle: breast lung thyroid kidney prostate)
  normal calcium homeostasis: absorption = elimination
etiology: humoral most common by parathyroid-hormone-related protein (PTHrP) stimulates osteoclasts in bone marrow; local osteolytic by cytokines/PTHrP
s/s
  mild: renal (polyuria, polydipsia), GI (const, anorexia), neurologic (fatigue)
  mod: renal (dehydration), GI (NV), neurologic (lethargy, confusion, muscle weak, lost reflexes), cardiac (shortened QT, widened T)
  severe: renal (decreased GFR, nephrocalcinosis), neuro (seizures, stupor, coma), cardiac (EKG, heart block, arrhythmias, asystole)
corrected calcium = serum calcium + 0.8(4 - serum Albumin) normal Ca = 8.5-10.5 mg/dl [ex serum Ca=13.5, serum Alb = 2.4, corrected Ca 14.8)
degree of hypercalcemia: mild <12 mod 12-14 severe >14 patient specific age, performance status, comorbid renal, tumor sites
treatment
  Ca <12 mild sx: counsel to drink 3L/day; repeat calcium level in 4 weeks moderate sx: consider alternate cause
  Ca >12 rehydrate with 0.9%NS IV and administer bisphosphonate
    Ca 12-14 or no life-threatening sx: zoledronic acid 4mg or pamidronate 60 to 90mg
    Ca >14 or severe sx: zoledronic acid 4mg or pamidronate 60mg to 90mg (same shit)

IV bisphosphonates
pamidronate, zoledronic acid
Inhibit osteoclast activity through induce direct osteoclast apoptosis and inhibit differentiation and maturation; Affinity for hydroxyapatite
Decreasing bone resorption, Increasing mineralization, Concentrate at active bone remodeling sites, Decrease skeletal morbidity by a third
Tx:
Calcium >12 mg/dl
  hydration: hyperhydration and forced diuresis with loops; lowers calcium by 1.6-2.4 in 12-24hrs; reduces calcium more quickly than bisphosphonates
  ZA superior for treatment of mod-severe hypercalcemia; can repeat 7 days later (ZA usually renal dosed; but for this always use 4mg IV over 15 minutes)
Calcium >14 and/or life-threatening sx
  hydration
  zoledronic acid
  calcitonin: tachyphylaxis after 48 hours (auto-stop); used for severe sx or high Ca after bisphos use

Treatment Comparison

	Onset	**Duration**	**Severity**	**MoA**
0.9% NS	min-hrs	duration of infusion	mild (asx/sx)-severe	dilutes Ca, improves renal elim
Loop diuretics	hrs	duration of therapy	mod-severe	increase urinary Ca excretion
Bisphosphonates	24-72 hrs	2 to 4 weeks	mild (sx)-severe	blocks bone resorption
Calcitonin	4-6 hrs	48 hours	severe (arrythmias)	blocks bone resorption and increases urinary Ca excretion

Monitoring
  48 hrs: calcium normal-send pt home; calcium high-maintain hydration, continue monitoring
  day5-7: calcium normal-send pt home; calcium high-repeat bisphosphonate on day 7, add calcitonin; repeat 48hr and day 5-7 monitoring
  calcium refractory to bisphosphonates: consider second agent: corticosteroid, phosphates, denosumab
    phosphates: 1-3g in div doses; MoA drives Ca into tissues; use: mild hyperCa with normal/low PO4; caution mod-severe hyperCa, N, induce metastic calc, diarr
    denosumab: 120mg SC monthly; MoA RANKL inhibitor; use: patients refractory to other treatments

Chronic management: ZA 4mg IV over 15min monthly PA 90mg IV over 2-4hrs monthly (risk for ADEs increases with repeated doses)

Skeletal Related Events (SREs)

Normal bone: consant remodeling; osteoclast/blast balance
Bone in cancer: tumor cells secrete cytokines and growth factor, increased RANKL, increased osteoclasts, increased bone resorption
  - breast, prostate, myeloma, lung, kidney - usually metastasizes to axial skel; can be lytic or blastic lesions

Fracture: risk factors
Women with breast cancer, bone mineral density score < -2.5, AI use, age >65 yo, OCS > 6mo, BMI < 20, FH of hip fracture, Hx fracture before age 50, smoking
Men with prostate cancer: androgen deprivation therapy

Bone Metastases: Treatment (Goal - Palliation of symptoms)
Radiation, Chemotherapy, Radioisotopes (Radium-223), IV Bisphosponates (Agents: zoledronic acid and pamidronate; Delay time to first SRE by 50%)
- zoledronic acid must **renal** dose adjust*; 4mg IV over 15-30min q3-4wk supplement Ca500-VitD400; for solid tumor bone metastis and MM (only OS myeloma)
- pamidronate 90mg IV over 2-4hr q3-4wk; slight dose adjust SCr>3 or CrCl <30 consider slower inf; for bone metastases in myeloma and breast cancer
- denosumab (Xgeva) 120mg sc q4wk for bone metases from solid tumors; should correct hypocalc prior; supplement calcium-vitD daily; no renal adj

ADEs
- osteonecrosis of the jaw (ONJ); caused by dental/hygiene; monthly bisphos risk; IV>PO higher risk; zoledronic=denos>PA
- renal dysfunction: zole>pami; not rec'd CrCl <30
- hypocalcemia denosumab>ZA; always be on calcium-vitD supplement
- bone pain, nausea, diarrhea, fatigue

Duration: for 2 years, may go longer; restart if new SRE develops

Nausea and Vomiting

Review risk factors for chemotherapy – induced nausea and vomiting (CINV) and types of CINV
Evaluate studies determining CINV prophylactic regimens
Discuss appropriate prophylactic and breakthrough options for patients

Classification	Definition (Emesis)
Acute	Occurring <24 hours after initiation of chemo; peaks after 5-6hrs
Delayed	Occurring >24 hours after initiation of chemo; (days 2 to 5)
Breakthrough	Occurring on day of treatment despite appropriate antiemetic prophylaxis
Anticipatory	Learned response to the occurrence of CINV in previous cycles
Refractory	Recurring in subsequent cycles of therapy, excluding anticipatory CINV

Level	Emetogenic Potential	% with Emesis
4	High (HEC)	>90%
3	Moderate (MEC)	>30 to 90%
2	Low	10 to 30%
1	Minimal	0 to <10%
based on drug with highest emetic risk		

Risk factors, Patient-related: younger, female, no/minimal prior history of alcohol use, prior CINV, expectations of developing CINV
Risk factors, Treatment-related: chemotherapy dose, schedule and route of administration, *intrinsic emetogenicity of chemotherapy, repeated cycles of chemo
Pathophys:
acute: peripheral pathway—chemo kills enterochromaffin cell of GI tract, serotonin release, acts on 5HT3 receptors then CINV
delayed: central pathway—medulla oblongata in brain, substance P released from vagus binds to NK-1 (neurokinin-1) receptors and induces NV

Pharmacologic Options
Serotonin Antagonists (ondansetron, granisetron, dolasetron, palonosetron) NK-1 Antagonists (aprepitant/fosaprepitant, netupitant-palonosetron, rolapitant)
Dopamine Antagonists (metoclopramide, haloperidol) Phenothiazines (prochlorperazine, promethazine) Glucocorticoids (dexamethasone)
Benzos (lorazepam, alprazolam) Antihistamines (scopolamine, dimenhydrinate) Cannabanoids (dronabinol, nabilone) olanzapine ginger

5HT3 Antagonists
PK: palonosetron 3mg/kg IV HL 40hrs (higher binding affinity;stays in body 3 days; maybe inhibit substance P) ondansetron 0.15mg/kg IV HL 4hr
1st generation (ondansetron, granisetron, dolasetron) considered therapeutically equivalent
palonosetron 0.25 mg IV is indicated for: prevention of acute CINV (MEC/HEC) and delayed CINV (MEC)
Prevention, not treatment!

NK-1 Antagonists
aprepitant (PO/IV-less inf rxn) and fosaprepitant (IV) are indicated for: prevention of acute CINV (MEC/HEC) and delayed CINV (MEC/HEC)
netupitant-palonosetron and rolapitant included in NCCN and ASCO guidelines: prophylaxis for HEC, prophylaxis for MEC (NCCN only)
Prevention, not treatment!

Recommendations for Prophylaxis

Level	Emetogenic Potential	% with Emesis	
4	High (HEC)	>90%	NK1-RA + 5HT3-RA + dexamethasone +/- olanzapine
3	Moderate (MEC)	>30 to 90%	dexamethasone + 5HT3-RA
2	Low	10 to 30%	prochlorperazine or dexamethasone or metoclopramide or 5HT3-RA
1	Minimal	0 to <10%	no prophylaxis required
based on drug with highest emetic risk			

Breakthrough: IV/PO/PR: dexamethasone, prochlorperazine, metoclopramide, diphenhydramine, lorazepam, haloperidol, promethazine, ondansetron, dronabinol

Determining Emetogenic Risk
Risk classifications: HEC, MEC, low, minimal
Single-agent chemo regimen: based on drug's emetic risk
Multi-agent chemo regimen: based on drug with highest emetic risk:
mod: oxaliplatin+5FU+leucovorin high: cisplatin+etoposide high: anthracycline+cyclophos (exception)

General Principles
Schedule doses of antiemetics throughout the period CINV risk; breakthrough meds should be available, additional agent from a different class prn; use ATC PR/IV
Select appropriate antiemetic therapy corresponding to emetogenic potential of chemo given each day of a regimen (i.e. **antiemetic therapy may need to be increased or reduced depending on the individual chemotherapy agents that are administered each day**.) Example – TIP, MVAC, EPOCH

Acute phase: Grade 1 vomiting or Grade 2 nausea with last cycle? escalate acute prevention to next risk level; may change 5HT3 to palonosetron
Delayed phase: Grade 1 vomiting or Grade 2 nausea with last cycle? assess compliance with meds; escalate delayed prevention to next risk level; change 5HT3 to palonosetron; if breakthrough medication worked, schedule it around the clock x 3-4 days and provide patient with different rescue agent; add lorazepam (anxiety); add PPI or H2 blocker (reflux)

Summary/Pearls
Scheduled doses of antiemetics should be available throughout the period of CINV, with breakthrough meds if needed
CINV: easier to prevent than treat, may intensify across cycles; nausea remains a bigger problem than vomiting
Antiemetic efficacy - PO and IV have similar efficacy
Aprepitant drug interactions (inhibits CYP 3A4, induces 2C9)
QTc warnings with IV ondansetron and IV dolasetron
Consider alternate causes of nausea/vomiting
Assessment on subsequent cycles is the key to success

Critical Care: Exam 5

https://www.uptodate.com/contents/evaluation-of-and-initial-approach-to-the-adult-patient-with-undifferentiated-hypotension-and-shock

Intro to Critical Care and ICU

Recognize role of pharmacist on critical care team
Define and assess key aspects for all critically ill patients
Review ICU pharmacology focus on vasopressor, neuromuscular blockers and ICU sedatives

FASTHUG – **F**eeding, **A**nalgesia, **S**edation, **T**hromboembolic Prevention, **H**ead of Bed Elevation, Stress **U**lcer Prophylaxis, **G**lucose Control

Feeding

- Consequences of malnutrition
  - Impaired immune system function, Increased Infections
  - Poor wound healing
  - Increased decubitus ulcers
  - Disruption to GI Microbiota
  - Nutrient losses in stool
- Feed Early if hemodynamically stable: Initiate enteral nutrition within 24-48 hours; In well nourished adults wait 7 days to initiate TPN

Analgesia and Sedation

↓ • Anxiety • Ventilator dyssynchrony • Disloding lines or devices
↑ • Prolonged ventilator requirements • Inability to assess patient • Unable to mobilize patient • Delirium

Thromboembolic Prevention

- Venous Thromboembolism (VTE) common serious complications: Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE)
- ~10% of hospital deaths attributed to PE
- Virchows Triad for Risk
  – Surgery – Trauma – Immobility – Malignancy – Age – Heart or Respiratory failure – Obesity – Smoking – Central Venous Catheters
- Heparin 5000 units Subcutaneous (SQ) q8h
- Enoxaparin 40 mg SQ q24h
- Enoxaparin 30 mg SQ q12h high risk
- Mechanical Methods: Intermittent Pneumatic Compression, Venous foot pumps

Head of Bed Elevation

- Reduce incidence of, Gastroesophageal reflux, Nosocomial Pneumonia, Aspiration of gastric contents and Pneumonitis

Stress Ulcer Prophylaxis

- Not all patients need stress ulcer prophylaxis: consider low Plt, high INR, PTT; mechanical ventilation >48hrs, hx GI, trauma brain/SC, burn; nsaids or antiplatelets
- Primary pharmacotherapy Agents: H2 Antagonists IV/NG/PO (Famotidine, Ranitidine); Proton Pump Inhibitors IV/NG/PO (Typically only daily)
- Inhibiting Gastric Acid Secretion HAS risks: Bacterial overgrowth, Pneumonia, Clostridioides Difficle

Glucose Control

- Hyperglycemia in ICU patients increase Morbidity & Mortality: Decrease wound healing, Increased infection risk, Impaired GI Motility, Risk Acute Kidney Injury
- Hypoglycemia increase risk of mortality
- Target glucose between 100-180 mg/dl
- Management: Sliding scale regular insulin typically ever 6 hours if NPO; Insulin infusion for glucose > 200 mg/dL

Receptors and Action

α1	blood vessels	vasoconstriction glycogenolysis, gluconeogen	↑SVR ↑MAP
α2	presyn neuron smooth muscle	negative feedback constriction inhibits insulin release, induce glucagon	α2a ↓SVR ↓HR α2b ↑SVR ↓HR
β1	heart blood vessels	chronotropy/inotropy vasodilation	↑CO ↑HR
β2	lungs blood vessels	bronchodilation vasodilation	↓SVR
D1 D2	kidney blood vessels	↑UOP vasodilation	↓SVR
vasopressin	blood vessels	vasoconstrict, Na-H2O retention, ↑cortisol	↑SVR
angiotensin II	blood vessels	vasoconstrict, aldosterone release	↑SVR

Vasopressors

epinephrine 0.005-0.02 mcg/kg/min >0.05 mcg/kg/min	mixed α β more β1 β2 more α1 α2	 ↑chronotropy/inotropy vasoconstriction
norepinephrine	α1 α2 primarily (some β1 β2)	vasoconstriction ↑chronotropy/inotropy
phenylephrine	α1 α2	vasoconstriction
vasopressin	vasopressin	vasoconstriction
dopamine 1-5 mcg/kg/min 5-10 mcg/kg/min 10-20 mcg/kg/min	 D1 D2 β1 β2 α1 α2	 ↑UOP ↑chronotropy/inotropy vasoconstriction
angiotensin II	angiotensin II	vasoconstriction; ↑Na ↓K, thrombosis

Vasopressors						
	DA	**α1**	**β1**	**β2**	**Other**	
dopamine*	+++++	+++	++++	++		2.5-20 mcg/kg/min
epinephrine*		++++	++++	+++		0.02-1 mcg/kg/min
norepinephrine*		+++++	+++	++		0.02-3.3 mcg/kg/min
phenylephrine		+++++				0.5-9 mcg/kg/min
vasopressin					V1 V2 agonism	0.01-0.04 units/min
angiotensin II					ATII agonism	5-30 ng/kg/min (up to 80 for 3h); lower if ACEi, won't work ARB
Inotropes						
dobutamine		+	++++	++		2.5-20 mcg/kg/min
milrinone					$PDE_{3/4}$ inhibitor	0.25-0.75 mcg/kg/min

*higher doses more α1 activity **DA** selective vasodilation (renal) **α1** vasoconstriction **β1** chronotropy/inotropy **β2** vasodilation

Vasopressor Adverse Effects

- hypertension tissue necrosis, acute renal failure
- ischemia: cardiac, mesenteric, decreased peripheral perfusion
- epinephrine, norepinephrine, dopamine: tachycardia, hyperglycemia
- angiotensin II: hypernatremia, hypokalemia, thrombosis
- dopamine: decreased peristalsis
- arrythmias: dopamine >> Epi/NE > phenylephrine/vasopressin (unsure arrhythmia potential ATII)

IV Inotropes

dobutamine	↑HR	- MAP	↑CO	-/↓SVR
milrinone	-/↑HR	-/↓MAP	↑CO	↓SVR

dobutamine
MoA: β1 β2 α1 agonist to increase cAMP
Dosing 2-10 mcg/kg/min (max 20 mcg/kg/min)
HL 2-3min Metabolism: plasma clearance
ADEs: tachyarrhythmia, hypotension, eosinophilia (rare)
considerations: concomitant beta-blocker therapy

milrinone
MoA: PDE3 inhibitor to increase intracellular Ca; also works in vascular so SVR
Dosing: 0.2-0.5 mcg/kg/min (max 0.75 mcg/kg/min)
HL 1-3hrs Metabolism: renal
ADEs: tachyarrhythmia, hypotension, thrombocytopenia
considerations: delayed onset, prolonged HL in renal dysfunction

Neuromusclar Blockers
• Facilitation of procedures (endotracheal intubation) • Facilitation of mechanical ventilation (decrease airway pressures, lessen risk of barotrauma)
• Decrease O2 consumption (status epilepticus) • Tetanus • Management increased intracranial Pressure

Depolarizing: succinylcholine
Non-depolarizing: benzylisoquinolinium structure (atracurium, cisatracurium); aminosteroidal structure (pancuronium, pipercuronium, rocuronium, vecuronium)

succinylcholine
Use for facilitation of ET intubation only
Dose 1 mg/kg IV
Onset 15-30 sec; Duration 5-10 min
Contraindicated Burn, trauma, hyperkalemia
Adverse Effects: Muscle weakness and fasciculation, ↑Intraocular & intracranial pressure, Tachycardia, Hyperkalemia, Malignant Hyperthermia

Non-depolarizing – won't cause Hyperkal, but slower onset (~1min)
- all neuromuscular blockers cause muscle weakness, myalgia, neuropathies with long use
pancuronium Tachycardia, hypertension CAD; potential ADR in renal or liver failure
vecuronium Bradycardia; potential ADR in renal or liver failure
rocuronium Minimal BP changes ; potential ADR in severe liver failure
atracurium Histamine release
cisatracurium Minimal histamine release

Reversal: sugammadex (modified cyclodextrin that encapsulates rocuronium and vecuronium); also neostigmine AChE inhibitor

propofol
Produces sedation without amnesia nor analgesia
Onset 1-2min, quick offset, HL 26-32hrs
Available as 10% lipid emulsion, 1.1kcal/ml
Dosing 5-80 mcg/kg/min or 0.4-5 mg/kg/hr (OR up to 200mcg/kg/min)
ADRs: Respiratory depression, Decreased Cardiac output and BP, hypertriglyceridemia, pancreatitis, Infections – Change Lines and bottle every 12 hours

Propofol-Related Infusion Syndrome (PRIS): mortality to 80% if not recognized quickly
PRIS clinical manifestations: ARF, Bradyarrhythmias, Cardiac arrest, Dyslipidemia, Hypotension, Myocardial failure, Rhabdomyolysis, Severe metabolic acidosis
Risk factors: Dosages > 83 mcg/kg/min (5 mg/kg/hr) especially >48 hours; Concomitant catecholamine or glucocorticoids; <18yo; Inborn error in mitochondrial fatty acid ox; Ketogenic

dexmedetomidine (Precedex)
MoA: α2 agonist, produces cooperative sedation and analgesia; 7-8x more specific than clonidine
ADR: Hypotension, bradycardia, hypertension*, Nausea, vomiting, Heart block
No respiratory depression
Onset 5-30min HL 2-3hr; labeled for <24h in ICU (Load 1mcg/kg, maint 0.2-1.5 mcg/kg/hr)

ketamine
Non-barbiturate anesthetic & analgesic
Blockade: N-methyl-D-asparate (NMDA) receptor, nicotinic acetyl-choline receptors, L-type calcium channels, Hyperpolarization-activated cyclic nucleotide channel (HCN1)
•↑ Glutamate, NE, Dopamine, Cortical Ach (but ↓Pontine Ach)
Onset 1-2min; Duration 5-10min; HL 2-4hrs
Hypnosis (Blockade NMDA , HCN1), Dissociative Anesthesia/Phychotomimesis, Status Asthmaticus
Dosing procedures/anesthesia – IV Bolus 1-2 mg/kg; IM 4-6 mg/kg – Continuous infusion 0.5-2 mg/kg/hr
Dosing adjunctive Bolus 0.2-3 mg/kg (typically up to 2 mg/kg except SE) • Infusion 0.2-2 mg/kg/hr (except SE up to 8-10 mg/kg/hr)
ADEs: Emergence reactions, hallucinations, hypertension, tachycardia, lacrimation, salivation, Increased intracranial pressure, may cause apnea with high dose rapid, nystagmus, apnea with rapid high dose administration

etomidate
Ultra short activing non-barbiturate anesthetic; Produces hypnosis without analgesia - use for procedures
Onset 10-20 seconds, duration 4-10 minutes Dose 0.2-0.3 mg/kg
ADEs: Myoclonus, may decrease seizure threshold, tachycardia but little or no decreases in BP or cardiac output, decrease cortisol in dose dependent manner

prothrombin complex concentrate (PCC)
Factor IX complex prepared from human plasma with blood factors II, VII, IX, and X
3-Factor vs 4-Factor; Varying amounts of Factor VII Approved for use in hemophilia B
Kcentra (4-factor) approved for emergent warfarin reversal
Dose based on INR for warfarin reversal: INR<4 25 units/kg INR 4-6 35 units/kg INR>6 50 units/kg *Use factor IX units when dosing
Dose for factor Xa inhibitor reversal is 25-50 units/kg

DOAC reversal agents
idarucizumab: targets dabigatran; dose 5g; ADEs thrombosis, Ab production
andexanet alfa: targets apix, betrix, edox, rivarox; dosing; ADEs thrombosis, immune rxns
ciraparantag: targets DOACs, LMWH, UFH, fondaparinux; binds heparins, Xainh, direct thrombin inh; (phase 2 trials)

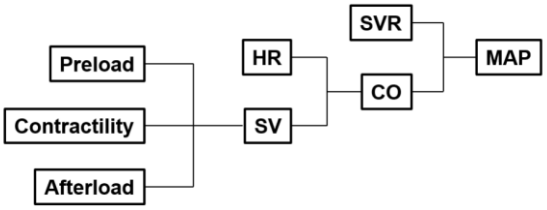
P2Y12 inhibitors
clopidogrel, prasugrel, ticagrelor, cangrelor
cangrelor: IV*, 30mcg/kg LD, 4mcg/kg/min 2hr then 0.75mcg/kg/min; time to 50% platelet inhibition 2min*, offset 60min*, reversible*, max inhib 95%*

Glycoprotein IIb/IIIa inhibitors
eptifibatide: peptide, renal elim (CI dialysis); dose bolus 180mcg/kg x2 then IV gtt 2mcg/kg/min x18-24h (CrCl <50 1mcg/kg/min); HL 1.5h, revers, 9-11% bleeding
tirofiban: nonpeptide, renal elim (dose adj); dose bolus 25mcg/kg over 3min, IV gtt 0.15 mcg/kg/min up to 18hr (CrCl <60 0.075), HL 2hrs, revers, 10-12% bleeding

Hemodynamics and Management of Shock

Define hemodynamics and shock
Identify invasive and non-invasive options for monitoring hemodynamics
Utilize hemodynamic parameters to differentiate between types of shock
Create general treatment recommendations for each type of shock (vasopressor pharmacology, septic shock and cardiogenic shock will be covered in more detail in other lectures)

hemodynamics: physiology of blood circulation; purpose is oxygen delivery and waste removal
shock: oxygen supply does not meet demand; lack of adequate perfusion to the tissues; often associated with hypotension (SBP <90 or MAP <70)



MAP = CO*SVR product of cardiac output and systemic vascular resistance.
i.e. BP is the product of our cardiac function and blood vessel tone
CO = HR*SV product of HR and volume ejected by the heart
Stroke Volume is impacted by preload, afterload, contractility
Preload volume in ventricle at end of diastole just prior to systole
CVP preload right side volume status: measured by central venous catheter (normal 2-8 mmHg, goal for fluid resus 8-12-15 mmHg)
PCWP preload left side volume status: (normal 6-12)
Afterload: resistance the left ventricle has to overcome to eject blood volume into aorta; controlled by vasoconstriction and vasodilation
SVR: for left heart: pressure LV has to pump against
PVR: for right heart: pressure RV has to pump against
Contractility (aka inotropy) and HR (aka chronotropy)
- increase in preload = increased contractility (exception in HF where SV for a given preload is less than a normal heart)
  - inotropic agents used to increase contractility and increase SV for given preload
Altternatives to CO
- mixed venous oxygen saturation (ScVO2): if oxygen supply insufficient or demand is increased, ScVO2 is decreased, body on last leg
- central venous oxygen saturation (ScvO2)

MAP	Mean Arterial Pressure (mean BP) MAP = (1/3 SBP) + (2/3 DBP)	70-100 mmHg
SV	Stroke Volume (from LV per beat) SV = CO/HR	60-130 mL/beat
CO	Cardiac Output CO = SV*HR	4-8 L/min/m^2
CI	Cardiac Index CI = CO/BSA	2.5-4 L/min/m^2
CVP	Central Venous Pressure (Preload R)	2-8 mmHg
PCWP	Pulmonary Capillary Wedge Pressure (Preload L)	6-12 mmHg
RAP	Right Arterial Pressure	2-6 mmHg
RVP	Right Ventricle Pressure	15-25 mmHg
PAP	Pulmonary Artery Pressure	10-22 mmHg
SVR	Systemic Vascular Resistance (Afterload L, pressure LV has to pump against) SVR = 80*(MAP-CVP)/CO SVR ≅ MAP/CO	800-1200 dyn*s/cm^5
PVR	Pulmonary Vascular Resistance (Afterload R, pressure RV has to pump against) PVR = 80*(mPAP-PCWP)/CO	150-250 dyn*s/cm^5
PaO_2	partial pressure O_2	90 mmHg
SaO_2	oxygen saturation	98%
pCO_2	partial pressure CO_2	40 mmHg (arterial)
$ScVO_2$	mixed venous oxygen saturation	
$ScvO_2$	central venous oxygen saturation	

Noninvasive Hemodynamic Monitoring
Mental status Urine output BP HR RR Pulse oximetry Capillary refill Skin temperature Skin color Skin turgor Transthoracic echocardiogram (TTE)

Invasive Hemodynamic Monitoring
Serum lactate Transesophageal echocardiogram (TEE) Arterial line Central venous catheter Pulmonary artery (PA) catheter (Swanz-Ganz catheter)

Initial Resuscitation (VIP method) - early resuscitation is crucial to prevent organ failure
Ventilate: admin oxygen to restore oxygen delivery
Infuse: fluid resuscitation to restore BP and oxygen transport; to improve overall blood flow and increase cardiac output
Pump: vasoactive drugs to restore cardiac output (reserved for persistent hypotension despite adequate fluid resus)

Fluid Resuscitation

Benefits: Maintain intravascular volume; Maintain blood pressure and allow adequate delivery of oxygen to tissues
Risks: Peripheral and/or pulmonary edemal Can result in decreased cardiac output or longer time receiving mechanical ventilation
General resuscitative goals: MAP > 65 mmHg, Urine output > 0.5 mL/kg/hr, Improved mentation, Reduction in lactate
Prolonged expansion of the **intravascular** resuscitation is key
D5W never since it's hypotonic, leads to increase in intracellular shift of fluid rather than intravascular
slide 28: lacted ringers and plasmalyte contain lower NaCl content than normal saline NS; colloids such as 5% albumin in NS contains significant NaCl load
crystalloid vs. colloid (crystalloid usually agent of choice due to SAFE trial and SALT trial)
75% of NS distributes extravascularly, leading to increased edema albumin 60bucks a bag, NS a dollar
albumin however contains large molecules that don't diffuse outside of vasculature and maintains more osmotic pressure to keep volume intravascularly
crystalloids: NS, Lactated Ringers, Plasmalyte
colloid: 5% albumin in NS, 6% Hetastarch Lactate

epinephrine 0.005-0.02 mcg/kg/min >0.05 mcg/kg/min	mixed α β more β1 β2 more α1 α2	 ↑chronotropy/inotropy vasoconstriction
norepinephrine	α1 α2 primarily (some β1 β2)	vasoconstriction ↑chronotropy/inotropy
phenylephrine	α1 α2	vasoconstriction
vasopressin	vasopressin	vasoconstriction
dopamine 1-5 mcg/kg/min 5-10 mcg/kg/min 10-20 mcg/kg/min	 D1 D2 β1 β2 α1 α2	 ↑UOP ↑chronotropy/inotropy vasoconstriction
angiotensin II	angiotensin II	vasoconstriction; ↑Na ↓K, thrombosis

Vasoactive Medications

Vasopressors						
	DA	**α1**	**β1**	**β2**	**Other**	
dopamine*	+++++	+++	++++	++		2.5-20 mcg/kg/min
epinephrine*		++++	++++	+++		0.02-1 mcg/kg/min
norepinephrine*		+++++	+++	++		0.02-3.3 mcg/kg/min
phenylephrine		+++++				0.5-9 mcg/kg/min
vasopressin					V1 V2 agonism	0.01-0.04 units/min
angiotensin II					ATII agonism	5-30 ng/kg/min (up to 80 for 3h); lower if ACEi, won't work ARB
Inotropes						
dobutamine		+	++++	++		2.5-20 mcg/kg/min
milrinone					$PDE_{3/4}$ inhibitor	0.25-0.75 mcg/kg/min

*higher doses more α1 activity **DA** selective vasodilation (renal) **α1** vasoconstriction **β1** chronotropy/inotropy **β2** vasodilation

Dopamine SOAP II trial: higher mortality with dopamine vs. NE
- remember that doses must be maximized before alpha-agonist effect can take place (which means beta-agonist effect is gonna be maximized); could lead to tachyarrh and mortality
*Dopamine: beta-agonist effect is gonna be maximized before the alpha-agonist effect can take place

Shock States

Shock results from four potential (not necessarily exclusive) pathophysiologic mechanisms:
- Hypovolemic (16%): Hemorrhagic, Non-hemorrhagic
- Distributive (66%): Septic, Anaphylactic, Neurogenic
- Cardiogenic (16%)
- Obstructive (2%)

Hypovolemic Shock

- most common shock syndrome post-trauma
- decreased circulatory volume (preload): invasive monitoring CVP or PCWP

Types: 1.Hemorrhagic: volume loss secondary to blood loss (trauma, surgery, GI bleed, anticoag tox) 2.Nonhemorrhagic: intravascular volume depletion (dehydra, burns, pancreatitis)

Management of hemorrhagic shock
- identify source of bleed; treat coagulopathies (platelets, fresh frozen plasma FFP, cryoprecipitate, reversal agents)
- volume resuscitate: crystalloids in immediate phase; packed red blood cells for blood loss
- vasopressors to maintain MAP ≥60 mmHg

Distributive Shock (Vasodilatory)

- most common shock state; septic shock accounts for 94% of distributive shock cases

Types: 1. Septic 2. Anaphylactic 3. Neurogenic

Extremely vasodilated so decreased SVR (afterload)

1. Septic shock

pathogen: dysregulated host response to infecting organism (maldistr of blood flow) - infection host expression of inflamm mediators then extreme vasodilation, capillary leak
- early goal directed therapy: UOP >0.5, MAP >65, CVP 8-12 - fluid resuscitation: 30ml/kg of crystalloid septic shock 40% inhospital mortality
- vasopressors if hypotension persists, to maintain MAP >65: norepi 1st-line, vasopressors or epi 2nd
- empiric antimicrobial therapy: within 1st hour of presentation; antibacterial +/- antifungals and antivirals

2. Anaphylactic shock

pathogen: IgE-mediated hypersens rxn; rapid-onset cardio collapse, manifest in mins (edema, flush, rash, hypo, bronchospasm); common offenders: abx, anesth, contrast dye, beesting
- 1st-line: epi 0.3-0.5 IV or IM stat; fluid resuscitation; if persistent hypotension give epi infusion to maintain MAP ≥65
- supportive care: antihistamine (DPH/famot), steroids to reduce 2nd phase sx (occur 1-8hrs, 1-2mg/kg methylpred qd); albuterol for bronchospasm

3. Neurogenic shock

pathogen: injury to SC above 6th thoracic vertebrae, decreased autonomic output; results in vasodilation, bradycardia, hypotension
- fluid resuscitation; vasopressors to maintain BP if refractory to fluids; specific BP goals not defined (suggest MAP 85-90); atropine for sx bradycardia

Cardiogenic Shock

- hypoperfusion due to cardiac failure ("cold" subtype (i.e. shock) but may be "wet" or "dry"); may coexist with other shock syndromes

pathogen: acute MI, end-stage cardiomyopathy or HF, valvular heart disease, myocarditis, arrhythmia
- decreased cardiac function (contractility or HR)

Monitor: noninvasive (hypo despite fluid, ECHO, fluid overload, edema); invasive (PCWP, CVP, CO, ScVO2)

Management: dependent on cause and subtype of HF
- early and definitive restoration of coronary blood flow cold/wet subtype: inotrope + diuresis cold/dry subtype: inotrope +/- fluid resuscitation
- when inotropes fail, epi, norepi, or mechical circ device (ECMO or intra-aortic balloon pump)

Obstructive Shock

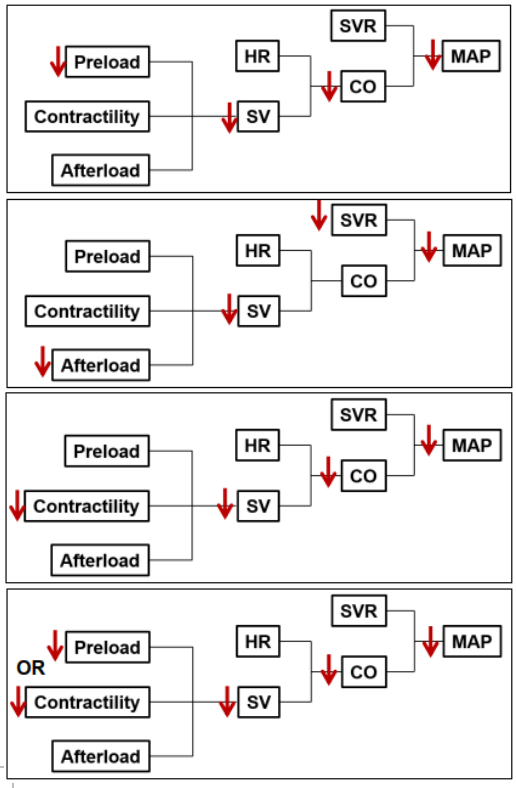
- result of extra-cardiac obstruction (may cause impaired cardiac filling or contraction)

pathogen: pulmonary embolism, cardiac tamponade, tension pneumothorax
- obstruction of flow in cardiovascular circuit with decreased cardiac function # PCWP↑ for impaired diastolic filling PCWP ↓or— for impaired systolic contraction

Monitor: invasive generally not required (PCWP, CVP, CO, ScVO2)

Management
- cardiac tamponade: pericardiocentesis, drainage
- tension pneumothorax: fine needle decompression
- pulmonary embolism: heparin infusion with or without thrombolysis or embolectomy

Hemodynamic Management Review



	MAP	CVP	PCWP	CO	SVR	
Hypovolemic	↓	↓	↓	↓	↑	
Distributive	↓	↓	↓	↑↓	↓	
Cardiogenic	↓	↑	↑	↓	↑	
Obstructive	↓	↑	#	↓	↑	

↓ Low Values	**Hemodynamic Parameter**	**↑High Values**
volume expansion	CVP/PCWP—preload	diuresis or venodilators
vasopressors	SVR/PVR—afterload	arteriovasodilators
positive inotropes	CO/CI—inotropy/contractility	negative inotropes
positive chronotropes	HR—chronotropy	negative chronotropes

Hemodynamic Parameter	CVP/PCWP preload	SVR/PVR afterload	CO or CI inotropy/contractility	HR chronotropy
↓ Low Values	volume expansion	vasopressors	positive inotropes	positive chronotropes
↑High Values	diuresis or venodilators	arteriovasodilators	negative inotropes	negative chronotropes

	MAP	CVP	PCWP	CO	SVR	
Hypovolemic	↓	↓	↓	↓	↑	
Distributive	↓	↓	↓	↑↓	↓	
Cardiogenic	↓	↑	↑	↓	↑	
Obstructive	↓	↑	#	↓	↑	

Sepsis and Septic Shock

Outline the pathophysiology, definitions, and diagnosis of sepsis
Discuss current guidelines and evidence based recommendations for therapy management
Develop a patient care plan for patients with septic shock
AMS – altered mental status, GCS – Glasgow Coma Scale, qSOFA – quick sequential organ failure assessment, SOFA – sequential organ failure assessment, SIRS – systemic inflammatory response syndrome

Sepsis 2—2012	Sepsis 3—2016
sepsis: the presence of infection together with systemic manifestations of infection [known/suspected infection + two SIRS criteria]	**sepsis:** life-threatening organ dysfunction caused by a dysregulated host response to infection [known/suspected infection + qSOFA ≥2 or change in SOFA ≥2]
severe sepsis: sepsis and sepsis-induced tissue hypoperfusion or organ dysfunction [sepsis + SBP <90 or signs of end organ damage]	
septic shock: sepsis induced hypotension persisting despite adequate fluid resuscitation resulting from marked reduction in systemic vascular resistance [sepsis + hypotension requiring vasopressors or lactate >4]	**septic shock:** a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [sepsis + hypotension requiring vasopressors or lactate >2]

SIRS Criteria (≥2 criteria for SIRS dx): **Temp** >38°C or <36°C, **HR** >90 bpm, **RR** >20, **WBC** >12k or <4K or >10% immature bands
qSOFA Criteria (≥2 criteria greater risk of poor outcomes): **SBP** <100 mmHg, **RR** >22, **AMS** mental status
SOFA Score (categories 0-4): **Respiration** (PaO2/FIO2), **Coagulation** (Platelets), **Liver** (bilirubin), **Cardio** (MAP, vasopressors), **CNS** (GCS score), **Renal** (SCr, UOP)

Treatment: fluid resuscitation, antimicrobial therapy, vasopressors, steroids

Fluid Resuscitation
IV fluid resuscitation is initiated to stabilize sepsis-induced tissue hypoperfusion
- at least 30ml/kg IV crystalloid fluid in first 3 hours
- target MAP 65
- resuscitated with goal of normalizing lactate
- avoid hydroxyethyl starches

Consider the 5 D's of fluids (drug, dose, duration, de-escalation, drug) and ROSE (resuscitation, optimization, stabilization, evacuation)
4 phases of therapy: ROSE (sine wave)
resuscitation (minutes) [net-positive]: 1st hit: shock; early goal-directed fluid management; early administration of fluid boluses
optimization (hours) [net-neutral): 2nd hit: ischemia + reperfusion; organ rescue, guided fluid boluses
stabilization (days) [net negative-neutral]: 2nd hit: cont'd; organ support, late conservative fluid management
evacuation (weeks) [net negative]: 3rd hit: global increased permeability syndrome; late goal-directed fluid removal

Antimicrobials
Early administration of appropriate antibiotics is associated with mortality benefit
- obtain cultures prior to antimicrobial therapy (but do not delay administration of antibiotics)
- give empiric broad spectrum coverage for likely source of infection using one or more IV antimicrobials
- daily assessment to de-escalate therapy when appropriate

Source control in sepsis
most common sources of infection: pulmonary, intra-abdominal, urinary tract
most common pathogens: gram-positive (Staph aureus, Strep pneumoniae); gram-negative (E. coli, Klebs, Pseudomonas); fungal infections

Vasopressors
For refractory hypotension, vasopressors may be added to titrate to a goal measuring perfusion.
- norepinephrine is the first choice of vasopressor
- vasopressin or epinephrine may be added to norepinephrine to achieve MAP goals
- dopamine may be used in bradycardic patients with a low risk of tachyarrhythmias (low-dose dopamine should not be used for renal-protection)

	α1	β1	β2	Other	Pearls (*higher doses more α1 activity)
dopamine*	+++	++++	++	Dopamine	associated with more arrhythmia than NE, useful in bradyarrhythmias
epinephrine*	++++	++++	+++		2nd-line vasopressor, may cause increase in lactate level
norepinephrine*	+++++	+++	++		1st-line vasopressor for most patients
phenylephrine	++++++				pure alpha-activity, may be useful in patients with tachyarrhythmias
vasopressin				V1 V2 agonism	2nd-line vasopressor, administered fixed rate (0.03-0.04 unit/min) for septic shock

Steroids
The addition of steroids in septic shock may help to modulate adequate patient response.
- may be considered for patients with hemodynamic instability despite IV fluid resuscitation and vasopressors
- if indicated, use hydrocortisone 200 mg IV daily (often administered as 50 mg IV every 6 hours)

Stress-dose steroids
Benefits: shock reversal, shorter LOS (ICU/hosp), decreased vasopressor requirements; may have mortality benefit and/or reduced time on ventilator
Risks: hyperglycemia, hypernatremia, infection, delirium, neuromuscular weakness
When do we add them?
Do we need fludrocortisone?

PADIS

Understand the etiology of pain, agitation, and delirium in the critically ill population
Describe key principles and goals of analgesia and sedation management
Analyze available agents for pain, agitation, and delirium in the critically ill
Design an appropriate regimen based on patient specific characteristics in the critically ill
ICU triad: pain, agitation, delirium

Table 1

Pain

Should a protocol-based (analgesia/analgosedation) pain assessment and management program be used in the care of critically ill adults when compared with usual care?
Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered (Good Practice Statement).
We suggest using an assessment-driven, protocol-based, stepwise approach for pain and sedation management in critically ill adults.
Should acetaminophen be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?
We suggest using acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill adults.
Should ketamine be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?
We suggest using low-dose ketamine (1–2 μg/kg/hr) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU.
Should a neuropathic pain medication (gabapentin, carbamazepine, pregabalin) be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?
We recommend using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for neuropathic pain management in critically ill adults.
We suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids for pain management in ICU adults after cardiovascular surgery.
We suggest not routinely using a COX-1 selective NSAID as an adjunct to opioid therapy for pain management in critically ill adults.
We suggest using an opioid, at the lowest effective dose, for procedural pain management in critically ill adults.

Agitation/sedation

Does light sedation (vs deep sedation), regardless of the sedative agent(s) used, significantly affect outcomes in critically ill, mechanically ventilated adults?
We suggest using light sedation (vs deep sedation) in critically ill, mechanically ventilated adults.
We suggest using propofol over a benzodiazepine for sedation in mechanically ventilated adults after cardiac surgery.
We suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults.

Delirium

Should we assess for delirium using a valid tool (compared with not performing this assessment with a valid tool) in critically ill adults?
Critically ill adults should be regularly assessed for delirium using a valid tool (Good Practice Statement).
Should a pharmacologic agent (vs no use of this agent) be used to "prevent" delirium in critically ill adults?
We suggest not using haloperidol, an atypical antipsychotic, dexmedetomidine, a HMG-CoA reductase inhibitor (i.e., statin), or ketamine to prevent delirium in all critically ill adults.
Should a pharmacologic agent (vs no use of this agent) be used to "treat subsyndromal delirium" in all critically ill adults with subsyndromal delirium?
We suggest not using haloperidol or an atypical antipsychotic to treat subsyndromal delirium in critically ill adults.
Should a pharmacologic agent (vs no use of this agent) be used to treat delirium in all critically ill adults with delirium?
We suggest not routinely using haloperidol, an atypical antipsychotic, or a HMG-CoA reductase inhibitor (i.e., a statin) to treat delirium.
We suggest using dexmedetomidine for delirium in mechanically ventilated adults where agitation is pre-cluding weaning/extubation.
Should a multicomponent, nonpharmacologic strategy (vs nosuch strategy) be used to reduce delirium in critically ill adults?
We suggest using a multicomponent, nonpharmacologic intervention that is focused on (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults. Remarks: These multicomponent interventions include (but are not limited to) strategies to reduce or shorten delirium (e.g., reorientation, cognitive stimulation, use of clocks), improve sleep (e.g., minimizing light and noise), improve wakefulness (i.e., reduced sedation), reduce immobility (e.g., early rehabilitation/mobilization), and reduce hearing and/or visual impairment (e.g., enable use of devices such as hearing aids or eye glasses).
For critically ill adults, is rehabilitation or mobilization (performed either in-bed or out-of-bed) beneficial in improving patient, family, or health system outcomes compared with usual care, a different rehabilitation/mobilization intervention, placebo, or sham intervention?
We suggest performing rehabilitation or mobilization incritically ill adults.
Should noise and light reduction strategies (vs not using these strategies) be used at night to improve sleep in critically ill adults?
We suggest using noise and light reduction strategies to improve sleep in critically ill adults.
Should a sleep-promoting medication (i.e., melatonin, dexmedetomidine, or propofol) (vs no use of medication) be used to improve sleep in critically ill adults?
We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults.
We make no recommendation regarding the use of dexmedetomidine at night to improve sleep.
We suggest not using propofol to improve sleep in critically ill adults.

Table 2

Pain

What are the most reliable and valid pain assessment methods to use in critically ill adults?
Self-report scales: A patient's self-report of pain is the reference standard for pain assessment in patients who can communicate reliably. Among critically ill adults who are able to self-report pain, the 0–10 numeric rating scale administered either verbally or visually is a valid and feasible pain scale.
Behavioral pain assessment tools: Among critically ill adults unable to self-report pain and in whom behaviors are observable, the BPS and BPS-NI patients and the CPOT demonstrate the greatest validity and reliability for monitoring pain.

Agitation/sedation

In critically ill intubated adults, is there a difference between DSIs vs NP-targeted sedation in the ability to achieve and maintain a light level of sedation?
In critically ill intubated adults, DSIs and NP-targeted sedation can achieve and maintain a light level of sedation.
Remarks: A DSI or a spontaneous awakening trial is defined as a period of time, each day, during which a patient's sedative medication is discontinued and patients can wake up and achieve arousal and/or alertness, defined by objective actions such as opening eyes in response to a voice, following simple commands, and/or having a Sedation-Agitation Scale score of 4–7 or a Richmond Agitation-Sedation Scale score –1 to +1. NP-targeted sedation is defined as an established sedation protocol implemented by nurses at the bedside to determine sedative choices and to titrate these medications to achieve prescription-targeted sedation scores.

Delirium

For the following risk factors, strong evidence indicates that these are associated with delirium in critically ill adults:
1) Modifiable: benzodiazepine use and blood transfusions
b) Nonmodifiable: greater age, dementia, prior coma, pre-ICU emergency surgery or trauma, and increasing Acute Physiology and Chronic Health Evaluation and Anesthesiology scores
What are the short- and long-term outcomes of delirium in critically ill adults and are these causally related?
Positive delirium screening in critically ill adults is strongly associated with cognitive impairment at 3 and 12 mo after ICU discharge and may be associated with a longer hospital stay.
Delirium in critically ill adults has consistently been shown not to be associated with posttraumatic stress disorder or post-ICU distress.
Delirium in critically ill adults has not been consistently shown to be associated with ICU length of stay, discharge disposition to a place other than home, depression, functionality/dependence, or mortality.
What risk factors that exist prior to the onset of critical illness affect sleep quality in critically ill adults in the ICU?
Patients who report poor-quality sleep and/or use of a pharmacologic sleep aid at home are more likely to report poor-quality sleep in the ICU.

Pain

causes: endotracheal tube, vascular access, procedures, underlying illness/injury, rolling/moving patient, immobilization
consequences: suffering, increased stress response, chronic pain, PTSD< impaired wound healing

Assessment Tools
Numerical Pain Scale
Behavioral Pain Scale (**BPS**): goal 0 to 3
Critical Care Pain Observation Tool (**CPOT**): goal 0 to 2 mainstay in ICU
--none of scales take into account vital signs in ICU, since many other reasons why the could change

Pain Management
multimodal: multiple mechanisms, opioid sparing
pharmacokinetics: rapid acting, short duration, accumulation
administration: enteral vs. IV, patches, continuous vs. intermittent

Treatment Options
opioids mainstay therapy: SE resp depression, decreased gastric motility, sedation, hypotension, GI upset
multimodal agents: APAP, epidurals, gabapentin, lidocaine, NSAIDs, ketamine
analgosedation: analgesia-based sedation regimen (pain treated first)
- allows intermittent dosing (preferred over CI to allow for drug clearance, prevention of accumu/over sedation)

oxycodone 3-6 hrs	continuous: n/a intermittent: 5-15 mg PO q4-6h	IR tablets can be crushed and put down NGT good enteral option
fentanyl 15-30 min	continuous: 50-200 mcg/hr intermittent: 25-100 mcg IVP q15-60min	accumulation in hepatic impairment, chest wall rigidity can use in true morphine allergy; tachyphylaxis occurs @ ~200-300 mg/hr
hydromorphone 2-3 hrs	continuous: 0.2-2 mg/hr intermittent: 0.2-1 mg IVP q1-2h; 2-4mg PO q4-6h	accumulation in renal and hepatic impairment therapeutic option in morphine/fentanyl tolerance
morphine 3-5 hrs	continuous: 2-10 mg/hr intermittent: 2-4 mg IVP q1-2h; 10-20 mg PO q4-6h	accumulation renal impairment (typically not used in ICU) **histamine** release results in increased **hypotension**, itchiness, rash

acetaminophen	PO: 325-1000 mg q4-6h IV: 650-1000 mg q4-6h	max 4000 mg/day reduce dose in hepatic impairment and elderly ≥65yo
gabapentin	PO: 100-300 mg TID, then 300-1200 mg TID	renal dose adjust SE drowsiness, dizziness, altered mental status
ketamine	bolus: 0.1-0.5 mg/kg infusion: 0.05-0.4 mg/kg/hr	hallucinations, hypertension analgesic + sedative
NSAIDs	ibuprofen: 200-800 mg PO q3-6h (max 2400 mg/day) ketorolac: 15-30 mg IV q6h (max 5 days)	avoid renal impairment and GI bleed contraindicated post-CABG

Example first line PRN opioid regimens could include: oxycodone 5-10mg per tube every 4 hrs as needed or hydromorphone 0.2-0.5mg IVP every 2 hrs as needed or fentanyl 25-50mcg IVP every 2 hrs as needed.
Example regimens may be fentanyl or hydromorphone continuous infusion plus midazolam or lorazepam continuous infusion titrated to goal RASS of -4 to -5

Agitation

causes: pain, lines/tubes, delirium, hypoxemia, sleep disturbances, withdrawal
consequences: increased cost, anxiety/PTSD, ventilator dyssynchrony, delirium, dislodging lines, harm

Richmond Agitation Sedation Scale (RASS) gold standard for assessing agitation/sedation; where where +4 combative, -5 unarousable
light sedation = RASS -2 to +1 preferred goal for critically ill, mechanically ventilated patients
deep sedation = RASS -4 to -5 preferred goal for ventilator dyssynchrony, paralytics, status epilepticus, intracranial pressure management
Sedation Light vs. Deep: *"We suggest using light sedation (vs deep sedation) in critically ill, mechanically ventilated adults."*
- study: light sedation leads to ↓mortality, ↓time on ventilator, ↓delirium, ↓hospital stay
- study: Spontaneous Awakening Trial (SAT): ↓time on ventilator, ↓ICU length of stay, ↓hospital length of stay
  - daily interruption of sedative and analgesic agents to assess patients

+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

benzos: amnesia, anticonvulsion, anxiolysis, sedation, hypotension, respiratory depression
propfol: amnesia, anticonvulsion, anxiolysis, sedation, hypotension, respiratory depression
dexmed: analgesia, sedation, hypotension, bradycardia
ketamine: amnesia, analgesia, anticonvulsion, sedation, hypertension, tachycardia, respiratory depression

Sedative Agents: Benzos
Risks: ↑risk of delirium, ↑duration of mechanical ventilation, ↑ICU/hospital length of stay - wouldn't be first-line sedation
Place in therapy: status epilepticus, alcohol withdrawal, deeper sedation (i.e. paralytics, ventilator dyssynchrony), chronic medication, hemodynamic instability

midazolam* 1-2 hrs	continuous: 1-10 mg/hr intermittent: 1-2 mg IVP q2h	accumulation in renal and hepatic impairment
lorazepam 6-8 hrs	continuous: 0.5-6 mg/hr intermittent: 1-2 mg IVP/PO q2h	propylene glycol toxicity (with CI and higher doses)
diazepam 2-8 hrs	continuous: n/a intermittent: 5-10 mg IVP/PO q6-8h	accumulation in renal and hepatic impairment quick onset, long acting (active metabolite)

Sedative Agents: Non-Benzos

dexmedetomidine	continuous: 0.2-1.5 mcg/kg/hr	bradycardia, hypotension, heart block light sedation/*no resp depression (no ventilation needed); *no delirium
ketamine	continuous: 0.5-2 mg/kg/hr	hallucinations, hypertension analgesic + sedative
propofol* quick onset short dur	continuous: 5-80 mcg/kg/min	hypotension, hyperTGs, resp depress, PRIS (prop-rel infusion syndrome) quick onset, short duration; lipid emulsion; must be ventilated

Overview of Agitation Management
Implement non-pharmacologic interventions (bed positioning, day-night cycles, etc.)
Identify and correct underlying cause (pain, sleep disturbances, delirium, etc.)
- Treating pain first is the most important when addressing agitation (analgosedation, analgesic-based sedation regimen)

Target light sedation with lowest effective dosages & minimal benzodiazepines

Delirium

hyperactive: irritable, angry, restless, combative/violent, uncooperative, nightmares, inappropriate behavioral response (i.e. laughter)
hypoactive: lethargic, apathetic , depressed, anorexia, sleep pattern disturbances, altered speech/mental status, decreased alertness/awareness

causes: pain, lines/tubes, immobility, ICU environment, sleep/wake disturbances, withdrawal, medications, procedures
medications associated with delirium: benzos, anticholinergics, corticosteroids
complications: increased length of stay and costs, increased agitation + long-term cognitive deficits, increased mortality, increased duration mechanical ventilation

CAM-ICU: Confusion Assessment Method for the ICU Flowsheet
- assessment of the CAM-ICU takes into account these four components of the definition of delirium:
1. acute changes/fluctuating mental status 2. inattention (letters) 3. altered level of consciousness (RASS level) 4. disorganized thinking (questions)

Nonpharm Management and Prevention
- treat underlying cause or disease - daily spontaneous awakening, breathing trials
- early mobilization -optimize senses (glasses, hearing aids, etc.)
- sleep hygiene - optimization of analgesic and sedative agents

Pharmacologic Management
Antipsychotics: SGAs: quetiapine, risperidone, olanzapine FGAs: haloperidol ("There is no evidence that treatment with haloperidol reduces duration of delirum.")

	Dosing	QTc	Sedation	Anticholinergic
haloperidol	2-5 mg IV q4h prn	moderate	low	low
olanzapine	2.5-10 mg PO QD	low	moderate	moderate
quetiapine	12-5-100 mg PO BID	low	moderate	moderate
risperidone	0.25-1 mg PO/ODT BID	low	low	low

Pharmacologic management probably doesn't play a role in preventing/treating/reducing duration of delirium in patients with ***hypoactive*** delirium.

Delirium Take Home Points
Prevention is key: nonpharmacologic interventions are first line
No medications have shown to reduce duration or prevent delirium; however, may be beneficial in **hyperactive** delirium to prevent harm

Key Points
- Opioids are considered mainstay in ICU to treat pain, however, a multimodal approach should be utilized to spare opioids
- Target light sedation in mechanically ventilated critically ill patients unless indication for deep sedation is present
- Treating the underlying cause for agitation or delirium (i.e. pain) should be addressed first prior to initiating sedatives
- Minimize benzodiazepine use as they increase ICU delirium, duration of mechanical ventilation, and ICU length of stay
- No medication evidence to support use in the prevention/treatment of delirium; however, there may be a role in hyperactive delirium

NMBA

Understand the indications for continuous neuromuscular blockade in critically ill patients
Select an appropriate neuromuscular blocking agent based on patient's end-organ function
Understand the implications of neuromuscular blockade use on sedation choices
Identify monitoring parameters for continuous neuromuscular blockade

Indications for Neuromuscular Blockade in ICU

- Facilitate procedures – Endotracheal intubation with rapid sequence intubation (RSI)
- Optimize mechanical ventilation in refractory hypoxemia – Acute Respiratory Distress Syndrome (ARDS)
- Prevent shivering in Therapeutic hypothermia
- Prevent muscle spasms in tetanus
- Reduce intracranial pressure (ICP)

Classification of NMBAs

- Type of blockade – Depolarizing vs Non-Depolarizing
- Chemical structure – ACh derivative, aminosteroidal, benzylisoquinolinium compound
- Duration of action

Depolarizing NMBA: succinylcholine

- Use only as one time dose (usually for intubation)
- Short acting – Onset: 15-30 seconds – Duration: 5-10 minutes
- Dose 1 mg/kg IV
- Contraindications – Hyperkalemia – Burn – Crush injury – Denervating injuries/diseases (ie, spinal cord injury)
- Adverse Effects – Muscle weakness and fasciculation – ↑intraocular & intracranial pressure – Hyperkalemia
  - Malignant Hyperthermia (treatment: dantrolene)
    - Rare genetic predisposition – Precipitated by succinylcholine or inhaled anesthetic – Rapid muscular rigidity, high fever – Cardiac ischemia, ventricular arrhythmias

Non-Depolarizing NMBA

- Can be used as one time doses for intubation or as continuous infusions
- Sequence of paralysis: – Ocular – Digits – Abdominal muscles – Diaphragm
- Agent selection is based on drug pharmacokinetics, end-organ function, adverse effects, and cost
  - Aminosteroidal – Pancuronium – Vecuronium – Rocuronium
  - Benzylisoquinolinium – Atracurium – Cisatracurium

	Dosing	Elimination	HL min	Metab	Adverse Effects	Cost	Avoid Use In
pancuronium	LD 1, 1-2 mcg/kg/min	renal hepatic	100-300	Yes	Histamine release, Vagolytic, Tachycardia, HTN	$	CAD, liver/renal dysfunction
vecuronium	LD 1, 1-2 mcg/kg/min	renal hepatic	80-300	Yes	Bradycardia, Prolonged blockade on discontinue	$$	liver/renal dysfunction
rocuronium	LD 6-12, 10-15 mcg/kg/min	renal hepatic bile	80-130	Yes	Some histamine release but less CV effects	$$	liver/renal dysfunction
atracurium	LD 3, 5-15 mcg/kg/min	Hofmann/ester hydrolysis	20-25	No	Histamine release	$$$	possibly hypotension?
cisatracurium	LD 1, 3-5 mcg/kg/min	Hofmann/ester hydrolysis	20-30	No	No significant histamine release or CV effects	$$$$$	none

NMBA Long Term Adverse Effects

• Prolonged Neuromuscular Blockade
– Due to accumulation of drug from diminished clearance due to renal or hepatic dysfunction
– Can last from several hours to days
– Most reported with pancuronium and vecuronium
– Treatment is supportive until drug is cleared
– To avoid this, choose agent based on end-organ function and perform daily interruption of NMBA when possible to avoid accumulation/minimize duration
• Critical Illness Myopathy / ICU Acquired Weakness
– Diffuse weakness after drug is gone
– Acute paresis, myonecrosis with increased CK and abnormal electromyography (EMG)
– Possible increased risk with corticosteroids and aminoglycosides
– Most commonly reported with pancuronium and vecuronium
– Cumulative dose and duration of NMBA found to be significant risk factors in several studies
• Recommendation is to use lowest dose for the shortest duration possible to minimize risk

Implications of NMBAs for Patient Care

• NO effect on consciousness
• NO amnestic or analgesic properties
• Prone to: – Decubitus ulcers – Corneal erosions – DVT/PE – Muscular atrophy

Sedation with Contuous NMBA

• Ensure RASS -4 to -5 prior to initiation of NMBA
– Deep sedation
• Recommendation is to be on continuous infusion opioid and sedative
– Gold standard sedative for this situation is continuous infusion benzodiazepine
– Propofol may not achieve deep enough sedation in some patients
– Dexmedetomidine only achieves light sedation
• Sedation should never be titrated down while patient is paralyzed

Monitoring for patients on NMBA

• Assess sedation:
– RASS
– Vital signs: BP, HR, diaphoresis
• Assess level of paralysis:
– Muscle movements
– Spontaneous breaths
– Ventilator Dyssynchrony
– Train of Four (TOF): goal 1-2 twitches

Train of Four Monitoring

• Peripheral nerve stimulator (PNS)
– Two stimulator pads placed on ulnar or facial nerve
– 4 electrical impulses delivered over 2 seconds
– With no NMBA, this would cause 4 muscle contractions (twitches)
• Placement of PNS
Table: Goal on NMBA: 1-2 twitches
Train of four vs. Clinical Assessment: compared titration of vecuronium according to PNS versus titration to patient symptoms (ie, breathing over ventilator, moving)

ROSE Trial

Essential Adjunct Therapies

• Mechanical ventilation • Sedation • Analgesia • DVT prophylaxis • Eye care • Mouth care • Prevention of decubitus ulcers • Range of motion exercises

Pharmacist's Role

• Use of most appropriate NMBA agent – Co-morbidities – Side effects – End-organ function
• Adjunctive therapy – Adequate sedation/analgesia – DVT prophylaxis – Eye care – Stress Ulcer Prophylaxis
• Drug Interactions

Acute Coronary Syndromes

List the time-to-treatment goals for primary percutaneous coronary intervention (PCI) and administration of fibrinolytic therapy for a patient with a STEMI
Explain why primary PCI is preferred over fibrinolysis for STEMI
Formulate a plan for a patient with STEMI/UA/NSTEMI receiving fibrinolytics (STEMI), aspirin, anticoagulation (UFH, LMWH, bivalirudin), Glycoprotein IIb/IIIa inhibitor, P2Y12 receptor inhibitor, B-blocker, ACEI/ARB, aldosterone antagonist, statin, and nitroglycerin; Recognize the appropriate dosing for UFH and LWMH (UA/NSTEMI)
List the long-term goals for patients following MI

Catheterization
ACS s/s: chest pain, chest tightness/heaviness; however elderly or DM might not have s/s, others such as pain radiating to arm/neck/back, SOB, fatigue, NV.
STEMI: cath lab, obtain access, xrays (display contrast dye on monitor)
  gain access: femoral artery in groin or in radial artery in arm; OSU radial lower pressure vessel lower bleeding
  contrast dye injected into coronary artery, take pictures, see any thrombus plaque formed/ruptured, or occlusions or coronary arteries
  two stents: BMS/DES; then need DAPT
Essentials of Thrombosis
Two pathways for thrombus formation:
  Collagen → TXA2 and ADP → platelet activation → platelet aggregation
  Tissue Factor → plasma clotting cascade → prothrombin → Factor Xa → Thrombin → Fibrinogen → Fibrin

Medications During PCI

Anticoagulants (inhibiting the clotting factors): Heparin/LMWH, Bivalirudin
Antiplatelet (inhibiting the enzymes that cause the platelets to clump together): Aspirin, P2Y12 receptor inhibitor, GP IIb/IIIa inhibitors, Cangrelor

Anticoagulants: Heparin/LMWH: both UFH and LMWH bind to AT III then Factor Xa; UFH has higher inhibitory activity for Factor IIa (thrombin) than LMWH
Unfractionated Heparin
MoA: bind to AT III then Factor Xa; UFH has higher inhibitory activity for Factor IIa (thrombin) than LMWH
*Dosing
  Bolus prior to PCI: 60 units/kg (max 4,000 units, if give more increased bleed risk)
  Continuous IV: 12 units/kg/hr for 48hrs or until end of PCI
Monitoring
  Target activated partial thromboplastin time (aPTT) of 1.5 – 2 times control (varies by site/reagent)
  PCI Activated Clotting Time (ACT) 300 – 350 sec if no GP IIb/IIIa or 200 - 250 sec if on a GP IIb/IIIa inhibitor (shorter, potent, we want balance clot/bleed)
  H/H (hemoglobin/hematocrit) and platelets to make sure not bleeding
  Hemodynamic changes (retroperitoneal bleed most significant bleeding complications: hypotensive, tachycardia)
Side effects: excessive bleeding, thrombocytopenia (heparin-induced HIT)
Limitations
  Does not inhibit clot-bound thrombin
  Inconsistent anticoagulant effect (dosing, predictability)
  Frequency of monitoring
  Thrombocytopenia (HIT)

LMWH: enoxaparin (Lovenox)
MoA: bind to AT III then Factor Xa
*Dosing
  1 mg/kg sc q12h
  0.3mg/kg IV should be given if
    <2 therapeutic subcutaneous doses of enoxaparin
    Last dose was 8 – 12hr before PCI
  Continue for 24 – 48 hr or until end of PCI
Monitoring
  Not necessary when using for short duration
  Can not reliably monitor PTT or ACT (cannot monitor bleed or clot risk); can monitor antiXa activity though takes time, not useful in cath lab
  Caution in patients with renal impairment (CrCl <30); not recommended: HL significantly prolonged, can't monitor, bleed risk
Side effects: bleeding, thrombocytopenia (HIT/HITT)

Factor Xa inhibitors: fondaparinux (Arixtra)
Dosing: 2.5mg sc q24h
Monitoring: Can not monitor aPTT or ACT; Caution renal impairment and contraindicated CrCl <30 (HL very long, reason why not seen a lot)
Side effects: bleeding, thrombocytopenia
Note: because of risk of catheter thrombosis, fondaparinux should not be used as sole anticoagulant to support PCI; gotta give heparin on top of it

bivalirudin (Angiomax)
MoA: reversible inhibitor of thrombin; alternative to heparin/LMWH +/- GPIIb/IIIa inhibitor; Used in 10-15% of patients Side effects: bleeding
Dosing Bolus: 0.75 mg/kg IV Continuous: 1.75 mg/kg/hr (CrCl <30: 1 mg/kg/hr Dialysis: 0.75 mg/kg/hr)

Bleeding Risk
NCDR Cath PCI Bleeding Risk Score: STEMI, Age, previous PCI, CKD, shock, cardiac arrest <24h, female, Hb, PCI status
≤25 Low risk (≤2.0%) 25 to 65 Medium risk (≤6.5%) >65 High risk (>6.5%)

Alternative to PCI for STEMI: PCI not available; goal for transfer (<120minutes), if can't do it, pharmacotherapy to open up the clots

Primary PCI
STEMI symptoms within 12 hours
Severe heart failure of cardiogenic shock
Contraindications to fibrinolytic therapy
Clinical or ECG evidence of ongoing ischemia between 12-24hrs after onset
Note: Within 90 minutes if PCI capable hospital or 120 minutes if hospital without PCI capabilities

Fibrinolytics
MoA: Initiates local fibrinolysis by binding to fibrin in a thrombus (clot) and converts entrapped plasminogen to plasmin.
reteplase: Dosing: 10 units IVP over 2min x2 administered 30min apart; Bleeding: 15.5%
tenecteplase: Dosing: bolus over 5 seconds; weight based 30mg (<60kg), 35mg (<70kg), 40mg (<80kg), 45mg (<90kg), 50mg (≥90kg); Bleeding: 22%
alteplase: Dosing: 15mg bolus, 0.75 mg/kg over 30min (≤50mg), 0.5 mg/kg over 60min (≤35mg); Bleeding: 15% ["Accelerated" 90-minute weight-based infusion]
Indications: sx of ACS with an onset within 12 hours of first medical contact; ST-segment elevation; anticipated that primary PCI cannot be performed within 2h
Contraindications
- Previous hemorrhagic stroke at any time; or other strokes within one year
- Known intracranial neoplasm; intracranial hemorrhage is biggest risk
- Active internal bleeding
- Suspected aortic dissection

Precautions
- Severe uncontrolled HTN (BP>180/100mmHg)
- Current use of anticoagulants in therapeutic dose (INR 2-3)
- Recent trauma (within 2-4 weeks), including head trauma or traumatic or prolonged CPR or major surgery(<3 weeks)
- Noncompressible vascular punctures
- Recent internal bleeding (within 2-4 weeks)
- Active PUD
- H/O chronic severe HTN
- Oral anticoagulant therapy

Monitoring
- EKG: resolution of ST segment elevation
- BP/HR
- Sites of bleeding
- Mental status
- CBC (H/H, platelets)

STEMI
aspirin LD 324mg, MD 81mg qday
clopidogrel (preferred): MD 75mg qday

LD at time of lytics	or	LD follow up PCI
≤75yo 300mg		fibrinolytic ≤24h ago: total of 300mg (regardless of age)
>75yo 75mg		fibrinolytic >24h ago: 600mg

heparin LD 60 units/kg (max 4000units), MD 12 units/kg/hr; (keep on heparin after gotten thrombolytic for 48h or until back to cath lab)

P2Y12 inhibitors

	clopidogrel	**prasugrel**	**ticagrelor**	**cangrelor**
Loading Dose	600mg PO	60mg PO	180mg PO	30 mcg/kg IV
Maintenance Dose	75 mg PO qday	10mg PO qday	90mg PO bid	4 mcg/kg/min for >2hrs or duration of PCI then 0.75 mcg/kg/min
Time to 50% plt inhibition*	2-6 hrs	1 hr	30 min	2 min
Max platelet inhibition	35%	79%	88%	>95%
Offset of action	5–10 d	7–10 d	3–5 d	**60 min**
Half-life	Parent 6 h, Active 30 min	Active 7 h	Parent 7 h, Active 9 h	3-6 min
Excretion	Renal 50%, Fecal 46%	Renal 68%, Fecal 27%	Renal 26%, Fecal 58%	Renal 58%, Fecal 35%
Receptor blockade	Irreversible	Irreversible	Reversible *Noncomp*	Reversible
Prodrug	Yes	Yes	No	No
CYP drug interaction	2C19	No (3A4, 3B6)	3A4	No (plasma)
Approved settings	ACS, stable CAD, PCI, PAD, ischemic stroke	ACS undergoing PCI	ACS or history of MI	PCI w or w/o ACS
Limitations	- modest inhibition - delayed onset - genetics (2C19, polymorphisms) - in DM, obese not as responsive - d/c 5 days prior to CABG	- higher efficacy, worse bleed risk* - CI: intracranial hemorrhage, and Hx TIA or stroke - in 75yo, use if DM + STEMI - precautions <60kg, bleeding - d/c 7 days prior to CABG	- higher efficacy, equal bleed risk - CI intracranial hemorrhage - use ASA less than 100mg - d/c 5 days prior to CABG - SE: bradycardia, dyspnea - simva/lova max 40mg	

Problems with P2Y12 inhibitors
Clopidogrel delayed time to 50% platelet inhibition
Decresed absorption (opioids)
Have to be given via the enteral route; Nausea and Vomiting; No enteral access
Duration of action if surgery is needed; bleed risk

cangrelor
FDA approved label (very specific patient group)
- Decrease rate of thrombotic CV events (including stent thrombosis) in patients not treated with an oral P2Y12 inhibitor or GP IIa/IIIb inhibitor undergoing PCI

Labeled: Percutaneous coronary intervention (PCI): Adjunct to PCI to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.
Off-label: bridge patients that have a stent that need antiplatelets but have to go to surgery
Dosing
LD 30 mcg/kg IV
MD: 4 mcg/kg/min for at least 2hrs or duration of PCI then 0.75 mcg/kg/min
Advantages: Time to 50% platelet inhibition **2 min**; Max platelet inhibition **>95%; Offset 60 min**; **Reversible**

Coronary Artery Bypass Graft (CABG)
Who? Preferred over stenting in:
Left main disease (widowmaker, top artery that comes off aorta that branches off into last circumstance flex and left anterior descending artery)
Multiple blocked vessels: severe 2 or 3 vessel disease
Advantage: bypass occluded vessel completely
Disadvantage: invasive; infection; if already got oral P2Y12i and don't wait long enough, can have bleeding
Procedure CABG: take saphenous vein (from leg) or left internal mammary artery (main BV goes down your heart) and bypass where the blockages are

Glycoprotein IIb/IIIa inhibitors
eptifibatide (Integrillin) peptide
Dose
Bolus*: 180 mcg/kg x2 [DOUBLE BOLUS]
IV gtt: 2 mcg/kg/min x18-24h
Elimination: renal (contraindicated dialysis); CrCl<50: 1 mcg/kg/min
Platelet binding: reversible; HL 1.5hrs
Bleeding: 9-11%

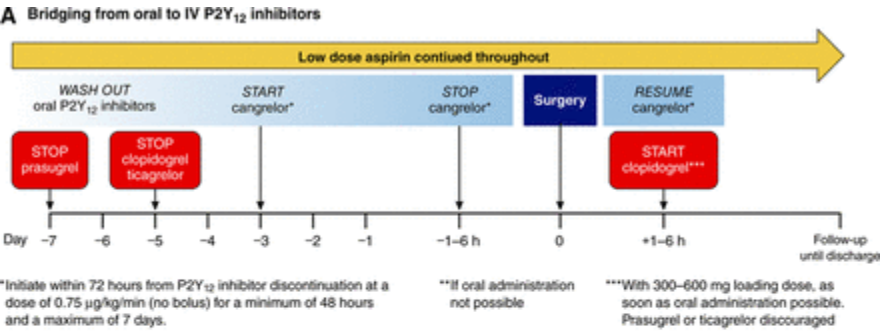
tirofiban (Aggrastat) non-peptide
Dose
Bolus*: 25 mcg/kg x1 over 3 mins [SINGLE BOLUS]
IV gtt: 0.15 mcg/kg/min up to 18h
Elimination: renal; CrCl ≤60: 0.075 mcg/kg/min; okay in dialysis
Platelet binding: reversible; HL 2hrs
Bleeding: 10-12%

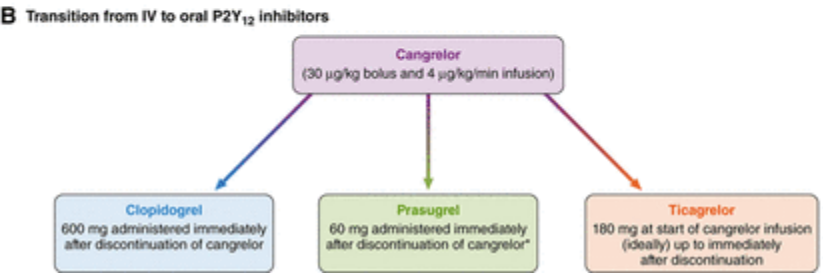
Timing of cangrelor after holding oral P2Y12 inhibitors
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.031164

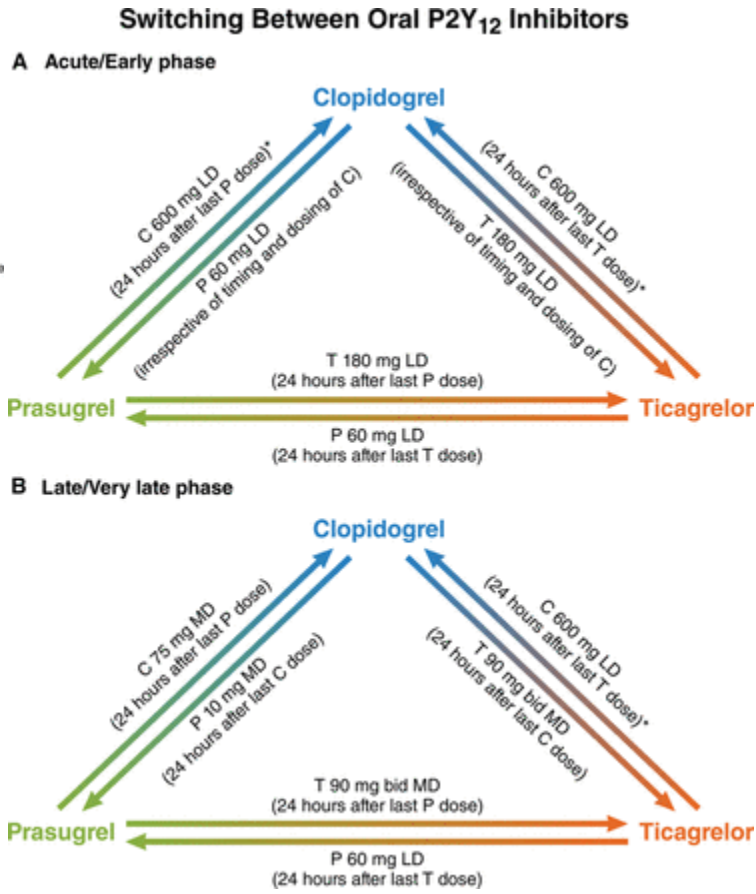
If cangrelor present, blocking 90-95% platelets, and we give clopidogrel/prasugrel, it can't bind.
If ticagrelor is bound, blocking 88% of platelets, being a noncompetitive inhibition where ADP stuck in inactive conformation, clopidogrel/prasugrel can't bind.

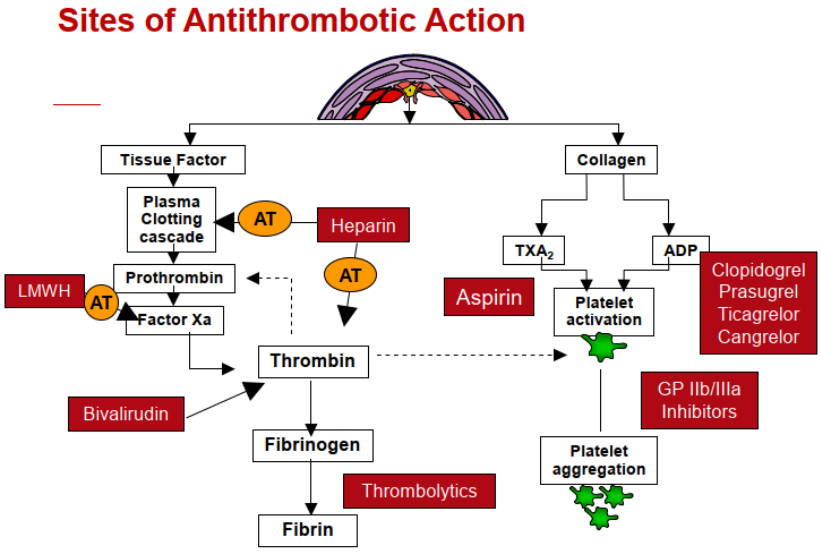
B. Switching from cangrelor to oral P2Y12 inhibitors
Turn cangrelor off when ready to give oral P2Y12i; then give PO loading dose.

A. Switching between oral P2Y12 inhibitors
ticagrelor → clopidogrel - C 600mg LD 24 hours after last T dose
ticagrelor → prasugrel - P 60mg LD 24 hours after last T dose
clopidogrel → either - LD irrespective of timing and dosing









	UA	NSTEMI	STEMI
Symptoms	+	+	+
Troponin (normal <0.11ng/mL)	-	+	+
EKG (ST)	-	-	+

TABLE 18-1 Typical Anginal Symptoms

Description	Character	Radiation of Pain	Provoking Factors	Associated Symptoms
Discomfort	Gradual in onset and offset	Upper abdomen	Physical activity	Shortness of breath
Squeezing	Not localized to one specific area	Shoulders	Emotional stress	Sweating
Tightness		Arms	Sexual intercourse	Dizziness or lightheadedness
Pressure		Lower jaw/teeth	Cold weather	

Acute Decompensated Heart Failure

Classify ADHF patients according to hemodynamic subclass based on clinical signs/symptoms
Evaluate appropriateness of pharmacotherapy for ADHF including diuretics, vasodilators, and inotropes
Describe management of chronic heart failure therapies during an episode of ADHF
https://accesspharmacy-mhmedical-com.proxy.lib.ohio-state.edu/content.aspx?bookid=2577&sectionid=226723170

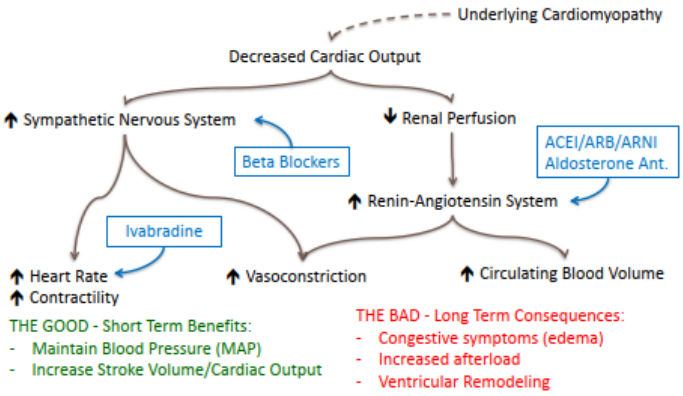
What is HF?
ACC/AHA: a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
HFSA: a progressive syndrome (rather than a diagnosis) caused by cardiac dysfunction characterized by fluid retention, shortness of breath, and fatigue

Cardiomyopathies

Reduced Ejection Fraction (HFrEF)	EF ≤40%	aka systolic	related to ischemia, idiopathic (genetic); ischemia most common cause of HFrEF
Preserved Ejection Fraction (HFpEF)	EF ≥50%	aka diastolic	related to hypertension, infiltrative diseases

Neurohormonal Model of HFrEF
underlying cardiomyopathy manifests as decreased cardiac output:
1. ↑activation of the sympathetic nervous system (baroreceptors) leading to downstream to ↑HR ↑contractility, ↑vasoconstriction
2. ↓renal perfusion in kidneys, ↑activation renin-angiotensin RAAS system further ↑vasoconstriction and ↑circulating blood volume (fluid retention)

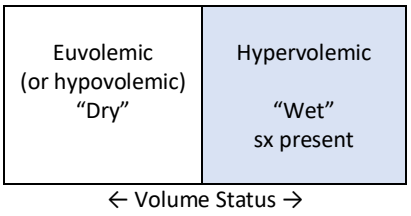
Short term GOOD: maintain BP, ↑SV/CO
Long term BAD: congestive sx (edema), ↑afterload, ventricular remodeling



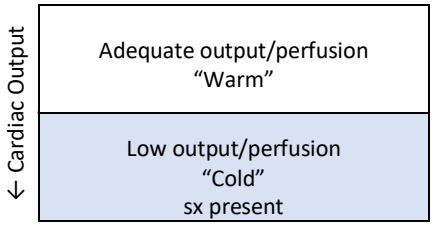
Exacerbating factors
– Intrinsic changes to structure/function of heart
(i.e. progression/change in underlying cardiomyopathy like ischemia heart attack)
– Increased workload on heart:
- Volume overload (renal failure)
- Pressure overload (uncontrolled HTN)
- Increases in metabolic demands of body (infection)

F – Failure to comply with fluid/sodium restriction
A – Arrhythmia (atrial fibrillation), Apnea (sleep)
I – Ischemia (MI), infection
L – Levothyroxine – hyper/hypothyroidism
U – Uncontrolled HTN
R – Renal Failure
E – Embolus (pulmonary), Electrolyte disturbance
D – Drugs: associated with worsening HF
– NSAIDs – Corticosteroids – Thiazolidinediones – NonDHP CCBs – Probenecid, Bile Acid Sequestrants – New initiation/titration of BB
– Anti-arrhythmics that are negative inotropes, decrease CO further (Class I - quinidine, propafenone; Class III - dronedarone)

Acute Decompensated Heart Failure
Definition: new or worsening signs or symptoms (as a result of volume overload and/or hypoperfusion) requiring additional medical care
Significance: 1M HF hospitalizations/year, 25% readmitted in 30d, 50% in 6mo; 30% 1yr mortality
Clinical Signs/Symptoms
• Volume overload - "Wet"
– Shortness of Breath, Dyspnea On Exertion
– Orthopnea, Paroxysmal nocturnal dyspnea (PND, nighttime)
– Edema (peripheral and/or pulmonary), weight gain
– Elevated JVP, + HJR
– S3 gallop (third sound heard when atrium trying to force blood to ventricle that's already full)
– Rales (pulmonary edema)
– Pleural Effusions
– Elevated BNP/NT-ProBNP (increased volume status)
– Congestive hepatopathy – increased INR, LFTs



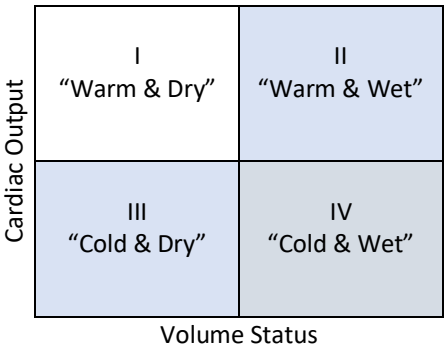
• Low Output/Hypoperfusion - "Cold"
– Fatigue (non-specific)
– Early satiety, nausea, anorexia (blood flow prioritized to other organs)
– Altered mental status
– Cool extremities
– Tachycardia
– Narrow pulse pressure (SBP-DBP; SV decreases, pulse pressure gets more narrow)
– Symptomatic hypotension
– Hyponatremia

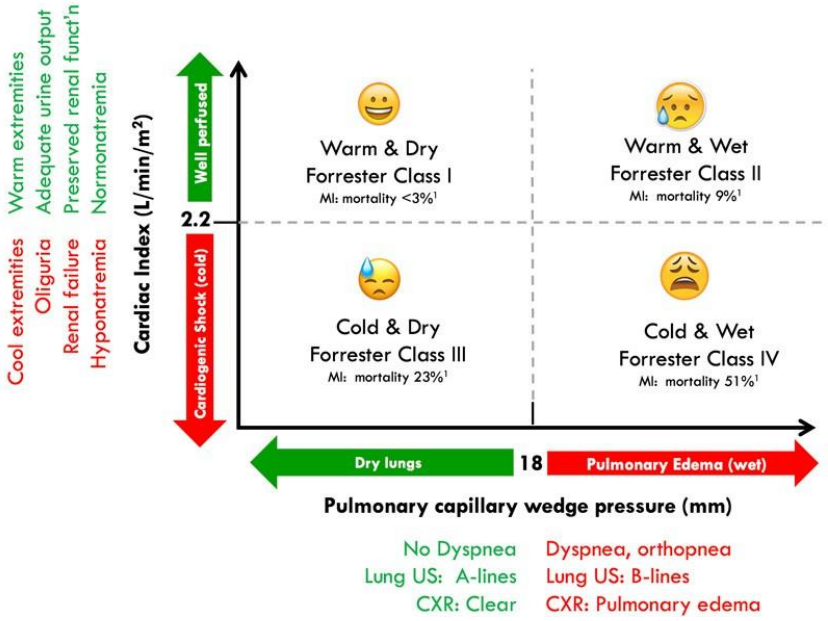


Forrester Clinical Classification

Volume Status: "Dry" Euvolemic (or hypovolemic) "Wet" Hypervolemic (presence of 1 or more of the symptoms)
Cardiac Output: "Warm" Adequate Cardiac Output/Perfusion "Cold" Low Cardiac Output/Perfusion sx

Subset I "Warm & Dry"
Subset II "Warm & Wet"
Subset III "Cold & Dry"
Subset IV "Cold & Wet"





Subset I —"Warm & Dry"

Goal status: Not typically admitted to hospital for HF; encourage non-pharmacologic behaviors
Optimize guideline directed medical therapy:
- ACEi/ARB/ARNI, beta blocker, aldosterone antagonist, SGLT2 inhibitor, diuretic (as needed), digoxin/ivabradine (select patients)

Goals of Therapy in ADHF
- Provide symptomatic relief
- Stabilize with acute therapies, minimize risks
  – IV diuretics, vasodilators, inotropes
- Identify exacerbating factors, treat/remove if able
- Maintain/transition back to oral HF therapies if able to reduce morbidity/mortality
- Evaluate for advanced HF therapies as appropriate (cardiac transplantation or ventricular assist devices)

Management of Chronic HF Treatment in ADHF
Goal is to continue whenever possible, hold if:
- β-blocker
  – Signs of cardiogenic shock (evidence of end organ malprofusion, severely low CO)
  – Symptomatic hypotension/bradycardia
  – Otherwise consider dose reduction before discontinuation
- ACEi/ARB/ARNI
  – Cardiogenic shock/symptomatic hypotension
  – Acute kidney injury/hyperkalemia
- Aldosterone antagonist
  – Renal dysfunction/hyperkalemia
- SGLT2 inhibitor
  – Concern for or at risk for euglycemic DKA (infection, NPO status, surgery)
  – Renal failure (CrCl < 25 mL/min)
- Ivabradine
  – Cardiogenic shock/symptomatic bradycardia/hypotension
  – New atrial fibrillation (will not control HR, only control sinus HR; associated with higher rate of Afib)

Subset II —"Warm & Wet"

Most common presentation of ADHF
Goal: get them back to Subset I "Warm & Dry"
First Line Therapy: IV Loop Diuretics
– Naïve: Furosemide 40 mg IV (or equivalent)
– Experienced: 2-2.5x individual home doses (not total daily dose) given as IV
- Relative Potency:

furosemide	40mg PO	20mg IV	F 50%	Duration 6 hrs
torsemide	20mg PO	--	F 80-100%	Duration 8-12 hrs
bumetanide	1mg PO	1mg IV	F 80-90%	Duration 4-6 hrs
ethacrynic acid	50mg PO	50mg IV	F 100%	Duration 4-8 hrs (OK in true sulfonamide allergy, $$$)

– Ex. Home: Furosemide 40 mg twice daily: Individual dose = 40 mg PO, Furosemide IV equiv = 20 mg; 2x home dose = 40 mg IV, 2.5x home dose = 50 mg IV

Why Loop 1st-line? Most potent single agents Site of Action: Ascending Loop of Henle: Inhibit Na+/K+/2Cl- transporter
Loop Adverse Effects (all): – Hypokalemia – "Contraction" – hypochloremic, metabolic alkalosis (retaining bicarbonate as an alternative to Cl)

Optimizing Loop Diuretics*
Goals of Therapy
– Relief of subjective dyspnea
– **1-2L net negative fluid balance per day**
Stepwise Approach
– Change PO to IV (standard)
– Increase dose if no response
– Increase frequency if response, but short of goal
– Change to continuous CI

Overcoming Diuretic Resistance

metolazone	2.5-5mg PO	q24-48h	
HCTZ	25-50mg PO	qday	
chlorothiazide	250-500 IV	q12h	($$)

29: Diuretic Response in HF
tend to have elevated diuretic threshold; higher concentration needed in HF, overall max response lower
diuretics only work if able to get to lumen where it can block Na/K/2Cl pump
30: Concentration-Dependent Effect
No ↑ in urine output if diuretic concentration < threshold
Yes ↑ in urine output if diuretic concentration > threshold
32: IV rapid concentration peak; PO delayed peak due to absorption and bioavailability
34: Diuretic Threshold may vary from patient to patient or vary over time
36: Increase Frequency may compensate for "Post-Diuretic Effect"
ex. furosemide initially q12h; if increasing urine output but falling short of goal, increase to q6-8h
38: Continuous Infusion may eliminate "Post-Diuretic Effect" FYI furosemide 5mg/hr infusion = 60mg bid IV
May switch to continuous infusion to avoid high peak concentration associated with harm/ototoxicity
Bolus vs. Infusion: no difference in subjective/objective outcome measures between bolus and continuous

Loop diuretics that work in the ascending loop of Henle, block that sodium potassium chloride exchange and deliver solutes to the more distal portions of the nephron. Initially, this results in more water entering the lumen and an increase in urine output. However, over time there could be hypertrophy of the distal convoluted tubules, leading to increased expression of the Na/Cl exchange pumps here and leading to increased solute reabsorption, which ultimately leads to diminished urine output response to loop therapy alone. However, if we use combination diuretic therapy or what's often referred to a sequential nephron blockade and add a thiazide diuretic on top of our loop diuretic therapy, these can work in the distal, convoluted tubule, block those sodium chloride pumps and then restore that delivery of solutes further through the nephron and again increase our urine output. So once we've optimized our loop diuretic therapy, we usually move to adding a thiazide agent to augment their diuresis.
Caution with Combination Diuretic Therapy: **hypokalemia** (monitor frequently bid, anticipate need for K replacement)

IV Vasodilatory Pharmacology

Properties:
- venous vasodilation
  - increase venous capacitance
  - decrease preload → decrease pulmonary congestion
- arterial vasodilation
  - decrease arterial vasoconstriction
  - decrease afterload → increase cardiac output

MoA: ↑NO, ↑cGMP, vasodilation

nitroglycerin (venous)	CVP↓↓	SVR -/↓	CO -/↑	PCWP↓
nitroprusside (mixed)	CVP↓	SVR ↓↓	CO ↑	PCWP↓

nitroglycerin (↓preload ↓↓CVP)
Use: acute relief of symptoms (dyspnea) that are refractory to or not improved with initial diuretic therapy
Dosing: Initial 5-10 mcg/min, titrated by 5-10 mcg/min every 5-10 minutes to effect (dosing range: 10-200mcg/min; higher doses for SVR effects)
HL 2-3min
ADEs: HA, hypotension
Considerations: tolerance (need for dose escalation due to NO cofactor required); niche use in patients with concern for ischemia

nitroprusside (↓afterload ↑CO ↓↓SVR)
Use: optimization of cardiac output/index; relief of symptoms; evaluation of pulmonary HTN
Dosing: 0.3-3mcg/kg/min
HL 1-3min
ADEs: cyanide/thiocyanate toxicity may limit duration of use (esp hepatic/renal impairment), hypotension
Considerations: cost; no toleration issues

Subset II --- "Warm & Wet" continued

IV loop diuretics +/- IV vasodilators (acute symptom relief)
If fail to respond to optimized diuretic regimen: consider need for invasive monitoring and evaluate for tailored vasodilator/inotrope

IV Inotropes

Reserved for:
– Failure to respond to diuretics/vasodilators
– Symptomatic hypotension/signs of end organ hypoperfusion or damage
– Palliation/Bridge to definitive therapy (Transplant/VAD)

May stabilize/improve symptoms, do not improve survival long-term
Trial: Short-term IV milrinone for acute exacerbation of HF; no difference in hospital LOS, 60-day readmission or survival
- increased risk of in-hosptal ADEs: Afib/flutter, hypotension, trend toward increase in v-arrhythmias and mortality

dobutamine: ↑HR
milrinone (inodilator): ↓BP, greater effects on vascular resistance; caution renal

dobutamine	β1 β2 α1 agonist 2-10 mcg/kg/min (max 20)	Onset <10min *HL 2-3min* metab: plasma clearance	HR ↑	MAP -	PCWP↓	CO↑	SVR -/↓
milrinone	$PDE_{3/4}$ inhibitor 0.2-0.5 mcg/kg/min (max 0.75)	Onset 5-15min *HL 1-3hrs* metab: renal clearance	HR -/↑	MAP -/↓	PCWP↓	CO↑	SVR ↓

Subset III —"Cold & Dry"

Do not have symptoms of volume overload, but do have symptoms of low cardiac output
Goal: increase cardiac output; get them to subset I
If symptomatic hypotension, SBP <90, or signs of end organ dysfunction: IV inotrope first line
If above absent, consider IV vasodilator first and change to inotrope if develops hypotension or fails to improve
Rarely, administer IV fluids (more commonly, withhold diuretics)

Subset IV —"Cold & Wet"

Both low cardiac output symptoms and volume overload symptoms
Goal: increase cardiac output and remove fluid; "Warm them up to dry them out" i.e. go to subset II then I
- may not respond adequately to diuretics alone without support of vasodilator/inotrope

If symptomatic hypotension, SBP <90, or signs of end organ dysfunction: inotrope + IV diuretics
If above absent, IV diuretics +/- IV vasodilators

Monitoring for Hospitalized Patients With Acute Decompensated Heart Failure

Electrolytes: K, Na
Fluid status: fluid intake and output
HF signs: ascites, edema, hepatojugular reflex, hepatomegaly, increased jugular venous, distension, liver tenderness, pulmonary rales
HF symptoms: dyspnea, fatigue, lightheadedness, nocturnal cough, orthopnea, paroxysmal nocturnal dyspnea
Renal function: SCr, BUN (blood urea nitrogen)
Weight: determine after voiding in morning, take possible food intake due to improved appetite into account
Vitals: orthostatic blood pressure if indicated, oxygen saturation daily until stable

Management of Oral Pharmacotherapy in Acute Decompensated Heart Failure

	ACEi/ARB/ARNI	β-Blocker	MRA	Diuretic	Digoxin
Subset I "Warm & Dry"	maintain or increase; check renal function	maintain or increase	maintain or increase	maintain or reduce, if possible	maintain; often not needed
Subset II "Warm & Wet"	maintain; defer uptitration	maintain; defer uptitration	maintain; defer uptitration	increase dosage and/or add second diuretic	maintain; verify plasma conc
Subset III "Cold & Dry"	reduce or withdraw	reduce or withdraw; evaluate need for inotropic support	reduce or withdraw	maintain/reduce with caution	maintain; verify plasma conc
Subset IV "Cold & Wet"	withdraw	withdraw; evaluate need for inotropic support	withdraw	individual cases evaluated	maintain; verify plasma conc
Hold if	signs cardiogenic shock (CO) symptomatic hypotension acute kidney injury hyperkalemia	signs cardiogenic shock sx hypotension/bradycardia try lower dose before dc	renal dysfunction hyperkalemia	SGLT2: risk of euglycemic DKA (inf, NPO, surg), CrCl <25 Ivabradine: cardiogenic shock, new Afib, sx hypo/bradycard	

Subset I "Warm & Dry"
maintain or increase ACEi/ARB/ARNI check renal, maintain or increase β-blocker, maintain or increase MRA, maintain or reduce diuretic if possible, maintain digoxin often not needed
Subset II "Warm & Wet"
maintain defer uptitration ACEi/ARB/ARNI, maintain defer uptitration β-blocker, maintain defer uptitration MRA, increase or add second diuretic, maintain digoxin verify Cp
Subset III "Cold & Dry"
reduce or withdraw ACEi/ARB/ARNI, reduce or withdraw β-Blocker eval need for inotropic support, reduce or withdraw MRA, maintain/reduce diuretic, maintain digoxin verify Cp
Subset IV "Cold & Wet"
withdraw ACEi/ARB/ARNI, withdraw β-blocker eval need for inotropic support, withdraw MRA, individualize diuretic, maintain digoxin verify Cp

Patients should be counseled prior to discharge on essential lifestyle modifications.

Dietary education points that should emphasized include restricting sodium intake to less than 2 g/d and fluid intake to less than 2 L/d or 1 to 1.5 L/d in patients with hyponatremia. Patients are encouraged to perform moderate exercise for 30 minutes at least 5 d/wk, if deemed safe. In addition, patients should be advised to quit smoking and limit alcohol consumption to 2 or less drinks per day for men and 1 or less drink per day for women. All patients with HF are at high risk for influenza and pneumococcal disease and should receive vaccinations according to recommended schedules. Also, patients should be counseled to avoid certain over-the-counter medications that may exacerbate HF symp- toms and affect disease progression including NSAIDs and sympathomimetic (eg, pseudoephedrine, amphetamines, and methylphenidate) medications.

TABLE 36-3 Diuretics Commonly Utilized for the Management of ADHF

	Furosemide	Torsemide	Bumetanide	Metolazone	Hydrochlorothiazide	Chlorothiazide
Mechanism	Loop diuretic	Loop diuretic	Loop diuretic	Thiazide-type diuretic	Thiazide-type diuretic	Thiazide-type diuretic
Oral bioavailability	50%	80%–100%	80%–90%	40%–65%	65%–75%	--
Dose equivalence (IV)	20–40 mg	10–20 mg	0.5–1 mg	--	--	--
intermittent dose (maximum)	40–160 mg IV once to three times daily (200 mg/dose)	--	0.5–4 mg IV once to three times daily (5 mg/dose)	2.5–5 mg PO once daily (20 mg/day)	25–50 mg PO once daily (100 mg/day)	500 mg–1 g IV once or twice daily (2 g/day)
continuous infusion dose (max)	5–20 mg/hr (40 mg/hr)	IV no longer available	0.5–2 mg/hr (4 mg/hr)	--	--	--
Onset of action (Peak effect)	30–60 min PO 5 mins IV (2 hrs)	1 hr PO (1–2 hrs)	30–60 min PO, 2–3 mins IV (1–2 hrs)	2–3 hrs (6–8 hrs)	2 hrs (4 hrs)	15 mins IV (30 mins IV)
Duration of action	4–6 hrs	18–24 hrs	4–6 hrs	12–24 hrs	5–15 hrs	6–12 hrs

TABLE 36-4 Vasodilators Commonly Utilized for the Management of ADHF

Drug (Vasodilatory effect)	HR	MAP	CVP	SVR	CO	PCWP	
Nitroglycerin (venous > arterial)	0/↑	0/↓	↓↓	0/↓	0/↑	↓	onset immediate, HL 2-3min, elim: Inactive metabolites in urine
Nitroprusside (venous = arterial)	0/↑	0/↓	↓	↓	↑	↓	onset immediate, HL 1-3min, elim: cyanide (hepatic), thiocyanate (renal)
Furosemide (venous only)	0	0/↓		0	0	↓	onset 1h PO, 5min IV, HL 2hr, elim: urine
Enalaprilat (arterial > venous)	0	0/↓		↓	↑	↓	onset <15min, HL 11hr, elim: urine

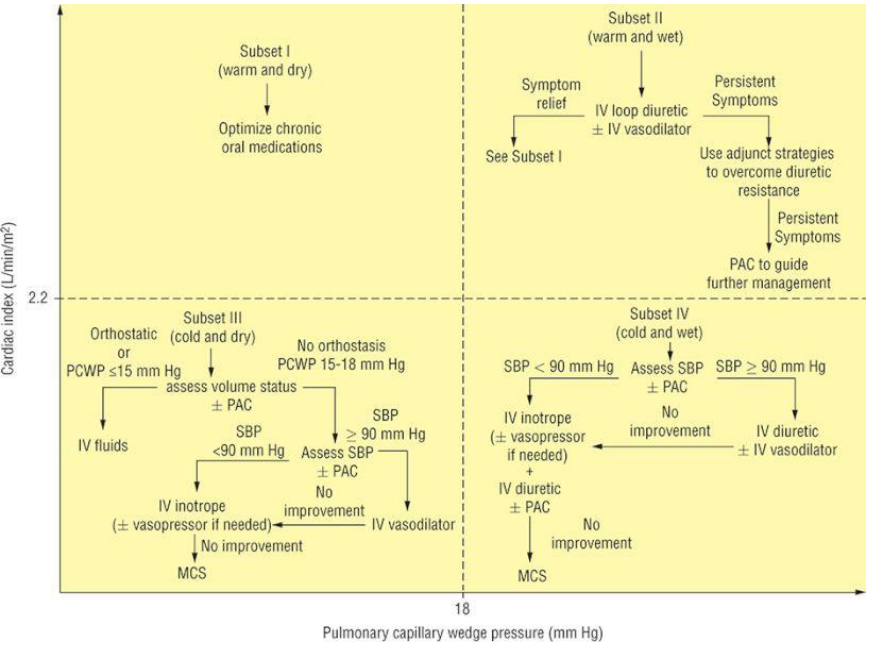
TABLE 36-5 Inotropes Commonly Utilized for the Management of ADHF

Drug	Onset, Half-life		Receptor Affinity ($\alpha_1/\beta_1/\beta_2/DA_1$)	HR	MAP	PCWP	CO	SVR
Dobutamine	<10 mins, 2 mins		↑/↑↑↑↑/↑↑/0	0/↑	0	↓	↑	↓
Milrinone	5–15 min, 1–4 hr		Phosphodiesterase inhibition	0/↑	0/↓	↓	↑	↓
Dopamine	< 5 mins, 2 mins	0.5–3 mcg/kg/min	0/0/0/↑↑	0	0	0	0/↑	↓
		3–10 mcg/kg/min	0/↑↑↑↑/↑↑/↑↑	↑	↑	0	↑	0
		10–20 mcg/kg/min	↑↑↑↑/↑↑↑↑/↑↑/↑↑	↑	↑	↑	↑	↑

TABLE 36-6 Monitoring Recommendations for Patients Hospitalized with ADHF

Parameter	Frequency	Notes
Weight	Daily	Assess after voiding in the morning
		Utilize same scale each day, if possible
		Account for increase or decrease in food intake
Fluid balance	Daily*	Strict intake and output
Vital signs	More than daily	Blood pressure and heart rate including signs/symptoms of orthostatic hypotension, rhythm (continuous)
Signs of congestion and/or low output	Daily*	Jugular venous distension, crackles, hepatomegaly, splenomegaly, hepatojugular reflux, ascites, lower extremity edema, hypotension, narrow pulse pressures, cool extremities, altered mental status, worsening renal or hepatic function
Symptoms of congestion and/or low output	Daily*	Dyspnea on exertion or at rest, orthopnea, paroxysmal nocturnal dyspnea, nausea/vomiting, early satiety, fatigue, lightheadedness, chest pain, palpitations
Electrolytes	Daily*	Potassium, magnesium, sodium
Renal function	Daily*	Blood urea nitrogen and serum creatinine including ratio to assess volume status (ie, over-diuresis)
Hepatic function	Variable*	Alk Phos and GGT primarily for fluid overload, AST and ALT primarily for hypoperfusion
BNP, NT-proBNP	Admission, discharge	Admission for diagnosis, discharge for prognosis
Other	Variable	Troponin and other cardiac enzymes if myocardial strain
		Arterial blood gas if hypoxic
		Lactate if hypoperfusion present

Alk Phos, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, B-type natriuretic peptide; GGT, gamma-glutamyltransferase; NT-proBNP, N-terminal pro-B-type natriuretic peptide. *Daily unless change in clinical status warrants more frequent assessment.



General management algorithm for acute decompensated heart failure based on clinical presentation. Patients may be categorized into a hemodynamic subset based on signs and symptoms or invasive hemodynamic monitoring. Adjunct strategies for overcoming diuretic resistance include increasing the dose of loop diuretic; switching to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and in select patients, adding MCS.

Other

Hyponatremia and Heart Failure

• Serum sodium <135 mEq/L associated with poor outcomes (OPTIMIZE-HF Registry) – Increased in-hospital mortality – Increased length of stay – Increased 60-day mortality
• Increased 7-year mortality from first admission for heart failure • 6% increase for every 1 mEq/L below 135 mEq/L

Tolvaptan

really only for symptomatic hyponatremia
• MOA: Selective V2 receptor antagonist
– Initial Dose: 15 mg – 30 mg daily
• Use: – Persistent, severe hyponatremia with active (or risk for) cognitive symptoms despite water restriction, maximized GDMT - may consider in short term (ACC/AHA)
• EVEREST, TACTICS, SECRET trials – Increased early weight loss, urine output – No impact on early dyspnea, LOS, 30-day mortality/readmission
• 3T Trial – No difference in augmenting diuresis compared to thiazide diuretics
• Considerations: – Cost ($$$) – CYP3A interactions – Monitor Na+ closely with initiation (in hospital only)

Ultrafiltration

• Mechanical volume removal – Similar concept to dialysis, but using only a filter – No dialysate, does not correct electrolyte/metabolic disturbances
• Generally reserved for patients who fail diuretics – CARRESS-HF trial
• UF not superior to diuretics when used first line
• Considerations: – Requires invasive (IV) access – Requires anticoagulation (heparin) – Cannot be used for patients with significant baseline renal impairment

Temporary Mechanical Support for ADHF

• For those failing medical therapy: – Intra-Aortic Balloon Pump (IABP)
• Indirectly augments cardiac output
• Generally no greater than 7 days – Temporary Ventricular Assist Devices
• Ex. Centrimag, Impella, etc. (numerous exist)
• Directly augment cardiac output
• Functionally bypass the LV (or RV)
• Percutaneous or surgical placement

Advanced HF (Stage D) Therapies

• Cardiac Transplantation – Gold Standard – best long-term survival – Limited by organ availability
• Durable Ventricular Assist Devices – Heartmate II/III, HeartWare – Total Artificial Heart – Bridge-To-Transplant (Decision) – Destination Therapy
• Home Inotrope (Dobutamine/Milrinone) – Short-term Bridge to Definitive Therapy (Transplant/VAD) – Palliative Care – 1 year mortality = 50-80%

Hospitalized HFpEF

• Exacerbating factors similar to HFrEF
  – HTN, Afib particularly common
• Diuretic management as with HFrEF
• Low output state rare
  – IV vasodilator used infrequently outside of HTN
  – Inotropes generally avoided in HFpEF

Transitions Out of Hospital

• Exacerbating factors identified
• Near euvolemic (adequate diuresis)
• On effective, oral diuretics for 24 hours
• HF Goal-Directed Medical Therapy; In place or documented rationale for omission
• Continuous Heart Failure education; HF Follow-up Scheduled, Phone call (or home health visit) w/in 72 hours, Follow up appointment w/in 7 days

Stroke

https://accesspharmacy-mhmedical-com.proxy.lib.ohio-state.edu/content.aspx?bookid=2577&sectionid=226723486

TABLE 20-2 Blood Pressure Treatment Guidelines in Acute Ischemic Stroke Patients Treated with tPA

Treatment	**Received tPA**
None	<180/105
Labetalol IV or nicardipine IV	180-230/105-120
Nitroprusside	Diastolic >120

TABLE 38-2 Blood Pressure Treatment Guidelines in Stroke

Ischemic Stroke with Alteplase Treatment
Pre-alteplase: lower BP to SBP <185 mm Hg and DBP <110 mm Hg
Post-alteplase: maintain SBP <180 mm Hg and DBP <105 mm Hg for 24 hours
Ischemic Stroke without Alteplase Treatment
Treatment benefit uncertain/not recommended unless BP >220/120 mm Hg
Lowering BP by 15% is probably safe when required by comorbid conditions (such as concomitant acute coronary event, acute heart failure, aortic dissection, symptomatic intracranial hemorrhage, preeclampsia/eclampsia)
Intracranial Hemorrhage
Treatment is reasonable for ICH patients with SBP >220 mm Hg
For ICH patients with SBP 150-220 mm Hg, acute lowering of SBP to 140 mm Hg is safe
Pharmacologic Options for Blood Pressure Lowering in Acute Stroke
Labetalol 10-20 mg IV over 1-2 minutes, may repeat
Nicardipine 5 mg/hr IV, titrate up by 2.5 mg/hr every 5-15 minutes, maximum 15 mg/hr
Clevidipine 1-2 mg/hr IV, titrate by doubling the dose every 2-5 minutes, maximum 21 mg/hr
Other agents to consider: hydralazine, enalaprilat, nitroprusside IV infusion, labetalol IV infusion

TABLE 38-3 Recommendations for Pharmacotherapy of Ischemic Stroke

Acute treatment	
Alteplase 0.9 mg/kg IV (maximum 90 mg), 10% as a bolus with the remainder given over 1 hour in selected patients Within 3 hours of onset (IA) Between 3 and 4.5 hours of onset (IB)	
Aspirin 160-325 mg daily started within 48 hours of onset (IA)	
Secondary prevention	
Stroke Etiology	
Noncardioembolic	Antiplatelet therapy Aspirin 50-325 mg daily [IA] Aspirin 25 mg + ER dipyridamole 200 mg twice daily [IB] Clopidogrel 75 mg daily [IIab]
Cardioembolic (especially Afib)	Anticoagulant therapy Vitamin K Antagonist (Warfarin) (INR = 2.5) [IA] Apixaban 5 mg twice daily [IA] Dabigatran 150 mg twice daily [IB] Edoxaban 60 mg daily [not graded] Rivaroxaban 20 mg daily [IIaB]
Patient	
Age ≤75	High-intensity statin therapy [IA]
Age >75	Moderate- or high-intensity statin therapy [IIaB-R]
BP >140/90	BP reduction [IB-R]

TABLE 38-4 Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke

Inclusion Criteria
Age ≥18 years
Clinical diagnosis of ischemic stroke with neurologic deficit
Time of symptom onset well established to be <4.5 hours from treatment initiation
Contraindications
Symptoms/Imaging consistent with subarachnoid hemorrhage or acute intracerebral hemorrhage
Current use of direct thrombin inhibitors or direct factor Xa inhibitors in prior 48 hours
Use of treatment-dose low molecular weight heparin in prior 24 hours
Infective endocarditis
Intra-axial, intracranial neoplasm
Aortic arch dissection
Active internal bleeding or coagulopathy (platelets <100,000/mm^3 [100 x 10^9/L], INR>1.7, aPTT>40s, PT>15s)
Severe head trauma in prior 3 months
Gastrointestinal malignancy or bleeding within prior 21 days
Warnings/Use Clinical Judgment
History of intracranial hemorrhage
History of ischemic stroke within prior 3 months
Unruptured/unsecured AVM or aneurysm >10 mm
Major surgery or nonhead trauma
History of bleeding diathesis
Extensive regions of clear hypoattenuation on initial CT scan

Acute Ischemic Stroke

Describe modifiable and non-modifiable risk factors for acute ischemic stroke (AIS)
Evaluate the appropriateness of using tPA for acute ischemic stroke and be able to recall the dose required
Create an appropriate medication regimen for secondary prevention of acute ischemic stroke

Epidemiology

ACA supplies frontal lobes. Oocclusion can cause leg weakness or profound mental symptoms.
MCA is largest branch off of the ICA; the most commonly occluded artery in an ischemic stroke. Resulting in primary motor and sensory areas of face, throat, hand, arm, speech areas.
PCA supplies temporal and occipital lobes. Occlusion can result in numerous syndromes but visual defect most common.
Basilar Artery arises from VA supplying brain stem and PCA blood supply. Occlusion can lead to "locked in" syndrome.
Circle of Willis-communication from carotid and vertebrobasilar arteries.
[Anterior Cerebral Artery (ACA), Middle Cerebral Artery (MCA), Posterior Cerebral Artery (PCA), Internal Carotid Artery (ICA), Vertebral Arteries (VA)]

AIS Presentation

BEFAST: Balance: sudden loss of balance? Eyes: lost vision? Face: face uneven? Arms: one arm hanging down? Speech: slurred, trouble speaking, confused? Time: call 911

Transient Ischemic Attack (TIA): A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction.
- classically described as lasting less than 1 hour; "mini-stroke", can resolve on own

Acute Ischemic Stroke (AIS): An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
- acute phase is the first week post ictus

Grading Severity

TIA: ABCD²

Likelihood of having stroke in next 48 hours:
Score 0-3 = Low 2 day stroke risk (1%)
Score 4-5 = Moderate 2 day stroke risk (4%)
Score 6-7 = High 2 day stroke risk (8%)

A	Age	≥60yo	1 pt
B	Blood Pressure	≥140/90	1 pt
C	Clinical Pressure	unilateral weakness	2 pts
		speech impairment w/o weakness	1 pt
D	Duration	>60min	2 pts
		10-59min	1 pt
D	Diabetes	Yes?	1 pt

AIS: NIH Stroke Scale
Score 0 = No stroke symptoms
Score 1-4 = Minor
Score 5-15 = Moderate
Score 16-20 = Moderate-Severe
Score 21-42 = Severe

*AIS: Risk Factors

NonModifiable: Age* (risk doubles each decade after 55yo); race (black 2x>white), FH stroke, hx stroke/TIA, gender (men>women)
Modifiable: HTN* (7x risk; BP <120/80 have half lifetime risk); DM (2x risk), CAD/CHF (2x risk), smoking (2x risk), others (estrogen, hypercoag, HA, diet, OSA, MHA, PFO)

Ischemic Stroke Primary Prevention

Stroke prevention: diet, smoking cessation, BP control, cholesterol, exercise (40min 3-4d/wk), wt loss (BMI <25), DM control, sleep-disorder, alcohol reduce

*ASA81

Takeaway: ASA no role in primary prevention
USPS Task Force: men no reduction in stroke (reduces MIs); women 55-79yo recommended for stroke prevention
AHA 2014: ASA for CV prevention reasonable with 10yr risk >10%
ASCEND: controlled DM (A1c <8) ASA reduces serious vascular events but increased major bleeding
ASPREE: >70yo ASA did not reduce disability-free survival but associated with higher major hemorrhage and all-cause mortality
ARRIVE: moderate-risk (10yr CV risk 10-20%), ASA did not reduce CV events but doubled GI bleeding

Afib

CHA_2DS_2-VASc: CHF 1, HTN 1, 65-74yo 1, >75yo 2, DM 1, hx stroke/TIA/VTE 2, vascular disease 1, female 1
When to anticoagulated?
- 2018 CHEST: AF ≥1 CHA_2DS_2-VASc; HAS-BLED ≥3 closer f/u; DOAC first-line;
  - assess SAMe-TT_2R_2: Sex F 1, Age <60yo 1, Medical hx 1 (≥2 HTN DM CAD/MI PAD CHF hxstroke pulmdisease hepatic/renal), DDIs 1, Tobacco within 2yrs 2, Race nonwhite 2
    - 0-2 suggests pt would achieve INR with warfarin; >2 DOAC referred (less likely to achieve INR)
- *2019 AHA: For patients with AF and an elevated CHA_2DS_2-VASc of ≥2 in men and >3 in women, oral anticoagulants are recommended

Goals of Therapy

• Reduce neurologic injury • Ensure medical stability • Screen for contraindications for interventions • Decrease mortality
• Decrease long-term disability (Modified Rankin Scale) • Prevent complications due to immobility and neurologic dysfunction • Prevent recurrence

Joint Comission "Core Measures" for Stroke Center

• NIHSS performed • Thrombolytic therapy • VTE prophylaxis • Antithrombotic therapy by end of hospital day 2 • Discharged on antithrombotic therapy (ASA)
• Anticoagulant therapy for Afib/flutter • Discharged on statin • Stroke education • Assessed for rehabilitation

AIS: Treatment Timeline

Door to doctor 10min, Door to stroke team 15min, Door to CT initiation 25min, Door to CT interpretation 45min, Door to treatment 60min, Door to stroke unit admission 180min

***Alteplase (tPA)** *know this dose
IV alteplase 0.9 mg/kg (actual body weight), maximum dose 90mg
10% given IV bolus over one minute, infuse the rest over 60 minutes
MoA: tPA acts as a thrombolytic by converting plasminogen to plasmin, which dissolves fibrin which breaks down the clot
***tPA inclusion criteria**
≥18yo AND symptom onset <3hrs AND BP <185/110 (extended window = 3 to 4.5 hours ~~and not >80yo, INR <1.7 if on warfarin, previous stroke+DM)~~
***tPA contraindications**
evidence of ICH
within last 3 months: ischemic stroke, severe head trauma, intracranial/intraspinal surgery
high clinical suspicion of SAH
GI malignancy or GIB within 21 days
coagulopathy (bleeding diathesis): platelet <100k, INR >1.7, aPTT >40s, or PT >15s
LMWH within 24hrs
NOAC within 48hrs with normal renal function [chart explaining half-life in renal impairment]
GPIIb/IIIa inhibitors (eptifibatide, tirofiban)
tPA reasonable to use
• Seizure at onset Blood glucose 50 – 400 • Moderate-severe symptoms rapidly improving • Unknown coagulopathies • Dural puncture within 7 days • Major trauma (excluding the head) within 14d
• Major surgery within 14 days • Previous GI/GU bleed (not within the 21 day exclusion for GI) • Active menstruation • Extracranial cervical dissections • Acute MI (use stroke tPA dosing) • Pregnancy
• Secured/small-moderate (<10mm) unsecured intracranial aneurysm • MI within 3 months (NSTEMI; STEMI of right inferior myocardium; STEMI of left ant myocard) • Malignancy with > 6 mo expected survival
tPA monitoring
STOP and obtain a CT if patient develops severe headache, acute hypertension, nausea, vomiting, worsening neurologic function
No Bleed: continue tPA
Bleed: cryoprecipitate 10 units and TXA 1g or AMICAR 4-5g (to reverse tPA effect on plasminogen)
Monitor BP, neurologic function, bleeding: q15min during and after infusion x2hrs; q30min x6hrs, q60min x16hrs
Follow-up CT or MRI 24hrs after tPA administered

<u>AIS Surgical Intervention</u>: Endovascular embolectomy (thrombectomy) *24hr window
• Performed in combination with IV tPA (may be used in the setting of distal ICA, MCA, or basilar artery thrombus) • May not reduce mortality but improves morbidity
Modified Rankin Scale (mRS): measures degree of disability/dependence after a stroke.
CT Perfusion Scanning (core pink, dead tissue; penumbra green, area you can save by giving tPA doing thrombectomy)
moderate oligemia (ischemia): local blood flow <18ml/100g per minute
severe oligemia (infarcation): local blood flow <12ml/100g per minute
AIS Surgical Intervention: Depressive Hemicraniectomy
• <60yo, unilateral MCA infarction who deteriorate neurologically due to cerebral edema within 48 hours despite medical therapy
• Reduces mortality 50% • Moderate disability (mRS 2 or 3) 55% • Independence (mRS 2) at 12 months 18%

<u>AIS: elevated BP</u>
Overtreat (hypotension): core pink expansion, compromise CBF, AKI
Undertreat (hypertension): hemorrhagic conversion (risk post-tPA based on NIHSS 0-10 = 2-3%, 11-20 = 4-5%, >20 = 17%); as NIHSS↑= risk conversion↑, more core fryable area overall, risk of hemorrhagic conversion with tPA ~6%

<u>AIS: BP goals</u>
received tPA <180/<105
no tPA no thrombectomy: <220/<120
no tPA + thrombectomy: SBP <160
hemorrhagic conversion: SBP <160

<u>AIS: BP treatment</u>
labetalol 10-20mg **IVP** (double dose if repeated, max 300mg at once)
hydralazine 10-20mg **IVP**
nicardipine initial 5mg/hr **IV gtt**, titrated up by 2.5mg/hr q5min (max 15mg/hr)
clevidipine initiate 4mg/hr **IV gtt**, titrate by doubling dose q2-5min (max 32mg/hr or 1L/24hrs--risk of TGs)

<u>Other therapies within acute/subacute setting</u>
O2 >94%, Temp <38C, euvolemia, Na 135-145, BG 140-180
ASA81 within 24-48h
BP control (reduce 15% during first 24h; <140/90 once neuro stable)
VTE prophylaxis after 24h

<u>Oral antihypertensive options</u>
Tier 1: ACEi/ARB, thiazides
Tier 2: DHP CCB
Tier 3: nonDHP CCB, K-sparing, β-blockers
Tier 4: Loop diuretics, central α2 agonists (clonidine)
Tier 5: direct arterial vasodilators (hydralazine), α1-blockers
Tier 6: mecamylamine (ganglionic blocking agent)

Stroke Etiology

TOAST Classification of Subtypes

Large-artery atherosclerosis (35%): stenosis of intra-/extracranial artery
Cardioembolic (30%): Afib, valve disease, ventricular thrombus
Small-artery occlusion (20%): AKA lacunar infarct; infract diameter <15mm
Stroke of other etiology: vasculopathies, hypercoaguable state, hematologic disorders
Unknown

Pathophys: "hardening of the arteries"

Cardioembolic: most commonly due to cardiac thrombus from Afib; 75% of cardioembolic emboli go to brain (LVT to MCA or ICA); carotid stenosis/plaque
Lacunar infarct: small infarcts (<15mm) seen in putamen, pons, thalamus, caudate, internal capsule; due to small vessel disease; commonly due to HTN
Blood disorders: consider <45yo, hx clotting dysfunction (VTE), cryptogenic origin: sickle cell anemia, polycythemia vera, thrombocytosis, HIT, protein C/S defic, prothrombin gene mut, Factor V Leiden defic, Antithrombin III defic, antiphospholipid syndrome (APLS), hyperhomocysteinemia

Diagnostic Tests

Computed Tomography (CT)**: gold-standard, used asap from door to rule out hemorhagic stroke; motorized x-ray generates cross-sectional images (Hounsfield scale)
Others: MRI, carotid doppler (shows degree of stenosis of carotid arteries), ECG, TTE or TEE (evaluate valve or wall motion abnormaltities and intracardiac thrombi)

Ischemic Stroke Secondary Prevention

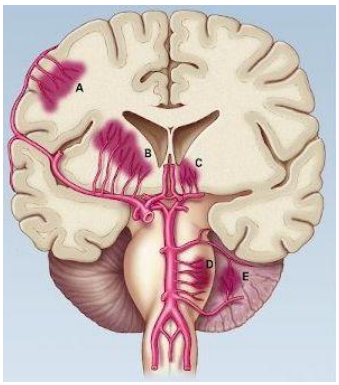
Main: BP <140/90, statin, exercise, DM control, diet (Na 2.4g/day), sleep apnea, alcohol, smoking, OAC with Afib
Statins: Secondary Prevention; Clinical ASCVD (post-stroke goal LDL <70)
- ASCVD very high risk: high-intensity/maximal statin
  - if on maximal statin and LDL ≥70, reasonable to add ezetimibe; add ezetimibe before PCSK9i; if LDL ≥70 or nonHDL ≥100 adding PCSK9i is reasonable
- ASCVD not very high risk
  - ≤75yo: high-intensity statin: if not tolerated, use moderate-intensity; if on maximal statin and LDL ≥70, adding ezetimibe may be reasonable
  - >75yo: initiate moderate-high intensity statin is reasonable; continuation of high-intensity statin is reasonable

Antiplatelets
- TIA: no prev therapy = ASA + clopidogrel x21d (better than ASA alone); prev on ASA = add clopidogrel (lacks evidence)
- AIS: ASA 50-325mg monotherapy; ASA 25mg + dipyridamole 200mg bid; clopidogrel 75mg qday (alternative to ASA/ASA-dipyridamole)

Hemorrhagic Stroke

Choose the appropriate reversal agent in the setting of ICH for a patient on an oral anticoagulant
Determine the appropriate initial SBP goal in the acute period of a hemorrhagic stroke
Identify the role nimodipine plays in the treatment of an aneurysmal subarachnoid hemorrhage

Epidemiology: hemorrhagic stroke accounts for only 15% of all stroke cases but 40% of all deaths; 2 types: Intracerebral Hemorrhage (ICH), Subarachnoid Hemorrhage (SAH)



Intracerebral Hemorrhage (ICH)

Pathophys: small arteries rupture and bleed into brain tissue "intracerebral hemorrhage with intraventricular extension"
Common locations
  Supratentorial: A. cerebellar lobes, B. basal ganglia, C. thalamus - more room to allow bleed without issues
  Infratentorial: D. pons, E. cerebellum - less room, death imminent
*Risk factors
  Nonmodifiable: >55yo, Male, AA/Japanese, cerebral amyloid angiopathy (CAA)
  Modifiable: HTN, alcohol, smoking, sympathomimetic use, anticoag use
Presentation
  acute HA, pupillary changes, NV, HTN
*Severity scale – ICH Score 0-6 points; 30-day mortality: 0-0%, 1-13%, 2-26%, 3-72%, 4-97%, 5-100%, 6-100%
  GCS (3-4 = 2 5-12 = 1 13-15: 0)
  Age (≥80=1)
  Bleed (infratentorial=1)
  ICH vol (≥30cc=1)
  intraventricular blood (yes=1)
Complications
  Hydrocephalus, Respiratory failure, Re-bleeding (expansion of bleed 3hrs), Thrombosis → permanent disability
Nonpharm
  external ventricular drain (EVD) placement for ICP mmHg, hematoma evacuation niko device
Pharmacologic therapy: BP control, anticoagulation reversal

ICH: BP control

INTERACT2: intensive lowering of SBP (<140) did not result in significant lowering of death or disability; however, it may lead to improved functional outcomes
ATACH2: intensive lowering of SBP (110 - 139) compared to standard treatment (140 - 179) did not result in significant lowering of death or disability.

***SBP goal <160 mmHg for most ICH**

	Dose	**Onset (min)**	**Duration (min)**	**ADE**
Continuous Infusion				
clevidipine	4-32 mg/hr (max 1000ml/24h)	2-4	5-15	HA, N, Afib, insomnia
nicardipine	5-15mg/hr	5-10	15-30->240	Tachycardia, HA, flushing, local phlebitis
nitroglycerin	5-100mcg/min	2-5	5-10	HA, V, methemoglobinemia, tolerance
labetalol	0.5-2mg/min	5-10	180-360	V, scalp tingle, bronchoconstrict, OH dizzy, heart block
Intravenous Bolus				
hydralazine	10-20mg	10-20	60-240	Tachycardia, HA, N, flushing, aggravation of angina
labetalol	10-20mg	5-10	180-360	V, scalp tingle, bronchoconstrict, OH dizzy, heart block

ICH: Anticoagulation Reversal

Patients who present with ICH and are also taking anticoagulation have higher likelihood of secondary hematoma expansion and increased risk of death and poor functional outcomes
Rapid anticoagulation reversal is vitally important

Warfarin Reversal

Warfarin competitively inhibits VKORC1.
Reversal targets: 1. functional vitamin K reserves are depleted (Vitamin K); 2. synthesis of active clotting factors II VII IX X are reduced (Kcentra)

***Vitamin K** (phytonadione) 1st target
- **Dose**: 10mg IV at 1mg/min (**know this dose)
- MoA: normalizes INR by providing necessary substrate to synthesize factors II VII IX X
- Limitations: slower reversal; reduction of INR to <1.4 may take up to 24hrs
- Advantage: vitamin K provides sustained and durable reversal of warfarin activity and is recommended to give in conjunction with other reversal agents

***Kcentra** (prothrombin complex concentrate **PCC**; 4-factor, unactivated) 2nd target
- **Dose**: INR <4: 25 units/kg INR 4-6: 35 units/kg INR >6: 50 units/kg (max weight 100kg)
- MoA: replaces factors II IX X and unactivated VII
- Limitation: the most serious adverse reaction is the risk of thrombotic events including stroke, DVT, PE
- Advantage: fast reconstitution and administration, low volume compared to FFP, **rapid** INR reversal

Dabigatran Reversal

Dabigatran is a specific and reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin.

idarucizumab
- Dose: 5g IV once, may repeat once for evidence of ongoing clinically significant bleeding
- MoA: humanized mAb fragment (Fab) that binds specifically to free and bound dabigatran with an affinity that is ~350x greater than thrombin; neutralizes anticoag effect
- Limitation: formation of antibodies may limit recurrent use, there is no readily available lab to monitor and assess appropriate reversal.
- Advantage: the neutralization effect is long lasting

Apixaban, Rivaroxaban; Direct Factor Xa Inhibitor Reversal

Apixaban and Rivaroxaban both act via direct, selective and reversible inhibition of free and clot-bound factor Xa.

andexanet alfa
- Dose: low dose and high dose regimen, depends on agent, dose, and time from last administration
- MoA: acts as a decoy protein (made to look like Factor Xa) and binds the oral Factor Xa inhibitor neutralizing the anticoagulant effect
- Limitation: cost, thrombosis risk
- Advantage: specific reversal agent for the direct Factor Xa inhibitors

Kcentra (prothrombin complex concentrate **PCC**; 4-factor, *unactivated*)
- Dose: 25-50 units/kg (max weight 100kg)
- MoA: replaces factors II IX X and unactivated VII
- Limitation: the most serious adverse reaction is the risk of thrombotic events including stroke, DVT, PE
- Advantage: fast reconstitution and administration, low volume compared to FFP

FEIBA (prothrombin complex concentrate, PCC, 4-factor, *activated*)
- Dose: 25-50 units/kg (max weight 100kg)
- MoA: replaces Factors II, IX, X, and activated VII
- Limitation: the most serious adverse reaction is the risk of thrombotic events including stroke, DVT, PE (theoretically higher compared to Kcentra)
- Advantage: Fast reconstitution and administration, and low volume compared to FFP

Heparin Reversal

Heparin (unfractionated) indirectly inhibits Factor Xa and Factor IIa via antithrombin III.

protamine
- Dose: 1 mg of protamine for every 100 units of heparin administered in the last 2 – 3 hours (maximum dose 50 mg over any 10 minute period)
- MoA: protamine (highly alkaline, positively charged protein) forms a stable salt with heparin (strongly acidic, negatively charged) to neutralize anticoagul effect
- Limitation: excessive protamine administration may exacerbate bleeding, since protamine itself is a weak anticoagulant, anaphylaxis
- Advantage: fast administration via slow IV push (50mg over 10 minutes), quick correction of aPTT

LMWH Reversal

LMWH (unfractionated) indirectly inhibits Factor Xa and Factor IIa via antithrombin III.

protamine
- Dose: Enoxaparin <8 hours: 1 mg of protamine for every 1 mg of LMWH administered
  Enoxaparin >8 hours: 0.5 mg of protamine for every 1 mg of LMWH administered
- MoA: protamine (highly alkaline, positively charged protein) forms a stable salt with heparin (strongly acidic, negatively charged) to neutralize anticoagul effect
- Limitation: excessive protamine administration may exacerbate bleeding, risk of anaphylaxis, only 60 – 75% of the anti-xa activity is neutralized
- Advantage: fast administration via slow IV push (50mg over 10 minutes), quick correction of aPTT

Subarachnoid Hemorrhage (SAH)

Common locations: Circle of Willis, Anterior Communicating Artery, Middle Cerebral Artery, Posterior Communicating Artery, Internal Carotid Bifurcation
Risk factors
  Nonmodifiable: >50yo, Female, AA/Hispanic, family history, certain genetic disorders
  Modifiable: HTN, alcohol, smoking, sympathomimetic use
Presentation: "worse headache of my life", loss of consciousness, NV, nuchal rigidity
Severity scale – Hunt and Hess (Survival%)
  Grade 0 unruptured aneurysm Grade I (70%) asymp-minimal HA normal neuro exam;
  Grade II (60%) mod-severe HA, nuchal rigidity, no neuro except cranial nerve palsy Grade III (50%) lethargy, confusion, or mild focal deficit
  Grade IV (20%) stupor, mod-sev hemiparesis, vegetative disturb, early decerebrate rigidity Grade V (10%) deep coma, moribund appearance, decerebrate rigidity
Severity scale – Fisher (Vasospasm%)
  Grade I (0-21%) no blood visualized Grade II (0-25%) a diffuse deposition or thin layer with all vertical layers of blood <1mm thick
  Grade III (23-96%) localized clots and/or vertical layers of blood >1mm thick Grade IV (0-35%) diffuse or no subarachnoid blood, but intracerebral or intraventricular clots
Complications
  Hydrocephalus, Vasospasm→Delayed Cerebral Ischemia (DCI), Re-bleeding, Seizures: permanent disability
Nonpharm therapy: securing the aneurysm
  clipping the aneurysm; coiling the aneurysm
Pharmacologic therapy: Initial: BP control Later: vasospasm management
<u>SAH BP control</u>
Prior to securing aneurysm goal is SBP <140; utilize same agents as you would for ICH
After securing aneurysm goal is SBP <220 (after no more bleeding risk, let BP ride up due to risk of vasospasm; let BP rise so adequate distal perfusion)

<u>SAH Vasospasm management</u>
Complication: Vasospasm is consistent vasoconstriction of the artery secondary to blood surrounding the vessel
  • Most likely to occur 4-21 days after ictus • Vasospasm leads to delayed cerebral ischemia (DCI)
***nimodipine** (Nimotop, Nymalize); lipid-soluble CCB; does not reduce vasospasm incidence; however, it significantly reduced DCI by 34% (improves morbidity)
Dose: 60mg PO q4h x21 days BBW: enteral administration only
ADE: hypotension; may reduce to 30mg PO q2h

Other vasospasm management: maintain euvolemia, vasopressor therapy, angioplasty, intra-arterial verapamil, intra-arterial nicardipine, intra-arterial milrinone

Acid/Base

Evaluate acid-base disorders using a systematic approach
Identify etiologies of acid-base disorders using patient cases
Predict the appropriate compensatory response for patients with acid-base disorders
Describe the role of a critical care pharmacist in the management of acid-base disorders

Why is acid-base homeostasis important?
A normal pH is required to maintain physiologic function in the body: Protein function, Enzyme function, Normal cellular processes, Oxygen delivery
Result of prolonged loss of acid-base homeostasis: Death

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

(acid)	carbonic acid	bicarbonate (base)
lungs		blood

Others: acids: chloride, proteins, lactic acid; bases: DNA

ROME – metabolic disorder = equal direction (both down)
ROME – respiratory disorder = opposite direction

Metabolic Acidosis

pH <7.35
HCO3 <22

Anion gap
Gap acidosis represents additional contribution of acid; aids in determination of etiology
Calculation: Na – (HCO3 + Cl) Normal anion gap <12
ex. 140-(150+12)=23, therefore pt has anion gap metabolic acidosis likely secondary to elevated lactate

Etiologies
Anion gap MA (MUDPLIES): Methanol, Uremia, Diabetic ketoacidosis, Propylene glycol, Isoniazid/Iron, *Lactic acid, Ethylene glycol, Salicylates
Nonanion gap MA (ACCRUED): Aldosterone inh, Compensation, Carbonic anhydr inh, Renal tubular acidosis, Ureteral diversion, Extra alimentation TPN, Diarrhea

Respiratory Acidosis

pH <7.35
CO2 >45

Etiologies
central respiratory depression (sedation), airway obstruction, *COPD, ARDS, pneumothorax, thoracic cage injury, rate too low on ventilator

Metabolic Alkalosis

pH>7.45
HCO3 >26

Etiologies
Chloride responsive (U_{Cl} <10): vomiting, nasogastric suctioning, previous diuretic use
  *overall depletion of chloride
Chloride unresponsive (U_{Cl} >20): current use of diuretics, refeeding syndrome (hypokalemia), excess mineralocorticoid
  *overall focused on hypokalemia that causes reabsorption of bicarb in proximal tubule

How compensation works
If your pH is normal, everything must be fine, right? Your body is designed to compensate for acid-base disorders and mixed disorders are possible.
Utilizes the buffer system to maintain homeostasis
Timing of compensation
  Respiratory: Response observed within minutes of acid-base derangement; Full compensation seen within hours
  Renal (metabolic): Initial response occurs within 6-12 hours after derangement; Full compensation may take 3-5 days
Compensation is classified as uncompensated, partially compensated, or fully compensated

Expected compensation

Disorder	Compensation	
Metabolic Acidosis	Winter's formula: $PaCO_2 = 1.5(HCO_3) + 8 \pm 2$	
	For each change in $PaCO_2$ (relative to 40 mmHg)	**Change in HCO_3**
Respiratory Acidosis		
Acute	↑10 mmHg	↑1 mEq/L
Chronic	↑10 mmHg	↑4 mEq/L
Respiratory Alkalosis		
Acute	↓10 mmHg	↓2 mEq/L
Chronic	↓10 mmHg	↓5 mEq/L

RPh role in acid-base disorders:
Sedation management, Pain management, TPN, Vasopressor effectiveness, Supplementation of bicarbonate or chloride, Diuresis management

Physiological Values

Parameter	Normal	Where can be found?
pH	7.35-7.45	arterial blood gas
$PaCO_2$	35-45 mmHg	arterial blood gas
HCO_3	22-26 mEq/L	chemistry/arterial blood gas
Na	135-145 mEq/L	chemistry
Cl	96-106 mEq/L	chemistry
lactate	<2 mEq/L	chemistry

pH <7.35 ↑CO_2 Respiratory Acidosis
pH <7.35 ↓HCO_3 Metabolic Acidosis
pH 7.35-7.45 Normal, Compensated, or Mixed
pH >7.45 ↓CO_2 Respiratory Alkalosis
pH >7.45 ↑HCO_3 Metabolic Alkalosis

	pH	$PaCO_2$	HCO_3
Respiratory Acidosis	↓	↑	↑
Respiratory Alkalosis	↑	↓	↓
Metabolic Acidosis	↓	↓	↓
Metabolic Alkalosis	↑	↑	↑

pH		$PaCO_2$	HCO_3	
↓	**Acidosis**	↑	↑	**Respiratory**
↑	**Alkalosis**	↓	↓	**Respiratory**
↓	**Acidosis**	↓	↓	**Metabolic**
↑	**Alkalosis**	↑	↑	**Metabolic**

Emergency Response

Describe the role of a pharmacist in emergency response scenarios
Identify the common causes of cardiac arrest and appropriate treatment
Design a patient specific medication regimen for rapid sequence intubation

Pharmacist Role

- Anticipate the medication needs of the team
- Prepare medications
- Ensure appropriateness and accuracy of medication dose
- Recommend medications per ACLS algorithm or clinical scenario
- Coordinate delivery/retrieval of medications not available in the unit

Cardiac Arrest

- Ventricular Fibrillation/Pulseless Ventricular Tachycardia (VF/VT)
- Pulseless Electrical Activity (PEA)
- Asystole (no pulse)

Reversible Causes

- Hypoxia
- Hypovolemia
- Hydrogen ion
- Hypo/Hyperkalemia
- Hypothermia
- Toxin
- Tamponade (cardiac)
- Tension Pneumothorax
- Thrombosis (pulmonary)
- Thrombosis (cardiac)

Hyperkalemia		
calcium gluconate	3g IV	stabilizes myocardium
regular insulin	10u IV	shifts K intracellular
albuterol	10-20mg inh	shifts K intracellular
sodium bicarbonate	50mEq IV	shifts K intracellular
furosemide	20mg IV	inhibits Na-K-Cl transporter; **removes K**
sodium polystyrene sulfonate	30-45g PO	Na-K exchanger; **removes K** (4-6h)

Advanced Cardiac Life Support (ACLS)

- Key components
  - Good quality chest compressions
  - Early defibrillation
  - Medications: Epinephrine, Vasopressin, Amiodarone, Lidocaine

ACLS: Asystole/PEA

- Non-shockable rhythm
- Pulse and rhythm check every 2 minutes
- Medications
  - Epinephrine 1mg every 3-5 minutes
  - Vasopressin 40 units (alternative to second epinephrine dose)
- Treat underlying cause!!

ACLS: VT/VF

- Shockable rhythm
- Pulse and rhythm check every 2 minutes
- Medications
  - Epinephrine 1mg every 3-5 minutes
  - Vasopressin 40 units (alternative to second epinephrine dose)
  - Amiodarone: First dose: 300mg, Second dose: 150mg
  - Lidocaine: First dose 1-1.5mg/kg, Second dose 0.5-0.75mg/kg
- Treat underlying cause!!

Team Work Makes The Dream Work

Rapid Sequence Intubation (RSI)

- Utilized to facilitate intubation in patients with respiratory compromise
- Utilization of pre-specified sequential steps including sedation followed by paralyzing agent
  - **SEDATION ALWAYS GOES FIRST!**
- Used to prevent aspiration and reduce sympathetic effects
- Optimal medication selection is imperative to reduce side effects

RIS Medications

	Onset	Duration	ADEs
Sedatives			
etomidate (GABA-A)	10-20 sec	4-10 min	myoclonus, adrenal suppression
ketamine (NMDA antag)	1-2 min	5-10 min	emergence phenomena, increased sympathetic response
propofol (GABA-A)	1-2 min	5-10 min	hypotension
midazolam (GABA-A)	3-5 min	1-2 hr	hypotension (less than propofol)
Paralytics			
succinylcholine (depolarizing)	15-30 sec	5-10 min	hyperkalemia
rocuronium (nondepol)	1-2 min	30-45 min	prolonged paralysis in hepatic failure
vecuronium (nondepol)	2-3 min	45-60 min	prolonged paralysis in hepatic/renal failure

give sedative first then paralytic

Trauma

- Ensure appropriateness and accuracy of antibiotics
- Recommending tetanus vaccine
- Fluid resuscitation
- Anticoagulation reversal

Stroke

- Aid in appropriate patient selection for TPA
- Assist in selection of appropriate agents for blood pressure management
- Anticoagulation reversal

Pulmonary Embolism Response Team (PERT)

- Determine appropriate therapy based on clinical picture
  - Systemic thrombolytic therapy
  - Catheter directed thrombolytic therapy
  - Anticoagulation: Heparin, Bivalirudin
- Assist with dosing and timing of thrombolytics and anticoagulation

STEMI/eCPR

- Optimal antithrombotic therapy is essential to prevent ongoing ischemia
- Determine most appropriate antithrombotic regimen
  - Aspirin
  - P2Y12 inhibitors: Clopidogrel, Prasugrel, Ticagrelor
  - Glycoprotein IIb/IIIa inhibitors
  - Heparin vs Bivalirudin

Blood Factor Stewardship

- Concentrated factor products
  - 3 Factor Prothrombin Complex Concentrate (PCC)
  - 4 Factor PCC
  - 4 Factor activated PCC
  - Concentrated fibrinogen
  - Factor IX
  - Factor VIII
- Utilized in
  - Life threatening bleeding
  - Anticoagulation reversal

Sepsis Alert

- Ensure adequate fluid resuscitation
- If needed provide recommendations on hemodynamic monitoring and presser support
- Assist in appropriate antibiotic selection

Pharmaceutics of Critical Care

Review pharmacokinetic (PK) processes
Evaluate pathophysiology and clinical impact of critical illness mediated pharmacokinetic (PK) alterations
Clinically assess potential PK alterations and implement adjustments needed in the critically ill population

Pharmacokinetics: impact of body on drug
Pharmacodynamics: impact of drug on body

PK-PD relationship … Cmax/MIC … Time >MIC … AUC/MIC … Efficacy

Absorption

Absorption Highlights

- When changing medications from IV to PO it is important to look up the IV to PO conversion
- Enteral feeds can interact with medications administered via the enteral route:
  - Enteral feeds can increase the pH of the stomach reducing the absorption of drugs that need an acidic environment for absorption
  - Tube feed ingredients can directly bind to some drugs causing decreased absorption (i.e., phenytoin, ciprofloxacin)
- To overcome drug and nutrient interactions enteral feeds can be held 1 hour before and 2 hours after drug administration
  - To avoid underfeeding, tube feed rates should be adjusted so patients can receive the total daily caloric goal

Distribution

Context Sensitive Half Life
Accumulation of lipophilic drugs in the deep adipose compartment causes longer duration of action than can be explained by the medications half lives; (context = infusion duration)

Distribution: Plasma Protein Binding

Distribution Highlights

- In critically ill patients with hypoalbuminemia, drugs like phenytoin, valproic acid, and ceftriaxone that are highly protein bound will have a greater free fraction of free drug, leading to increased pharmacologic effects even if the total drug level remains unchanged
  - When possible, in the critically ill, drugs that are highly protein bound should be monitored by free levels instead of total levels
  - Consider increased dosing

Metabolism

Transformation of parent compounds into metabolites: Liver (primary site), GI tract, Kidneys, Lungs, Brain
Several alterations in critical illness: Hepatic enzyme activity, Protein binding, Hepatic blood flow

Metabolism: Hepatic Blood Flow
Increased hepatic blood flow and metabolism: Early sepsis (increased cardiac output), Vasodilator use (i.e., nitroprusside), Inotropes
Decreased hepatic blood flow and metabolism: Late sepsis (decreased cardiac output), Hypovolemic shock, Myocardial infarction and acute heart failure, Vasopressor use

Metabolism: Hepatic Enzyme Activity
Many critically ill states will results in an increased hepatic metabolism: Traumatic brain injury, Burn patients
Decreased activity of CYP450 enzymes occur during stress response: Prolonged effects of parent compounds, Reduced effects of prodrugs, Increase in toxic metabolites

Elimination

Medications eliminated renally most impacted: Proportional to glomerular filtration rate or CrCl
Consider true CrCl collection/measurement: Challenging to assess due to fluctuations and fluid shifts; Consider true CrCl as opposed to calculations in some populations
Altered elimination in critically ill patients: Reduced clearance (kidney injury or failure); Augmented clearance

Augmented Renal Clearance

Hyperdynamic = ↑CO = ↑renal blood flow = ↑GFR
CrCl >130 ml/min (20-65% of critically ill); physiological mechanism poorly dilineated
Associated with subtherapeutic concentrations of renally-eliminated drugs

Effects of PK Alterations of Cp

Risk Factors

PK/PD Alterations: CRRT

Vd should be primary PK consideration for initial dosing: Critical illness, sepsis, AKI, CHF/reduced EF all potential factors
Remaining CLR and CLNR dictate maintenance dosing
CRRT clearance affected by protein binding, absorption, and CRRT settings
CRRT clearance will vary based on mode: CVVH – convective removal; CVVHD – diffusion of solute across filter membrane down a conc gradient; CVVHDF – combines both properties
Decreased CRRT clearance if: Large molecule, Highly protein bound, Vd > 1.5 L/kg

Factors Affecting Elimination

Clinical Implications

Antimicrobial success dependent on early initiation, appropriate selection, and dosing to attain PK/PD target
Negative impact on therapeutic level attainment
Affects renally cleared drugs, including B-lactams, vancomycin, & AG
Enhanced drug clearance will lead to shorter half-life, lower Cmax, and smaller AUC
May compromise drug efficacy and promote drug resistance

Elimination Highlights

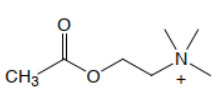
- Commonly critically ill patients combat multi-organ failure as a complication of their critical illness
- Patients should be monitored closely for increased or decreased renal function
- Consider therapeutic drug monitoring via drug levels or therapeutic effect for renally-eliminated medications
- Medications that are cleared primarily by the kidneys should be evaluated for the following: Dose, Interval, Therapeutic drug monitoring (drug levels or associated labs i.e. anti-Xa)

PK Changes to Critical Illness

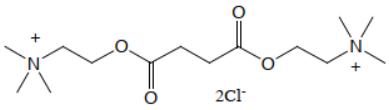
↑CO Cardiac Output = ↑CL = ↓Cp
Leaky capillaries or altered PPB = ↑Vd = ↓Cp
Normal organ function = unchanged Vd = normal Cp
End organ dysfunction (renal/hepatic) = ↓CL = ↑Cp

Li NMBA MC

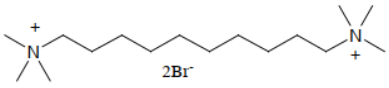
d-Tubo**cur**arine chloride: neuromuscular blocking effect has containing 2 positively charged ammonium ions separated by 10 – 12 carbons
post-synaptic side of neuron
Each Acetylcholine receptor has 2 receptive sites and activation of the receptor requires binding to both of them.
Each receptor site is located at one of the two α subunits of the receptor.



Acetylcholine



Succinylcholine



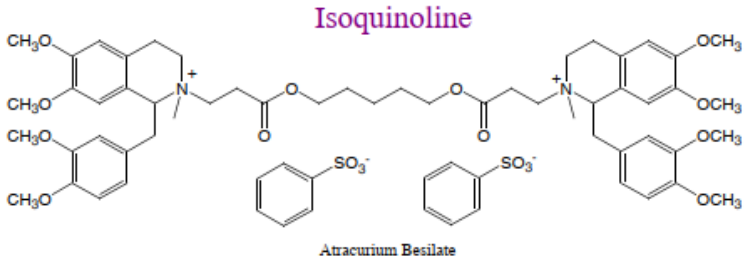
Decamethonium bromide

Depolarizing NMBA (Succinylcholine)

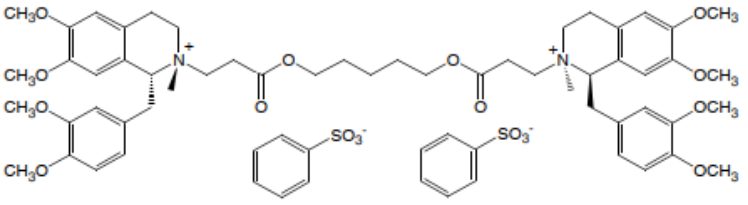
Depolarizing work by depolarizing plasma membrane of muscle fiber, similar to acetylcholine
Bind to acetylcholine binding site and open sodium channel
More resistant to degradation by acetylcholinesterase, thus more persistently depolarize muscle fibers
Constant depolarization and triggering of receptors keeps endplate resistant to activation by ACh (**densensitization**)
Phase I: depolarizing phase: membrane depolarizes, resulting in intiatl discharge that produces transient fasciulations followed by flaccid paralysis
Phase II: desensitizing phase: membrane repolarizes, but receptor densensitized to effect of ACh

Nondepolarizing NMBA

MoA: competitive antagonists by competitively block the binding of ACh to its nicotinic receptors and block muscle contraction
- neuromuscular blockade can occur even if only one alpha subunit blocked; since both subunits need to be occupied by ACh for receptor to work

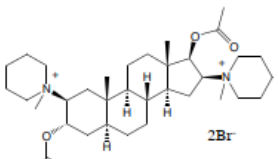


Atracurium Besilate

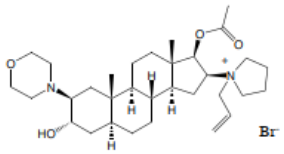


Cisaracurium Besilate

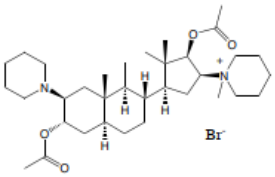
isoquinoline scaffold (atracurium, cisatracurium): quarternary nitrogen, permanently positively charged
atracurium (isoquinoline): ester hydrolysis x2, Hoffman elimination (nonenzymatic)
once you hydrolyze the first one, metabolite no longer active
steroidal (pancuronium, rocuronium, vecuronium): quarternary and tertiary amines
longer half-life, due to metabolism and metabolite still active



Pancuronium Bromide



Rocuronium Bromide



Vecuronium Bromide

Suggaamadex: selective relaxant binding agent (SRBA)
for reversal of neuromuscular blockade for rocuronium, vecuronium (not pancuronium due to both being quarternary charged amines)
γ-cyclodextrin with lipophilic core and hydrophilic periphery; negatively charged; bind to NMBA ionic intx
rocuronium bound within sugammadex's lipophilic core, is rendered unavailable to bind to ACh receptor at NMJ

Appendix

Classification of shock

Distributive	**Septic**	Gram positive (*Pneumococcus*, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Listeria*) Gram negative (*Klebsiella*, *Pseudomonas*, *Escherichia*, *Haemophilus*, *Legionella, Neisseria*, *Moraxella*, *Rickettsia*, *Francisella* [*tularemia*]) Fungal (*Candida*, *Aspergillus*) Viral (influenza, cytomegalovirus, Ebola, varicella) Parasitic (*Plasmodium*, *Ascaris*, *Babesia*) Mycobacterium (*Mycobacterium tuberculosis*, *Mycobacterium abscessus*)
	Non-septic	Inflammatory shock (systemic inflammatory response syndrome) – Burns, trauma, pancreatitis, postmyocardial infarction, post coronary bypass, post cardiac arrest, viscus perforation, amniotic fluid embolism, fat embolism, idiopathic systemic capillary leak syndrome Neurogenic shock – Traumatic brain injury, spinal cord injury (quadriparesis with bradycardia or paraplegia with tachycardia), neuraxial anesthesia Anaphylactic shock – IgE-mediated (eg, foods, medications, insect bites or stings), IgE-independent (eg, iron dextran), nonimmumnologic (eg, exercise or heat-induced), idiopathic Other – Liver failure, transfusion reactions, vasoplegia (eg, vasodilatory agents, cardiopulmonary bypass), toxic shock syndrome, toxicologic (eg, heavy metals), beriberi
Cardiogenic	**Cardiomyopathic**	Myocardial infarction (involving >40% of the left ventricle or with extensive ischemia) Severe right ventricle infarction Acute exacerbation of severe heart failure from dilated cardiomyopathy Stunned myocardium from prolonged ischemia (eg, cardiac arrest, hypotension, cardiopulmonary bypass) Advanced septic shock Myocarditis Myocardial contusion Drug-induced (eg, beta blockers)
	Arrhythmogenic	Tachyarrhythmia – Atrial tachycardias (fibrillation, flutter, reentrant tachycardia), ventricular tachycardia and fibrillation Bradyarrhythmia – Complete heart block, Mobitz type II second degree heart block
	Mechanical	Severe valvular insufficiency, acute valvular rupture (papillary or chordae tendineae rupture, valvular abscess), critical valvular stenosis, acute or severe ventricular septal wall defect, ruptured ventricular wall aneurysm, atrial myxoma
Hypovolemic	**Hemorrhagic**	Trauma, gastrointestinal bleeding (eg, varices, peptic ulcer), intraoperative and postoperative bleeding, retroperitoneal bleeding (eg, ruptured aortic aneurysm), aortic-enteric fistula, hemorrhagic pancreatitis, iatrogenic (eg, inadvertent biopsy of arteriovenous malformation, or left ventricle), tumor or abscess erosion into major vessels, ruptured ectopic pregnancy, postpartum hemorrhage, uterine or vaginal hemorrhage (eg, infection, tumors, lacerations), spontaneous peritoneal hemorrhage from bleeding diathesis
	Non-hemorrhagic	Gastrointestinal losses (eg, diarrhea, vomiting, external drainage); skin losses (eg, heat stroke, burns, dermatologic conditions); renal losses (eg, excessive drug-induced or osmotic diuresis, salt-wasting nephropathies, hypoaldosteronism); third space losses into the extravascular space or body cavities (eg, postoperative and trauma, intestinal obstruction, crush injury, pancreatitis, cirrhosis)
Obstructive	**Pulmonary vascular**	Hemodynamically significant pulmonary embolus, severe pulmonary hypertension, severe or acute obstruction of the pulmonic or tricuspid valve, venous air embolus
	Mechanical	Tension pneumothorax or hemothorax (eg, trauma, iatrogenic), pericardial tamponade, constrictive pericarditis, restrictive cardiomyopathy, severe dynamic hyperinflation (eg, elevated intrinsic PEEP), left or right ventricular outflow tract obstruction, abdominal compartment syndrome, aorto-caval compression (eg, positioning, surgical retraction)
Mixed/unknown		Endocrine (eg, adrenal insufficiency, thyrotoxicosis, myxedema coma) Metabolic (eg, acidosis, hypothermia) Other – Polytrauma with more than one shock category, acute shock etiology with pre-existing cardiac disease, late under-resuscitated shock, miscellaneous poisonings

Vasopressors and inotropes in treatment of acute hypotensive states and shock: Adult dose and selected characteristics

Agent	Initial dose	Usual maintenance dose range	Range of maximum doses used in refractory shock	Role in therapy and selected characteristics
Vasopressors (alpha-1 adrenergic)				
Norepinephrine (noradrenaline) Levophed	5 to 15 mcg/minute (0.05 to 0.15 mcg/kg/minute) Cardiogenic shock: 0.05 mcg/kg/minute	2 to 80 mcg/minute (0.025 to 1 mcg/kg/minute) Cardiogenic shock: 0.05 to 0.4 mcg/kg/minute	80 to 250 mcg/minute (1 to 3.3 mcg/kg/minute)	Initial vasopressor of choice in septic, cardiogenic, and hypovolemic shock. Wide range of doses utilized clinically. Must be diluted; eg, a usual concentration is 4 mg in 250 mL of D5W or NS (16 micrograms/mL).
Epinephrine (adrenaline) Adrenalin	1 to 15 mcg/minute (0.01 to 0.2 mcg/kg/minute)	1 to 40 mcg/minute (0.01 to 0.5 mcg/kg/minute)	40 to 160 mcg/minute (0.5 to 2 mcg/kg/minute)	Initial vasopressor of choice in anaphylactic shock. Typically an add-on agent to norepinephrine in septic shock when an additional agent is required to raise MAP to target and occasionally an alternative first-line agent if norepinephrine is contraindicated. Increases heart rate; may induce tachyarrhythmias and ischemia. For inotropy, doses in the higher end of the suggested range is needed Elevates lactate concentrations during initial administration (ie, may preclude use of lactate clearance goal); may decrease mesenteric perfusion. Must be diluted; eg, a usual concentration is 1 mg in 250 mL D5W (4 micrograms/mL).
Phenylephrine Neo-Synephrine, Vazculep	100 to 180 mcg/minute until stabilized (alternatively, 0.5 to 2 mcg/kg/minute)	20 to 80 mcg/minute (0.25 to 1.1 mcg/kg/minute)	80 to 360 mcg/minute (1.1 to 6 mcg/kg/minute); Doses >6 mcg/kg/minute do not increase efficacy according to product information in the United States	Pure alpha-adrenergic vasoconstrictor. Initial vasopressor when tachyarrhythmias preclude use of norepinephrine. Alternative vasopressor for patients with septic shock who: (1) develop tachyarrhythmias on norepinephrine, epinephrine, or dopamine, (2) have persistent shock despite use of two or more vasopressor/inotropic agents including vasopressin (salvage therapy), or (3) high cardiac output with persistent hypotension. May decrease stroke volume and cardiac output in patients with cardiac dysfunction. May be given as bolus dose of 50 to 100 mcg to support blood pressure during rapid sequence intubation. Must be diluted; eg, a usual concentration is 10 mg in 250 mL D5W or NS (40 mcg/mL).
Dopamine Inotropin	2 to 5 mcg/kg/minute	5 to 20 mcg/kg/minute	20 to >50 mcg/kg/minute	An alternative to norepinephrine in septic shock in highly selected patients (eg, with compromised systolic function or absolute or relative bradycardia and a low risk of tachyarrhythmias). More adverse effects (eg, tachycardia, arrhythmias particularly at doses ≥20 mcg/kg/minute) and less effective than norepinephrine for reversing hypotension in septic shock. Lower doses (eg, 1 to 3 mcg/kg/minute) should not be used for renal protective effect and can cause hypotension during weaning. Must be diluted; eg, a usual concentration is 400 mg in 250 mL D5W (1.6 mg/mL); use of a commercially available pre-diluted solution is preferred.
Antidiuretic hormone				
Vasopressin (arginine-vasopressin) Pitressin, Vasostrict	0.03 units per minute (alternatively 0.01 to 0.03 units/minute initially)	0.03 to 0.04 units per minute (not titrated)	0.04 to 0.07 units/minute; Doses >0.04 units/minute can cause cardiac ischemia and should be reserved for salvage therapy	Add-on to norepinephrine to raise blood pressure to target MAP or decrease norepinephrine requirement. Not recommended as a replacement for a first-line vasopressor. Pure vasoconstrictor; may decrease stroke volume and cardiac output in myocardial dysfunction or precipitate ischemia in coronary artery disease. Must be diluted; eg, a usual concentration is 25 units in 250 mL D5W or NS (0.1 units/mL).
Inotrope (beta$_1$ adrenergic)				
Dobutamine Dobutrex	0.5 to 1 mcg/kg/minute (alternatively, 2.5 mcg/kg/minute in more severe cardiac decompensation)	2 to 20 mcg/kg/minute	20 to 40 mcg/kg/minute; Doses >20 mcg/kg/minute are not recommended in heart failure and should be reserved for salvage therapy	Initial agent of choice in cardiogenic shock with low cardiac output and maintained blood pressure. Add-on to norepinephrine for cardiac output augmentation in septic shock with myocardial dysfunction (eg, in elevated left ventricular filling pressures and adequate MAP) or ongoing hypoperfusion despite adequate intravascular volume and use of vasopressor agents. Increases cardiac contractility and rate; may cause hypotension and tachyarrhythmias. Must be diluted; a usual concentration is 250 mg in 500 mL D5W or NS (0.5 mg/mL); use of a commercially available pre-diluted solution is preferred.
Inotrope (nonadrenergic, PDE$_3$ inhibitor)				
Milrinone Primacor	Optional loading dose: 50 mcg/kg over 10 minutes (usually not given)	0.125 to 0.75 mcg/kg/minute		Alternative for short-term cardiac output augmentation to maintain organ perfusion in cardiogenic shock refractory to other agents. Increases cardiac contractility and modestly increases heart rate at high doses; may cause peripheral vasodilation, hypotension, and/or ventricular arrhythmia. Renally cleared; dose adjustment in renal impairment needed. Must be diluted; eg, a usual concentration is 40 mg in 200 mL D5W (200 micrograms/mL); use of a commercially available pre-diluted solution is preferred.

• All doses shown are for intravenous (IV) administration in adult patients. The initial doses shown in this table may differ from those recommended in immediate post-cardiac arrest management (ie, advanced cardiac life support). For details, refer to the UpToDate topic review of post-cardiac arrest management in adults, section on hemodynamic considerations.

• Vasopressors can cause life-threatening hypotension and hypertension, dysrhythmias, and myocardial ischemia. They should be administered by use of an infusion pump adjusted by clinicians trained and experienced in dose titration of intravenous vasopressors using continuous noninvasive electronic monitoring of blood pressure, heart rate, rhythm, and function. Hypovolemia should be corrected prior to the institution of vasopressor therapy. Reduce infusion rate gradually; avoid sudden discontinuation.

• Vasopressors can cause severe local tissue ischemia; central line administration is preferred. When a patient does not have a central venous catheter, vasopressors can be temporarily administered in a low concentration through an appropriately positioned peripheral venous catheter (ie, in a large vein) for less than 24 hours. The examples of concentrations shown in this table are useful for peripheral (short-term) or central line administration. Closely monitor catheter site throughout infusion to avoid extravasation injury. In event of extravasation, prompt local infiltration of an antidote (eg, phentolamine) may be useful for limiting tissue ischemia. Stop infusion and refer to extravasation management protocol.

• Vasopressor infusions are high-risk medications requiring caution to prevent a medication error and patient harm. To reduce the risk of making a medication error, we suggest that centers have available protocols that include steps on how to prepare and administer vasopressor infusions using a limited number of standardized concentrations. Examples of concentrations and other detail are based on recommendations used at experienced centers; protocols can vary by institution.

Hemodynamic profiles of shock on pulmonary artery catheter in adults

Physiologic variable	Preload	Pump function	Afterload	Tissue perfusion
Clinical measurement	Pulmonary capillary wedge pressure	Cardiac output*	Systemic vascular resistance	Mixed venous oxyhemoglobin saturation¶
Hypovolemic	↔ (early) or ↓ (late)	↔ (early) or ↓ (late)	↑	>65% (early) or <65% (late)
Cardiogenic	↑	↓	↑	<65%
Distributive	↔ (early) or ↓ (late)	↑ or ↓ (occasionally)	↓	>65%
Obstructive				
PE, PH, tension pneumothorax	↔ (early) or ↓ (late)	↔ (early) or ↓ (late)	↑	>65%
Pericardial tamponade[Δ]	↑	↓	↑	<65%

PE: pulmonary embolus; PH: pulmonary hypertension; PAC: pulmonary artery catheter.

* Cardiac output is generally measured using the cardiac index. ¶ Mixed venous oxyhemoglobin saturation cutoff measured on PAC is 65%, but on triple lumen catheter is 70%.

Δ Equalization of right atrial, right ventricular end-diastolic and pulmonary artery wedge pressures is classic in pericardial tamponade; distinguishes it from primary cardiogenic shock.

Rapid overview: Emergency management of anaphylaxis in adults

Diagnosis is made clinically:

The most common signs and symptoms are cutaneous (eg, sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10 to 20% of patients have no skin findings.

Danger signs: Rapid progression of symptoms, respiratory distress (eg, stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), vomiting, abdominal pain, hypotension, dysrhythmia, chest pain, collapse.

Acute management:

The first and most important treatment in anaphylaxis is epinephrine. There are **NO absolute contraindications to epinephrine** in the setting of anaphylaxis.

Airway: Immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary.

Promptly and simultaneously, give:

- **IM epinephrine (1 mg/mL preparation):** Give epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-outer thigh. Can repeat every 5 to 15 minutes (or more frequently), as needed. If epinephrine is injected promptly IM, most patients respond to one, two, or at most, three doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion.
- **Place patient in recumbent position**, if tolerated, and elevate lower extremities.
- **Oxygen:** Give 8 to 10 L/minute via facemask or up to 100% oxygen, as needed.
- **Normal saline rapid bolus:** Treat hypotension with rapid infusion of 1 to 2 liters IV. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur.
- **Albuterol (salbutamol):** For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer, or 2 to 3 puffs by metered dose inhaler. Repeat, as needed.

Adjunctive therapies:

- **H1 antihistamine*:** Consider giving cetirizine 10 mg IV (given over 2 minutes) or diphenhydramine 25 to 50 mg IV (given over 5 minutes) – for relief of urticaria and itching only.
- **H2 antihistamine*:** Consider giving famotidine 20 mg IV (given over 2 minutes).
- **Glucocorticoid*:** Consider giving methylprednisolone 125 mg IV.
- **Monitoring:** Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

Treatment of refractory symptoms:

- **Epinephrine infusion¶:** For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, beginning at **0.1 mcg/kg/minute** by infusion pumpΔ. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation.
- **Vasopressors¶:** Some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure and cardiac rate/function and oxygenation monitored by pulse oximetry.
- **Glucagon:** Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15 mcg/minute. Rapid administration of glucagon can cause vomiting.

* These medications should not be used as initial or sole treatment.

¶ All patients receiving an infusion of epinephrine and another vasopressor require continuous noninvasive monitoring of BP, HR, function, and oxygen saturation.

Δ For example, the initial infusion rate for a 70 kg patient would be 7 mcg/minute. This is consistent with the recommended range for non-weight-based dosing for adults, which is 2 to 10 mcg/minute. Non-weight-based dosing can be used if the patient's weight is not known and cannot be estimated.

TABLE 41-1 Adrenergic, Dopaminergic, Vasopressin, and Angiotensin Receptor Pharmacology and Organ Distribution

Effector Organ	Receptor Subtype	Physiologic Response
Heart		
Sinoatrial node	β_1, β_2, AT-1	Increased heart rate
Atria	β_1, β_2	Increased contractility Increased conduction velocity
Atrioventricular node	β_1, β_2, AT-1	Increased automaticity Increased conduction velocity
His-Purkinje system	β_1, β_2, AT-1	Increased automaticity Increased conduction velocity
Ventricles	α_1, AT-1 β_1, β_2	Increased contractility Increased contractility Increased conduction velocity Increased automaticity Increased rate idioventricular pacemaker cells
Arterioles		
Coronary	α_1, α_2, V1, AT-1; β_2, D1, V2 (via NO)	Constriction; dilation
Skin and mucosa	α_1, α_2, V1, AT-1	Constriction
Skeletal muscle	α_1, V1, AT-1; β_2, AT-2	Constriction; dilation
Cerebral	α_1, V1, AT-1; V2 (via NO)	Constriction (slight); dilation
Pulmonary	α_1; β_2, V2 (via NO)	Constriction; dilation
Abdominal viscera (mesentery)	α_1, V1; β_2, D1	Constriction; dilation
Renal	α_1, α_2, V1, AT-1; β_1, β_2, D1, AT-2	Constriction; dilation
Veins (systemic)	$\alpha_{1, \alpha2; \beta2}$	Constriction; dilation
Lungs		
Tracheal/bronchial smooth muscle	β_2	Relaxation
Bronchial glands	α_1; β_2	Decreased; increased secretion
Stomach		
Motility and tone	α_1, α_2, β_1, β_2	Decreased (usually)
Sphincter	α_1	Contraction (usually)
Secretions	α_2	Inhibition
Intestine		
Motility and tone	α_1, α_2, β_1, β_2; V_1	Decreased (usually)
Sphincters	α_1	Contraction
Secretions	α_2	Inhibition
Kidney		
Aldosterone secretion	AT-1	Increased
Renin secretion	α_1; β_1	Decreased; increased
Reabsorption of water	V2, AT-1	Increased
Sodium reabsorption and H^+ excretion	AT-1; AT-2	Increased; decreased
Skeletal muscle	β_2	Increased contractility, glyconeogenesis, K^+ uptake
Liver	α_1, β_2	Glycogenolysis and gluconeogenesis
Fat cells	α_1, β_1, β_2	Lipolysis (thermogenesis)
Pituitary	V1, AT-1	Adrenocorticotropic hormone secretion
Hypothalamus	AT-1	Vasopressin secretion
Nervous	AT-1	Enhanced norepinephrine secretion
Immune		
Pro-inflammatory cytokine release, macrophage and T-cell activation	AT-1; AT-2	Increased; decreased
Coagulation system		
	V1	Thromboxane synthesis (platelet aggregation)
	AT-1	Release of plasminogen activator inhibitor-1, platelet activation

TABLE 41-4 General Indications and Concerns for Blood Products and Prothrombin Complex Concentrates[a]

Product	Major Indication	Major Concerns
Packed red blood cells	Increase oxygen-carrying capacity of blood. Usually indicated in patients with continued deterioration after volume replacement or obvious exsanguination	Hypocalcemia, hyperkalemia, hyperphosphatemia, circulatory overload, ARDS (lowest risk among blood products), immunomodulation, transfusion reactions, hypothermia, and virus transmission
Fresh frozen plasma	Replacement of clotting factors. Generally overused; indicated if ongoing hemorrhage in patients with PT/PTT >1.5 times normal, prolonged initial fibrin formation (R value) on viscoelastic testing, severe hepatic disease, or other bleeding diathesis	Hypocalcemia, circulatory overload, ARDS (highest risk among blood products, particularly transfusions from female donors), immunomodulation, transfusion reactions, hypothermia, and virus transmission
Platelets	Used for bleeding due to severe thrombocytopenia (ie, platelet count <20,000/μL [20 × 10^9/L]), rapidly dropping platelet counts as would occur with massive bleeding, or decreased clot strength (maximum amplitude value) on viscoelastic testing	Hypocalcemia, circulatory overload, ARDS, immunomodulation, transfusion reactions, hypothermia, and virus transmission
Cryoprecipitate	Contains concentrated fibrinogen, von Willebrand factor, factor VIII, and factor XIII. Generally not indicated in acute hemorrhage but rather used after specific deficiencies are identified (eg, decreased rate of clot formation [alpha value] on viscoelastic testing)	Hypocalcemia, circulatory overload, ARDS, immunomodulation, transfusion reactions, hypothermia, and virus transmission
Prothrombin complex concentrates (PCCs)	The most commonly used product contains inactivated factors II, VII, IX, and X, and Proteins C and S. Another product contains activate factors. Used for reversal of antithrombotic agents in the setting of acute major bleeding or prior to urgent surgery/invasive procedure.	Thrombosis (arterial and venous), anaphylactic reactions, and viral transmission. Some products contain heparin and should not be given to patients with heparin-induced thrombocytopenia

[a]Although whole blood can be used for large-volume blood loss, most hospitals use component therapy, and use crystalloids or colloids for plasma expansion.
ARDS, acute respiratory distress syndrome; PT, prothrombin time; PTT, partial thromboplastin time.

TABLE 41-5 Receptor Pharmacology and Adverse Events of Selected Vasopressor and Inotropic Agents Used in Shock

Agent (Adverse Events)	α_1	α_2	β_1	β_2	D	Other
Angiotensin II (5,000-10,000 ng/mL NS)	Tachycardia, thrombosis, peripheral ischemia, lactic acidosis, bronchospasm, infection					
1.25-80 ng/kg/min						AT-1 AT-2 ++++
Dobutamine (500-4,000 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, hypotension					
2-10 mcg/kg/min	+		++++	++		
>10-20 mcg/kg/min	++		++++	+++		
Dopamine (800-3,200 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, decreased PaO_2, mesenteric hypoperfusion, GI motility inhibition, T-cell inhibition					
1-3 mcg/kg/min			+		++++	
3-10 mcg/kg/min	0/+		++++	+	++++	
>10-20 mcg/kg/min	+++		++++	+		
Epinephrine (8-16 mcg/mL D_5W or NS)	Tachycardia, dysrhythmias, mesenteric hypoperfusion, increased lactate, hyperglycemia, immunomodulation					
0.01-0.05 mcg/kg/min	++	++	++++	+++		
0.05-3 mcg/kg/min	++++	++++	+++	+		
Norepinephrine (16-64 mcg/mL D_5W or NS)	Mixed effects on myocardial performance and mesenteric perfusion, peripheral ischemia					
0.02-3 mcg/kg/min	++++	+++	+++	+/++		
Phenylephrine (100-400 mcg/mL D_5W or NS)	Mixed effects on myocardial performance, peripheral ischemia					
0.5-9 mcg/kg/min	+++	+	+			
Vasopressin (0.2-1 units/mL D_5W or NS)	Mixed effects on myocardial performance, mesenteric hypoperfusion, peripheral ischemia, thrombocytopenia, hyperbilirubinemia					
0.01-0.1 units/min						V1 V2 ++++

[a]Activity ranges from no activity (0) to maximal (++++) activity.
AT, angiotensin; D, dopamine; D_5W, dextrose 5% in water; GI, gastrointestinal; NS, normal saline (0.9% sodium chloride); PaO_2, arterial oxygen pressure; V, vasopressin.

Pharmacokinetics and drug interactions of direct oral anticoagulants

Anticoagulant	Bioavailability	Metabolism and clearance*¶	Half-life	Potential for pharmacokinetic drug interactions*¶
Dabigatran (Pradaxa)	3 to 7% bioavailable Unaffected by food Capsule must be taken intact and requires gastric acidity for absorption	Over 80% renally cleared P-gp substrate*	12 to 17 hours Prolonged in renal impairment and older adults	P-gp inhibitors can increase dabigatran effect P-gp inducers can decrease dabigatran effect Avoidance of some combinations or dose adjustment may be needed
Apixaban (Eliquis)	50% bioavailable Unaffected by food	27% renally cleared Metabolized, primarily by CYP3A4¶ P-gp substrate*	12 hours Prolonged in older adults	Strong CYP3A4 inhibitors and/or strong P-gp inhibitors can increase apixaban effect Strong CYP3A4 inducers and/or strong P-gp inducers can decrease apixaban effect Avoidance of some combinations or dose adjustment may be needed
Betrixaban (Bevyxxa)	34% bioavailable Taken with food at the same time each day. Absorption is increased if taken without food.	Minimal renal clearance (5 to 7%) Undergoes minimal CYP metabolism P-gp substrate* 85% eliminated via hepatobiliary route	19 to 27 hours (effective half-life); peak-to-trough ratio is low and terminal serum half-life is 37 hours, and betrixaban may persist in the circulation for longer than predicted by the effective half-life	P-gp inhibitors can increase betrixaban effect P-gp inducers may decrease betrixaban effect Avoidance of some combinations or dose adjustment may be needed
Edoxaban (Savaysa, Lixiana)	62% bioavailable Unaffected by food	50% renally cleared Reduced efficacy in patients with NVAF and CrCl >95 mL/minute$^{\Delta}$ Undergoes minimal CYP metabolism¶ P-gp substrate*	10 to 14 hours Prolonged in renal impairment	P-gp inhibitors can increase edoxaban effect P-gp inducers can decrease edoxaban effect Avoidance of some combinations or dose adjustment may be needed
Rivaroxaban (Xarelto)	10 mg dose: 80 to 100% bioavailable Unaffected by food 20 mg dose: 66% bioavailable if taken when fasting; increased if taken with food	36% renally cleared Metabolized, primarily by CYP3A4¶ P-gp substrate*	7 to 11 hours[1] Prolonged in renal impairment and older adults	Strong CYP3A4 inhibitors and/or strong P-gp inhibitors can increase rivaroxaban effect Strong CYP3A4 inducers and/or strong P-gp inducers can decrease rivaroxaban effect Avoidance of some combinations or dose adjustment may be needed

Refer to UpToDate for dosing in specific clinical settings, including nonvalvular AF, VTE treatment, and VTE prophylaxis. Data on clearance may help assess the potential for accumulation in patients with renal impairment. Data on metabolism may help assess potential drug interactions through alteration of CYP3A4 metabolism and/or P-gp-mediated drug efflux. Refer to Lexi-Interact, the drug interactions tool included with UpToDate, for specific drug interactions. Tables of P-gp inhibitors and inducers and CYP3A4 inhibitors and inducers are available separately in UpToDate.

P-gp: P-glycoprotein drug efflux pump; CYP3A4: cytochrome p450 3A4 isoform; CrCl: creatinine clearance estimated by the Cockcroft-Gault equation; AF: atrial fibrillation; VTE: venous thromboembolism, includes deep vein thrombosis and pulmonary embolism; DOAC: direct oral anticoagulant.

* Examples of P-gp inhibitors that reduce metabolism of DOACs, leading to increased DOAC levels, include clarithromycin, ombitasvir- or ritonavir-containing combinations, and verapamil. Examples of P-gp inducers that increase DOAC metabolism, leading to lower DOAC levels, include phenytoin, rifampin, and St. John's wort.

¶ Examples of strong CYP3A4 inhibitors that reduce metabolism of some DOACs, leading to increased DOAC levels, include clarithromycin and ombitasvir- or ritonavir-containing combinations. Examples of strong CYP3A4 inducers that increase metabolism of some DOACs, leading to lower DOAC levels, include carbamazepine, phenytoin, and rifampin.

Δ Blood levels of edoxaban were reduced and a higher rate of ischemic stroke was observed in patients with AF and CrCl >95 mL/minute who were treated with edoxaban compared with those receiving warfarin. Refer to the UpToDate topic on anticoagulation in AF for additional information.

Emergency reversal of anticoagulation from warfarin for life-threatening hemorrhage in adults: Suggested approaches based upon available resources

A. If 4-factor prothrombin complex concentrate (4F PCC) is available (preferred approach):
1. Give 4F PCC* 1500 to 2000 units¶ IV over 10 minutes. Check INR 15 minutes after completion of the infusion. If INR is not ≤1.5, give additional 4F PCC (refer to topic or drug reference for details).
2. Give vitamin K 10 mg IV over 10 to 20 minutes.
B. If 3-factor prothrombin complex concentrate (3F PCC) is available but 4F PCC is not available:
1. Give 3F PCC* 1500 to 2000 units¶ IV over 10 minutes. Check INR 15 minutes after completion of the infusion. If INR is not ≤1.5, give additional 3F PCC (refer to topic or drug reference for details).
2. Give Factor VIIa 20 mcg/kg IV **OR** give FFP 2 units IV by rapid infusion. Factor VIIa may be preferred if volume overload is a concern.
3. Give vitamin K 10 mg IV over 10 to 20 minutes.
C. If neither 3F PCC nor 4F PCC is available:
1. Give FFP 2 units IV by rapid infusion. Check INR 15 minutes after completion of infusion. If INR ≥1.5, administer 2 additional units of FFP IV rapid infusion. Repeat process until INR ≤1.5. May wish to administer loop diuretic between FFP infusions if volume overload is a concern.
2. Give vitamin K 10 mg IV over 10 to 20 minutes.

These products and doses are for use in life-threatening bleeding only. Evidence of life-threatening bleeding and over-anticoagulation with a vitamin K antagonist (eg, warfarin) are required. Anaphylaxis and transfusion reactions can occur.

It may be reasonable to thaw 4 units of FFP while awaiting the PT/INR. The transfusion service may substitute other plasma products for FFP (eg, Plasma Frozen Within 24 Hours After Phlebotomy [PF24]); these products are considered clinically interchangeable. PCC will reverse anticoagulation within minutes of administration; FFP administration can take hours due to the volume required; vitamin K effect takes 12 to 24 hours, but administration of vitamin K is needed to counteract the long half-life of warfarin. Subsequent monitoring of the PT/INR is needed to guide further therapy. Refer to topics on warfarin reversal in individual situations for further management.

PCC: unactivated prothrombin complex concentrate; 4F PCC: PCC containing coagulation factors II, VII, IX, X, protein S and protein C; 3F PCC: PCC containing factors II, IX, and X and only trace factor VII; FFP: fresh frozen plasma; PT: prothrombin time; INR: international normalized ratio; FEIBA: factor eight inhibitor bypassing agent.

* Before use, check product label to confirm factor types (3 versus 4 factor) and concentration. Activated complexes and single-factor IX products (ie, FEIBA, AlphaNine, Mononine, Immunine, BeneFix) are NOT used for warfarin reversal.

¶ PCC doses shown are those suggested for initial treatment of emergency conditions. Subsequent treatment is based on INR and patient weight if available. Refer to topic and Lexicomp drug reference included with UpToDate for INR-based dosing.

Expected effects of anticoagulant drugs on commonly used coagulation tests

Drug class	Drug	Brand name(s)	PT	aPTT	Anti-factor Xa activity
Vitamin K antagonists	Warfarin	Coumadin, Jantoven	↑	↑/–*	–
	Acenocoumarol	Sintrom	↑	↑/–*	–
Heparins	Unfractionated heparin		–¶	↑	↑
	LMW heparins Enoxaparin Dalteparin Nadroparin	 Lovenox Fragmin Fraxiparine	–	↑/–	↑
	Fondaparinux	Arixtra	–	↑/–	↑
Direct thrombin inhibitors	Argatroban	Acova	↑	↑	–
	Dabigatran	Pradaxa	↑/–	↑	–
Direct factor Xa inhibitors	Rivaroxaban	Xarelto	↑/–	↑/–	↑Δ
	Apixaban	Eliquis	↑/–	↑/–	↑Δ
	Edoxaban	Lixiana, Savaysa			↑Δ
	Betrixaban	Bevyxxa			↑Δ

PT and aPTT are measured in seconds; anti-factor Xa activity is measured in units/mL. Upward arrow (↑) signifies an increase above normal due to the anticoagulant (prolongation of PT or aPTT; increase in anti-factor Xa activity). The effect magnitude will vary depending on the reagent formulation and instrument used. Dash (–) signifies no appreciable effect. Normal ranges for the PT, aPTT, and anti-factor Xa activity vary among laboratories and should be reported from the testing laboratory along with the patient result. Refer to the UpToDate topic on coagulation testing for details.

PT: prothrombin time; aPTT: activated partial thromboplastin time; LMW heparin: low molecular weight heparin.

* Warfarin has a weak effect on most aPTT reagents. However, warfarin use will increase the sensitivity of the aPTT to heparin effect.

¶ While heparin, LMW heparin, and fondaparinux should, in theory, prolong the PT as indirect thrombin inhibitors, in practice most PT reagents contain heparin-binding chemicals that block any heparin effect below a concentration of 1 unit/mL. Above concentrations of 1 unit/mL, heparin effect on the PT may be observed.

Δ Anti-factor Xa activity testing must be calibrated for the specific anticoagulant; this information should be verified with the clinical laboratory. Data are not available for betrixaban but would be expected to be similar to other direct factor Xa inhibitors.

Rapid overview: Management of ST-elevation myocardial infarction (STEMI) or non-ST-elevation acute coronary syndrome (NSTEACS)

Initial assessment:

Consider the diagnosis in patients with chest discomfort, shortness of breath, or other suggestive symptoms. Women, older adults, and patients with diabetes may have "atypical" presentations.

Obtain 12-lead ECG within 10 minutes of arrival; repeat every 10 to 15 minutes if initial ECG is nondiagnostic but clinical suspicion remains high (initial ECG often **NOT** diagnostic).

1. STEMI: ST segment elevations ≥1 mm (0.1 mV) in two anatomically contiguous leads or ≥2 mm (0.2 mV) in leads V2 and V3 **OR** new left bundle branch block and presentation consistent with ACS. If ECG suspicious but not diagnostic, consult cardiologist early.

2. Non-STEMI or unstable angina: ST segment depressions or deep T wave inversions without Q waves or possibly no ECG changes.

Obtain emergent cardiology consultation for ACS patients with cardiogenic shock, left heart failure, or sustained ventricular tachyarrhythmia.

Initial interventions:

Assess and stabilize airway, breathing, and circulation.

Attach cardiac and oxygen saturation monitors; provide supplemental oxygen as needed to maintain O_2 saturation >90%. Establish IV access.

Treat sustained ventricular arrhythmia rapidly according to ACLS protocols.

Give aspirin 325 mg (nonenteric coated) to be chewed and swallowed (unless aortic dissection is being considered). If oral administration is not feasible, give as rectal suppository.

Perform focused history and examination: Look for signs of hemodynamic compromise and left heart failure; determine baseline neurologic function, particularly if fibrinolytic therapy is to be given.

Obtain blood for cardiac biomarkers (troponin preferred), electrolytes, hematocrit/hemoglobin. Perform coagulation studies for patients taking anticoagulants or as otherwise indicated (eg, known coagulopathy).

Give three sublingual nitroglycerin tablets (0.4 mg) one at a time, spaced five minutes apart, or one aerosol spray under tongue every 5 minutes for 3 doses **IF** patient has persistent chest discomfort, hypertension, or signs of heart failure **AND** there is no sign of hemodynamic compromise (eg, right ventricular infarction) and no use of phosphodiesterase inhibitors (eg, for erectile dysfunction); add IV nitroglycerin for persistent symptoms.

Treat left heart failure if present: Give afterload-reducing agent (eg, nitroglycerin sublingual tablet and/or IV drip at 40 mcg/minute provided no hypotension and no phosphodiesterase inhibitors [eg, for erectile dysfunction]; titrate drip up quickly based on response); give loop diuretic (eg, intravenous furosemide); administer noninvasive positive pressure ventilation (eg, BLPAP) to appropriate patients.

Give beta blocker (eg, metoprolol tartrate 25 mg orally) **IF** no signs of heart failure and not at high risk for heart failure and no signs of hemodynamic compromise, bradycardia, or severe reactive airway disease. If hypertensive, may initiate beta blocker IV instead (eg, metoprolol tartrate 5 mg intravenous every 5 minutes for 3 doses as tolerated).

Give morphine sulfate (2 to 4 mg slow IV push every 5 to 15 minutes) for unacceptable, persistent discomfort or anxiety related to myocardial ischemia.

Start 80 mg of atorvastatin as early as possible and preferably before PCI in patients not on statin. If patient is taking a low- to moderate-intensity statin, switch to atorvastatin 80 mg.

Acute management STEMI:

Select reperfusion strategy: Primary PCI strongly preferred, especially for patients with cardiogenic shock, heart failure, late presentation, or contraindications to fibrinolysis. Activate cardiac catheterization team as indicated. For patients with symptoms of >12 hours, fibrinolytic therapy is not indicated, but emergent PCI may be considered, particularly for patients with evidence of ongoing ischemia or those at high risk of death.

Treat with fibrinolysis if PCI unavailable within **120 minutes of first medical contact,** symptoms <12 hours, and no contraindications.*

Give oral antiplatelet therapy (in addition to aspirin) to all patients:

1. **Patients treated with fibrinolytic therapy:** Give clopidogrel loading dose 300 mg if age 75 years or less; if age over 75 years, give loading dose of 75 mg.

2. **Patients treated with no reperfusion therapy:** Give ticagrelor loading dose 180 mg.

3. **Patients treated with primary PCI:** Give ticagrelor loading dose of 180 mg or prasugrel loading dose of 60 mg (if no contraindications: prior stroke or TIA, or relative contraindications for prasugrel such as those age 75 years or older, weight less than 60 kg). For patients at high risk of bleeding or those for whom prasugrel or ticagrelor cannot be used, we give clopidogrel 600 mg.

Give anticoagulant therapy to all patients:

1. **For patients treated with primary PCI,** we prefer UFH to bivalirudin. This recommendation assumes that patients will receive a potent oral antiplatelet agent (ticagrelor or prasugrel), which we prefer to clopidogrel. For those patients who receive clopidogrel, we prefer bivalirudin.

Dosing of UFH: An initial IV bolus of 50 to 70 units/kg up to a maximum of 5000 units. Additional heparin may be given in the catheterization laboratory based on the results of ACT monitoring.

Dosing of bivalirudin: Initial bolus of 0.75 mg/kg IV followed by IV infusion of 1.75 mg/kg per hour; can be discontinued after PCI.

2. **For patients treated with fibrinolysis,** we prefer enoxaparin for patients not at high bleeding risk or fondaparinux for those at high bleeding risk. For those patients in whom PCI is possible or likely after fibrinolytic therapy, UFH is reasonable.

Dosing of enoxaparin

Patients <75 years: Loading dose of 30 mg IV bolus followed by 1 mg/kg subcutaneously every 12 hours; maximum of 100 mg for the first two subcutaneous doses. The first subcutaneous dose should be administered with the IV bolus.

Dose adjustment for renal impairment (CrCl <30 mL/minute)*: Loading dose of 30 mg IV followed by 1 mg/kg subcutaneously every 24 hours. The first subcutaneous dose should be administered with the IV bolus.

Patients ≥75 years: No IV loading dose. Administer 0.75 mg/kg subcutaneously every 12 hours; maximum of 75 mg for the first two doses.

Dose adjustment for renal impairment (CrCl <30 mL/minute)*: No IV loading dose. Administer 1 mg/kg subcutaneously every 24 hours.

Supplemental IV bolus dose for patients who will receive PCI after >1 dose of therapeutic enoxaparin: 0.3 mg/kg if last enoxaparin dose was given 8 to 12 hours earlier; no supplemental IV dose if last enoxaparin dose was within 8 hours; use UFH if last enoxaparin dose was more than 12 hours ago.

Dosing of UFH: IV bolus of 60 to 100 units/kg to a maximum of 4000 units, followed by an IV infusion of 12 units/kg per hour (maximum 1000 units per hour) adjusted to achieve a goal aPTT of approximately 50 to 70 seconds (1.5 to 2 times control).

Dosing of fondaparinux: 2.5 mg intravenously, followed by 2.5 mg subcutaneously every 24 hours. This drug should be avoided in CrCl <30 mL/minute.

3. **For patients not receiving reperfusion therapy,** we use enoxaparin or UFH.

Dosing of enoxaparin: Dose same as for patients treated with fibrinolysis (refer to section 2 above).

Dosing of UFH: IV bolus of 50 to 70 units/kg to a maximum of 5000 units, followed by an IV infusion of 12 units/kg per hour adjusted to achieve a goal aPTT of approximately 50 to 70 seconds (1.5 to 2 times control).

Acute management of unstable angina or non-STEMI:

Give antiplatelet therapy (in addition to aspirin) to all patients:

1. **Patients not treated with an invasive approach:** Give ticagrelor loading dose 180 mg. For these patients who are at very high risk (eg, recurrent ischemic discomfort, dynamic ECG changes, or hemodynamic instability), consider adding a GP IIb/IIIa inhibitor (either eptifibatide or tirofiban).

2. **For patients managed with an invasive approach:** Give ticagrelor loading dose of 180 mg at presentation. Prasugrel loading dose of 60 mg may be used as an alternative if given after diagnostic coronary angiography.

For patients age 75 years or older, who weigh less than 60 kg, or with past stroke or TIA, ticagrelor or clopidogrel are preferred to prasugrel. Clopidogrel may be given in a dose of 300 to 600 mg, but we prefer 600 mg. For patients otherwise at high risk for bleeding due to prior hemorrhagic stroke, ongoing bleeding, bleeding diathesis, or clinically relevant anemia or thrombocytopenia, clopidogrel 300 to 600 mg is an option.

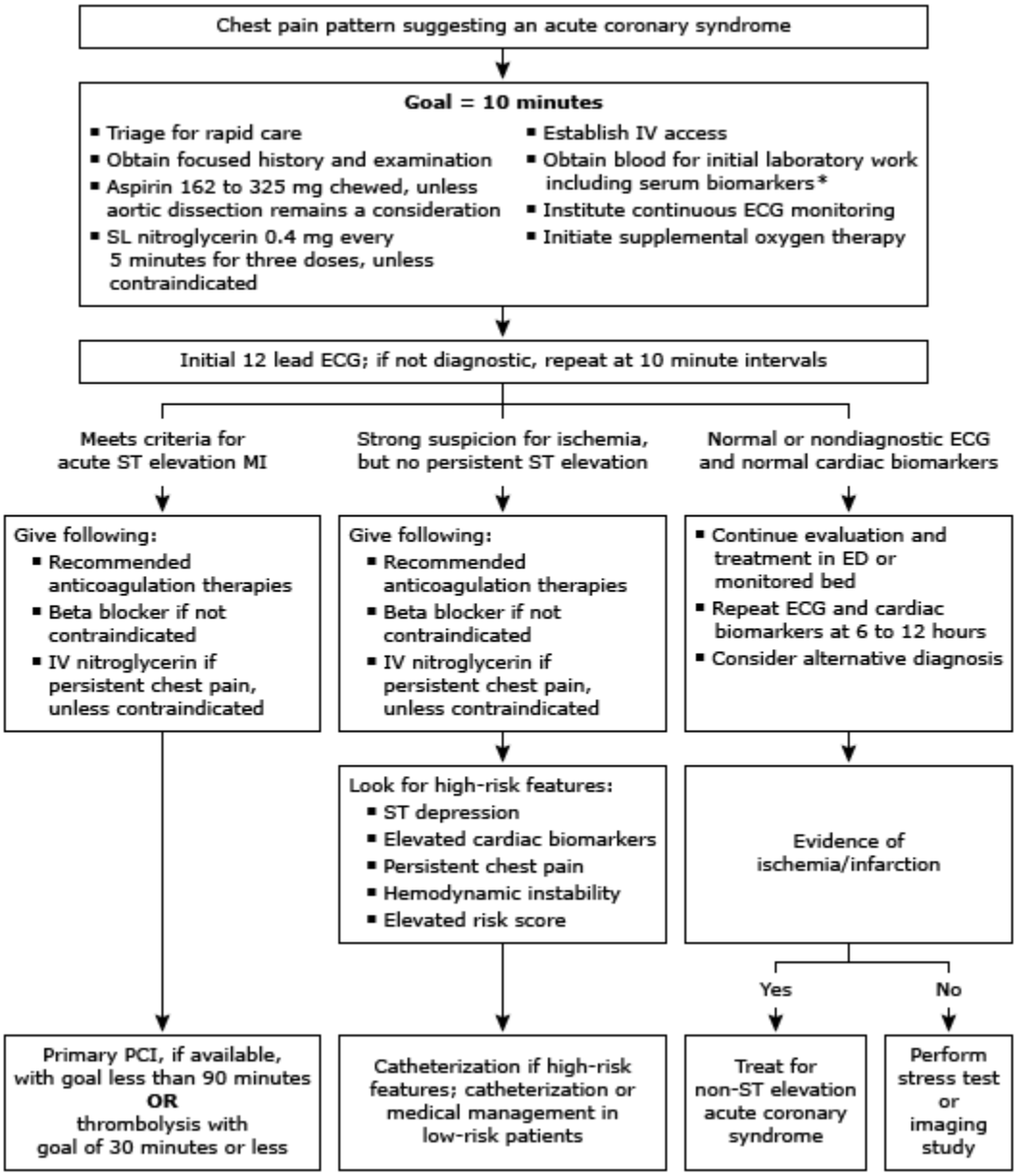
For patients treated with an invasive approach and who receive bivalirudin, we do not recommend routinely giving a GP IIb/IIIa inhibitor; for those patients treated with heparin and who are troponin-positive, we suggest adding a GP IIb/IIIa inhibitor (either abciximab or eptifibatide) given after diagnostic angiography. For those undergoing an invasive approach who are at very high risk (eg, recurrent ischemic discomfort, dynamic ECG changes, or hemodynamic instability), we consider adding a GP IIb/IIIa inhibitor prior to diagnostic angiography (either eptifibatide or tirofiban) or after diagnostic angiography (abciximab or eptifibatide). Refer to text for dosing.

Give anticoagulant therapy in all patients:

1. **For patients undergoing urgent catheterization (within four hours) or those managed with an early invasive strategy (angiography within 4 to 48 hours),** we use either heparin or bivalirudin. We prefer initiation of heparin in the emergency department and a switch to bivalirudin in the catheterization laboratory.
Dosing of UFH: IV bolus of 60 to 70 units/kg to a maximum of 5000 units, followed by an IV infusion of 12 units/kg per hour adjusted to achieve a goal aPTT of approximately 50 to 70 seconds (1.5 to 2 times control). **Dose of bivalirudin:** If bivalirudin is given in the emergency department, IV bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg per hour before angiography. If PCI is performed, an additional 0.5 mg/kg bolus is given and the infusion rate is increased to 1.75 mg/kg per hour.
2. **For patients receiving a noninvasive approach,** we recommend either fondaparinux or enoxaparin.
Enoxaparin is an alternative to UFH for patients not undergoing an early invasive approach. No loading dose is necessary. Dosing is 1 mg/kg subcutaneously every 12 hours. Dose adjustment for renal impairment (CrCl <30 mL/minute)*: 1 mg/kg subcutaneously every 24 hours. **Fondaparinux:** 2.5 mg subcutaneously every 24 hours. This drug should be avoided in patients with a CrCl <30 mL/minute.
Other important considerations:
Cocaine-related ACS: Give benzodiazepines (eg, lorazepam 2 to 4 mg IV every 15 minutes or so) as needed to alleviate symptoms; do **NOT** give beta blockers.
Stop NSAID therapy if possible.
Correct any electrolyte abnormalities, especially hypokalemia and hypomagnesemia, which often occur together.

ECG: electrocardiogram; ST: ST-segment; IV: intravenous; ACLS: advanced cardiac life support; BLPAP: bilevel positive airway pressure; PCI: percutaneous coronary intervention; TIA: transient ischemic attack; UFH: unfractionated heparin; ACT: activated clotting time; CrCl: creatinine clearance estimated using Cockcroft-Gault equation (a calculator is available in UpToDate); aPTT: activated partial thromboplastin time; GP: glycoprotein; NSAID: nonsteroidal antiinflammatory drug.

* Repeated doses of low molecular weight heparin in patients with renal insufficiency may lead to accumulation and increased risk of bleeding to varying degrees. By contrast, UFH is not dependent primarily upon renal function for clearance and may be a preferred option for patients with CrCl <20 mL/minute, kidney failure, or receiving dialysis.



* Initial laboratory work may vary by institution, but often includes: serum cardiac biomarkers, CBC with platelet count, PT and INR, aPTT, basic electrolytes, magnesium, BUN, creatinine, blood glucose, and serum lipid profile.

Contraindications to nitrates include severe aortic stenosis, hypertrophic cardiomyopathy with outflow obstruction, hypotension, suspected right ventricular infarct, recent use of phosphodiesterase 5 inhibitor (eg, Viagra).

TABLE 33-2 Acute Supportive Care Medications Initiated During the Initial 24 Hours of ACS Treatment

Drug	Indication (Class of Recommendation)*	Contraindication/Caution	Dose/Administration	Adverse Effects
Morphine	Refractory pain (IIb)	Known hypersensitivity Hypotension Bradycardia Lethargic or moribund patient	STEMI: 4-8 mg IV × 1 (lower dose in elderly), then 2-8 mg IV every 5-15 minutes PRN NSTE-ACS: 1-5 mg IV every 5–30 minutes PRN	Constipation, nausea, vomiting, hypotension, respiratory depression
Oxygen	Oxygen saturation <90% [0.90] (I)	Chronic obstructive pulmonary disease Carbon dioxide retention	2-4 L/min, increasing rate and/or changing to face mask PRN	Increased coronary vascular resistance, decreased coronary blood flow, increased mortality
Nitroglycerin (NTG)	Angina (I) Uncontrolled hypertension (I) Acute heart failure (I)	SBP less than 90 mm Hg or greater than 30 mm Hg below baseline Avoid if recent PDE_5 inhibitor use: Avanafil: within 12 hours Sildenafil: within 24 hours Vardenafil: within 24 hours Tadalafil: within 48 hours Use with caution if RV infarct suspected Avoid abrupt cessation of IV NTG; wean gradually	SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN IV: 10 mcg/min titrated to symptom relief and desired blood pressure	Flushing, headache, hypotension, tachycardia
β-blockers	All patients without contraindications (I) *Associated with mortality reduction, especially in patients with HFrEF*	Signs of heart failure Low cardiac output state Risk factors for cardiogenic shock: Age 70 years or greater SBP less than 120 mm Hg Sinus tachycardia (HR greater than 110 bpm) Sinus bradycardia (HR less than 60 bpm) Killip class III Prolonged time from symptom onset High-grade AV block Active asthma or reactive airway disease	Carvedilol 6.25 mg twice daily; target dose is 25 mg twice daily as tolerated Metoprolol Oral: 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose is 200 mg daily IV: 5 mg every 5 min as tolerated up to 3 doses, titrated to BP and HR; should only be considered if BP is uncontrolled or refractory symptoms Continue therapy for at least 3 years, indefinitely in patients with concomitant HFrEF Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease
Calcium channel blockers	Angina, normal LVEF, and contraindication or intolerance to β-blocker (I) Angina refractory to β-blocker and normal LVEF (I) Coronary vasospasm (I)	Signs of heart failure Low cardiac output state Risk factors for cardiogenic shock: Age 70 y or greater SBP less than 120 mmHg, sinus tachycardia (HR greater than 110 bpm) Sinus bradycardia (HR less than 60 bpm) Killip class III Prolonged time from symptom onset High-grade AV block	Diltiazem 120-360 mg/day orally† Verapamil 240-480 mg/day orally† Amlodipine 5-10 mg orally once daily Nicardipine 60-120 mg/day orally† Nifedipine ER 30-120 mg orally once daily	Hypotension,Diltiazem and verapamil: heart failure, cardiogenic shock, bradycardia, AV block

TABLE 33-8 Chronic Medications to Reduce Risk of MACE and Control Symptoms Following ACS

Drug	Indication in ACS Patients (Class of Recommendation)[a]	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Aspirin	All patients without contraindications	Hypersensitivity to aspirin or NSAID History of asthma, rhinitis, and nasal polyps History of upper GI bleeding Bleeding disorder/active bleeding	81 mg once daily	Dyspepsia, GI bleeding
$P2Y_{12}$ inhibitors	All patients without contraindications	Thienopyridine hypersensitivity Bleeding disorder/active bleeding Previous intracranial hemorrhage Prasugrel: prior TIA or stroke Ticagrelor: aspirin doses greater than 100 mg daily; strong CYP3A4 inhibitors or inducers	Clopidogrel 75 mg once daily Prasugrel 10 mg once daily; weight less than 60 kg: 5 mg daily Ticagrelor 90 mg twice daily	Bleeding, rash Ticagrelor: dyspnea, ventricular pauses, bradycardia
β-Blockers	All patients without contraindications	Signs of heart failure Low cardiac output state High-grade AV block Active asthma or reactive airway disease	Carvedilol 6.25 mg twice daily; target dose (in patients with HFrEF): 25 mg twice daily as tolerated Metoprolol 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose (in patients with HFrEF): 200 mg daily Continue therapy for at least 3 years, indefinitely in patients with concomitant HFrEF Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease
Statins	All patients without contraindications	Active liver disease Pregnancy Breastfeeding Concomitant use of fibrate	Atorvastatin 80 mg daily Rosuvastatin 20-40 mg daily	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity
Nonstatin therapies for cholesterol management	Patients with very high-risk ASCVD (eg, post-ACS) with LDL-C greater than 70 mg/dL (1.81 mmol/L) on maximally tolerated statin therapy	Hypersensitivity Simvastatin/ezetimibe: strong CYP3A4 inhibitors	Ezetimibe 10 mg daily Simvastatin 40 mg/ezetimibe 10 mg Alirocumab 75 mg SC every 2 weeks	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain Alirocumab: injection site pain, hypersensitivity
ACE inhibitors	All patients without contraindications	Hypotension Renal failure Hyperkalemia	Lisinopril 2.5-5 mg daily; target dose: 10-40 mg daily Enalapril 2.5-5 mg twice daily; target dose: 10-20 mg twice dailyCaptopril 6.25-12.5 mg three times daily; target dose: 25-50 mg three times daily Ramipril 2.5 mg twice daily; target dose: 5 mg twice daily Trandolapril 0.5-1 mg daily; target dose: 4 mg daily	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema
ARBs	Patients intolerant to ACE inhibitors	Hypotension Renal failure Hyperkalemia	Valsartan 20 mg twice daily; target dose: 160 mg twice daily	Hypotension, hyperuricemia, hyperkalemia, worsening renal function
Aldosterone antagonist	Patients with LVEF 40% (0.40) or less and either DM or symptoms of HF	Elevated serum creatinine Men: 2.5 mg/dL (221 µmol/L) or greater Women: 2.0 mg/dL (177 µmol/L) or greater CrCl 30 mL/min (0.5 mL/s) or less Serum potassium 5.0 mEq/L (mmol/L) or greater	Eplerenone 25 mg daily; target dose: 50 mg daily Spironolactone 12.5-25 mg daily; target dose: 25-50 mg daily	Hyperkalemia, worsening renal function
Nitroglycerin (NTG)	All patients without contraindications	Hypotension Avoid if recent PDE_5 inhibitor use Avanafil/ Sildenafil/Vardenafil: within 12 hour Tadalafil: within 48 hours	SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN	Flushing, headache, hypotension, tachycardia

TABLE 33-10 Therapeutic Drug Monitoring of Pharmacotherapy for ACS

Drug	Adverse Effects	Monitoring
Fibrinolytics	Bleeding (ICH)	Clinical signs of bleeding;[a] baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily; mental status every 2 hours for signs of ICH
Aspirin	Dyspepsia, GI bleeding	Clinical signs of bleeding;[a] GI upset; Hgb, Hct, and platelet count at baseline & every 6 months
$P2Y_{12}$ inhibitors	Bleeding, rash	Clinical signs of bleeding;[a] evidence of rash; Hgb, Hct, platelet count at baseline and every 6 months
	Ticagrelor: dyspnea, ventricular pauses, bradycardia	Ticagrelor: dyspnea, heart rate, telemetry during hospitalization
Glycoprotein IIb/IIIa inhibitors	Bleeding, thrombocytopenia (can be profound with abciximab)	Clinical signs of bleeding;[a] Hgb, Hct, and platelet count at baseline, 2 hours, then daily
		Eptifibatide and tirofiban: serum creatinine at baseline then daily
Anticoagulants	Bleeding	Clinical signs of bleeding;[a] baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily
	Unfractionated heparin and LMWH: heparin-induced thrombocytopenia	Unfractionated heparin: aPTT every 6 hours until two consecutive aPTT values are at goal, then every 24 hours; ACT during PCI
		Enoxaparin, bivalirudin, and fondaparinux: serum creatinine at baseline then daily
		Enoxaparin: may consider steady-state anti-Xa levels in special populations
β-Blockers	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease	Continuous telemetry (while hospitalized); blood pressure, heart rate, signs and symptoms of heart failure; monitor every 5 minutes before each IV bolus dose; monitor every shift while hospitalized then at each healthcare encounter after discharge
Nitroglycerin	Flushing, headache, hypotension, tachycardia	Blood pressure and heart rate; monitor every 5-15 minutes following dosage adjustment of intravenous nitroglycerin then every 1-2 hours; monitor every 5 minutes following administration of short-acting nitroglycerin
Morphine	Hypotension, respiratory depression, sedation, hypersensitivity	Blood pressure, heart rate, respiratory rate, sedation level 5 minutes after administration then every 1-2 hours for 4 hours after the last dose
Calcium channel blockers	Hypotension	Blood pressure, heart rate, every shift while hospitalized then at each healthcare encounter after discharge
	Verapamil and diltiazem: heart failure, cardiogenic shock, bradycardia, AV block	Verapamil and diltiazem: continuous telemetry (while hospitalized); signs and symptoms of heart failure every shift while hospitalized then at each healthcare encounter after discharge
Statins	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity	Liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatotoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4-12 weeks after initiation or dose adjustment, then every 3-12 months
Nonstatin therapies for cholesterol management	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain	Simvastatin/ezetimibe: liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4-12 weeks after initiation or dose adjustment, then every 3-12 months
	Alirocumab: injection site pain, hypersensitivity	Alirocumab: LDL-C at baseline and 4-8 weeks after initiation or dose adjustment; evaluation of injection site if injection site pain develops, signs and symptoms of hypersensitivity with each healthcare encounter
ACE inhibitors	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months; signs and symptoms of angioedema or cough with each healthcare encounter
ARBs	Hypotension, hyperuricemia, hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months
Aldosterone antagonist	Hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, after initiation or dose adjustment: at 3 days, 1 week, monthly for 3 months, then every 3 months

ACT, activated clotting time; aPTT, activated partial thromboplastin time; GI, gastrointestinal; Hct, hematocrit; Hgb, hemoglobin; ICH, intracranial hemorrhage; INR, international normalized ratio; PCI, percutaneous coronary intervention. [a] Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.

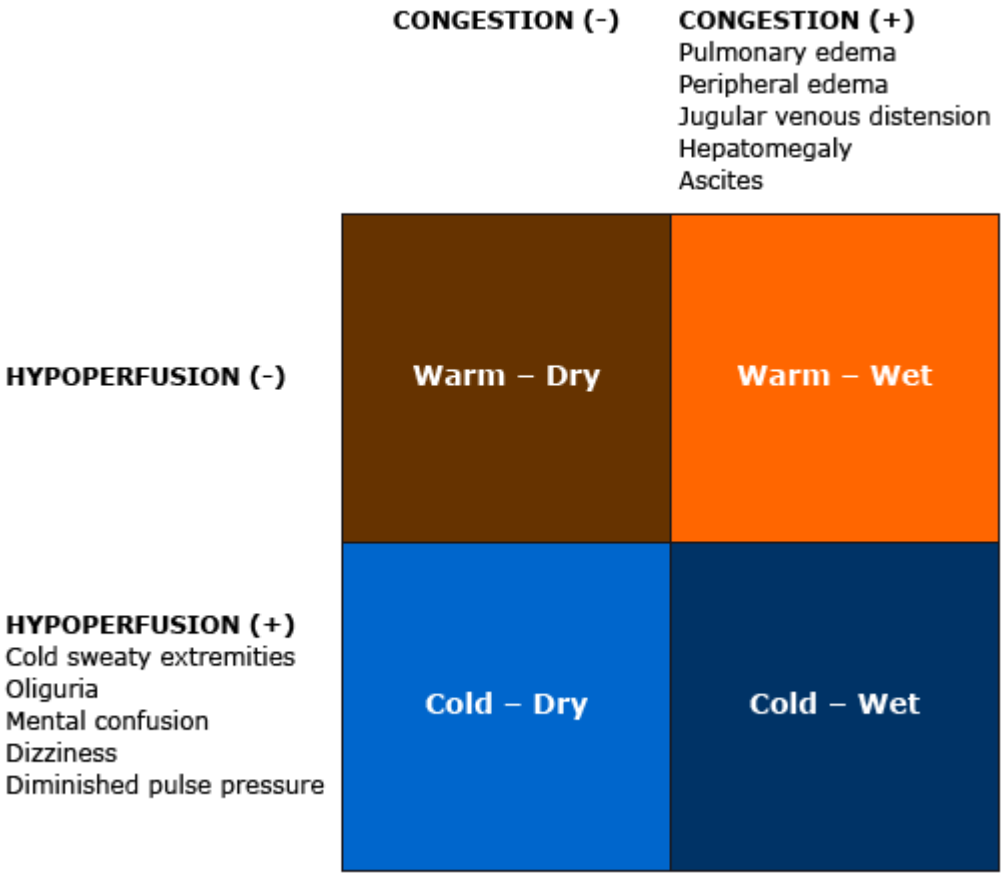
Rapid overview of emergency management: Acute decompensated heart failure

Differential diagnosis: Pulmonary embolism, acute asthma, pneumonia, noncardiogenic pulmonary edema (eg, adult respiratory distress syndrome), pericardial tamponade or constriction
Symptoms and signs
Acute dyspnea, orthopnea, tachypnea, tachycardia, and hypertension are common
Hypotension reflects severe disease, and arrest may be imminent; assess for inadequate peripheral or end-organ perfusion
Accessory muscles are often used to breathe
Diffuse pulmonary crackles are common; wheezing (cardiac asthma) may be present
S3 is a specific sign but may not be audible; elevated jugular venous pressure and/or peripheral edema may be present
Diagnostic studies
Obtain ECG: Look for evidence of ischemia, infarction, arrhythmia (eg, AF), and left ventricular hypertrophy.
Obtain portable chest radiograph: Look for signs of pulmonary edema, cardiomegaly, alternative diagnoses (eg, pneumonia); normal radiograph does not rule out ADHF.
Obtain: Complete blood count; cardiac troponin; electrolytes (Na^+, K^+, Cl–, HCO_3^-); BUN and creatinine; arterial blood gas (if severe respiratory distress); liver function tests; BNP or NT-proBNP if diagnosis is uncertain.
Perform bedside echocardiography if the cardiac or valvular function is not known.
Treatment
Monitor oxygen saturation, vital signs, and cardiac rhythm.
Provide supplemental oxygen if hypoxic (SpO_2 <90%), place 2 IV catheters, and position patient upright.
Provide NIV as needed, unless immediate intubation is required or NIV is otherwise contraindicated; have airway management equipment readily available; etomidate is a good induction agent for RSI in ADHF.
Initiate diuretic therapy without delay to relieve congestion/fluid overload:
Give IV loop diuretic furosemide 40 mg IV or torsemide 20 mg IV; or bumetanide 1 mg IV.
Higher doses are needed for patients taking diuretics chronically (eg, twice home dose) and in patients with renal dysfunction.
Search for cause of ADHF (including: acute coronary syndrome, hypertension, arrhythmia, acute aortic or mitral regurgitation, aortic dissection, sepsis, renal failure, anemia, or drugs) and treat appropriately.
Patients with ADHF and AF with rapid ventricular rate often require medication (eg, digoxin) to slow their heart rate.
Direct current cardioversion is indicated for patients with new onset AF and hemodynamic instability or refractory symptoms despite rate control.
Obtain immediate cardiac surgery consultation for acute aortic or mitral regurgitation or ascending aortic dissection.
For patients with adequate end-organ perfusion (eg, normal or elevated blood pressure) and signs of ADHF with fluid overload:
If urgent afterload reduction is required, early vasodilator therapy may be needed: Give nitroprusside* for severe hypertension, or if acute aortic regurgitation or acute mitral regurgitation is present; titrate rapidly to effect (eg, start nitroprusside at 5 to 10 mcg/min and titrate up every 5 minutes as tolerated to a dose range of 5 to 400 mcg/min).
If response to diuretics to treat congestion/fluid overload is inadequate, give vasodilator to reduce preload: Give IV nitroglycerin in addition to diuretic therapy if persistent dyspnea or as a component of therapy in refractory HF and low cardiac output.¶ Start nitroglycerin* infusion at 5 to 10 mcg/min and titrate every 3 to 5 minutes as needed and tolerated based upon mean arterial blood pressure or SBP to a dose range of 10 to 200 mcg/min.
For patients with known systolic HF (eg, documented low ejection fraction) presenting with signs of severe ADHF and cardiogenic shock, discontinue chronic beta blocker therapy and:
Give an IV inotrope* (eg, dobutamine or milrinone) and/or mechanical support (eg, intraaortic balloon counter pulsation).
For patients with known diastolic HF (ie, preserved systolic function) presenting with signs of severe ADHF and cardiogenic shock:
Treat for possible left ventricular outflow obstruction with a beta blocker, IV fluid (unless pulmonary edema is present), and give an IV vasopressor* (eg, phenylephrine or norepinephrine); do not give an inotrope or vasodilator. Obtain immediate echocardiogram as needed.
Consider possibility of acute mitral or aortic regurgitation, or aortic dissection, and need for emergency surgical intervention. Obtain immediate echocardiogram as needed.
For patients whose cardiac status is unknown but present with signs of severe ADHF (ie, pulmonary edema) and hypotension or signs of shock:
Give an IV inotrope* (eg, dobutamine or milrinone), with or without an IV vasopressor (eg, norepinephrine) and assess need for mechanical support (eg, intraaortic balloon counter pulsation); obtain immediate echocardiogram as needed.

ECG: electrocardiogram; BUN: blood urea nitrogen; BNP: brain natriuretic peptide; IV: intravenous; NIV: noninvasive ventilation; RSI: rapid sequence intubation.

* Patients receiving vasodilator, vasopressor, or inotrope infusions require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation.

¶ Treatment of patients with heart failure with reduced ejection fraction with volume overload unresponsive to diuretics is guided by hemodynamics, which are most commonly imputed from the physical examination with right heart catheterization performed when required for selected cases; refer to accompanying text and separate topic review of management of refractory heart failure.



Differentiation of noncardiogenic from cardiogenic pulmonary edema based on clinical data

Noncardiogenic	Cardiogenic
History	
Underlying disease (eg, pancreatitis, sepsis)	Acute cardiac event (eg, myocardial infarction)
Physical examination	
Warm periphery	Cool, mottled periphery
Bounding pulses	Small-volume pulse
Normal-sized heart	Cardiomegaly
Normal JVP	Elevated JVP
S3 absent	S3 present
No murmurs other than innocent flow murmurs	Systolic and diastolic murmurs
ECG	
ECG usually normal	ECG signs of myocardial infarction/ischemia
Chest radiograph film	
Peripheral infiltrates	Perihilar infiltrates
Laboratory test	
BNP <100 mg/mL	BNP >100 mg/mL
Ventilatory needs	
Prolonged need for ventilatory support with high FiO_2 and PEEP to oxygenate	Short duration of need for ventilatory support

JVP: jugular venous pressure; S3: third heart sound; ECG: electrocardiogram; BNP: brain natriuretic peptide; FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure.

Intravenous* sedative and analgesic dosing regimens for managing pain, agitation, and delirium in the intensive care unit

Drug	Loading dose	Maintenance dose range	Onset (min)	Duration of intermittent dose (min)	Characteristics and role
Opioid analgesics¶					
Fentanyl¶	1 to 2 mcg/kg$^{\Delta}$ (25 to 100 mcg)¶	0.35 to 0.5 mcg/kg every 0.5 to 1 hour intermittent (25 to 50 mcg)¶ **AND/OR** 0.7 to 10 mcg/kg/hour infusion (50 to 700 mcg/hour)[1] For most patients, 1 to 3 mcg/kg/hour infusion (50 to 200 mcg/hour)¶ with as-needed intermittent bolus doses is sufficient	<1 to 2	30 to 60$^{\Diamond}$	**Advantages:** Potent analgesic-sedative with immediate onset and less hypotension than other opioid analgesic choices due to relative lack of histamine release. Metabolized hepatically by cytochrome P450-3A4 (CYP3A4) to inactive metabolites. **Disadvantages:** Highly lipophilic parent drug accumulates in adipose and other tissue with repeated or prolonged administration. Chest wall rigidity may occur with higher dosing§. **Role:** A good choice for analgesia for most critically ill patients.
Hydromorphone	0.5 to 2 mg$^{\Delta}$	0.2 to 0.6 mg every one to two hours intermittent **AND/OR** 0.5 to 3 mg/hour infusion	5 to 10	240 to 300	**Advantages:** IV administration requires small volumes relative to other opioids. Non-CYP metabolism (glucuronidation) may be an advantage for patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Potentially neurotoxic (excitatory) metabolite(s) may accumulate in hepatic and/or renal dysfunction§. **Role:** Analgesic option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment.
Morphine sulfate	2 to 10 mg$^{\Delta}$	2 to 4 mg every one to two hours intermittent **AND/OR** 2 to 30 mg/hour infusion	5 to 10	240 to 300	**Advantage:** Non-CYP metabolism (glucuronidation) may be an advantage for selected patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Can accumulate in hepatic or renal dysfunction and prolong effects. Histamine release and vagally mediated venodilation, hypotension, and bradycardia can be significant§. **Role:** Analgesic alternative to fentanyl or hydromorphone where preload reduction and myocardial depressive effects are desirable or tolerable. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment. Avoid in patients with advanced or decompensated liver disease with renal impairment due to risk of accumulation of neurotoxic metabolite. Infusions are not generally used for sedation or analgesia in the ICU but are more commonly used for palliative purposes.
Remifentanil¶	Optional: 1.5 mcg/kg¶[1] Most ICU patients can be managed without bolus doses; if required, a bolus of 0.5 mcg/kg is usually sufficient; larger boluses are associated with significant reductions in HR and MAP	0.5 to 15 mcg/kg/hour infusion Use ideal body weight to determine dose for obese patients¶	1 to 3	5 to 10 (after cessation of infusion)	**Advantages:** Ultra-short-acting. Cleared by nonspecific plasma esterases to inactive metabolites. Does not accumulate in renal or hepatic impairment. Prompt reversal of analgesia and sedation upon discontinuation. **Disadvantages:** Anticipate pain and discomfort upon abrupt cessation. Glycine excipient may accumulate in renal impairment§. **Role:** An alternative to fentanyl for patients requiring frequent neurologic assessments or those with multiorgan failure.
Nonopioid analgesics (adjunctive or opioid sparing)					
Acetaminophen (paracetamol)	None	Oral, rectal: 325 to 1000 mg every four to six hours IV: 650 mg IV every four hours to 1000 mg IV every six hours, or 15 mg/kg IV every six hours for patients weighing <50 kg Maximum ≤4 g/day	Oral: 30 to 60 Rectal: Variable IV: 5 to 10	240 to 360	**Advantages:** Lacks dependence and tolerance of opioids. Lacks antiplatelet effect and gastrointestinal toxicity of NSAIDs. **Disadvantages:** Lacks significant anti-inflammatory effect. IV preparation requires administration over 15 minutes. Can cause hepatotoxicity in chronic or acute overdose. Avoid or use a lower daily dose in older adults and patients at risk for hepatotoxicity (eg, heavy alcohol use or malnourished). Interacts with warfarin (may prolong INR) and CYP450-inducing drugs (elevated risk of hepatic inflammation). **Role:** First choice for treatment of mild to moderate acute pain and febrile conditions. Adjunctive analgesic that may reduce opioid requirements. When hepatic dysfunction is significant, consider avoiding or reducing dose (eg, ≤2 g/day total).
Ketorolac	Optional: 30 mg once	Age <65 years and weight ≥50 kg: 15 to 30 mg every six hours; maximum 120 mg/day for up to five days Age ≥65 years or weight <50 kg: 15 mg every six hours; maximum 60 mg/day for up to five days	IV: ~30	360 to 480	**Advantages:** Lacks dependence and tolerance of opioids. Effective anti-inflammatory. **Disadvantages:** Can cause or worsen renal insufficiency. Dose-related risk of gastropathy. Reversibly inhibits platelet functioning. May alter cardioprotective effect of aspirin. **Role:** Adjunctive analgesic that may reduce opioid requirements. Avoid in renal impairment, gastrointestinal bleeding, platelet dysfunction, ischemic heart disease, heart failure, reduced cardiac output, hypovolemic state, asthma, or cirrhosis. Contraindicated in treatment of perioperative pain in coronary artery bypass graft surgery. Patients should be well hydrated.
Ibuprofen	None	Oral: 400 mg orally every four hours (maximum 2.4 g/day chronic) IV: 400 to 800 mg IV every six hours (maximum 3.2 g/day acute)	Oral: 30 IV: ~30	240 to 360	**Advantages:** Lacks dependence and tolerance of opioids. Effective anti-inflammatory. **Disadvantages:** Can cause or worsen renal insufficiency. Dose-related risk of gastropathy. Reversibly inhibits platelet functioning. Can alter cardioprotective effect of aspirin. **Role:** Short-term treatment of moderate acute pain and febrile conditions. Adjunctive analgesic that may reduce opioid requirements. Avoid in renal impairment, gastrointestinal bleeding, platelet dysfunction, ischemic heart disease, heart failure, reduced cardiac output, hypovolemic state, asthma, or cirrhosis. Contraindicated in treatment of perioperative pain in coronary artery bypass graft surgery. Patients should be well hydrated.
Gabapentin	None	Oral: Initially 100 mg three times per day Oral: Maintenance 900 to 3600 mg per day in three divided doses	Variable	--	**Advantages:** Effective for treatment of neuropathic pain. Low risk of drug interactions. **Disadvantages:** Requires enteral administration, scheduled dosing, and individualized titration over days to weeks. Oral bioavailability is variable (27 to 60%) and inversely proportional to dose. Adverse effects include sedation, dizziness, and ataxia, which may be intensified in renal impairment, requiring dose adjustment. Should not be abruptly stopped, due to risk of discontinuation symptoms. **Role:** Useful adjunct to other analgesics for treatment of neuropathic and postoperative pain or dysesthesias in patients who can be treated with enteral medication. Dose adjustment needed for renal impairment.
Pregabalin	None	Oral: Initially 75 mg once or twice per day Oral: Maintenance 150 to 300 mg twice per day	Variable (hours to days)	--	**Advantages:** Effective for treatment of neuropathic pain. Oral bioavailability (>90%) is more reliable than gabapentin and may provide for more rapid onset of analgesia with a shorter amount of time needed to titrate to full dose. Low risk of drug interactions. **Disadvantages:** Requires enteral administration, scheduled dosing, and titration over days to weeks. Adverse effects include sedation, blurred vision, dry mouth, dizziness,

					and ataxia, which may be intensified in renal impairment, requiring dose adjustment. Should not be abruptly stopped, due to risk of discontinuation symptoms. **Role:** Useful adjunct to other analgesics for treatment of neuropathic and postoperative pain or dysesthesias in patients who can be treated with enteral medication. Dose adjustment needed for renal impairment.
Anesthetic-sedative					
Propofol¶	Bolus doses are usually not given in the ICU	5 to 50 mcg/kg/**minute**¶ Titrate every 5 to 10 minutes in increments of 5 to 10 mcg/kg/**minute** Some patients require up to 70 mcg/kg/minute, which can increase risk of propofol infusion syndrome (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects)	<1 to 2	3 to 10◊	**Advantages:** Potent sedative-hypnotic associated with an immediate onset and rapid awakening upon discontinuation when administered for short-term use. Metabolism is reportedly unaltered in hepatic or renal impairment and subject to few significant drug interactions. Infusion is readily titratable to desired depth of sedation, minimizing risk of oversedation. Propofol effectively decreases intracranial pressure, lowers cerebral metabolism, controls intractable seizures, and may reduce shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest. **Disadvantages:** Adverse effects include hypotension, bradycardia, respiratory depression, decreased myocardial contractility, elevated triglycerides, peripheral injection site pain, and rarely propofol infusion syndrome (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects). Specific product presentations may include potential allergens (egg, soy, peanut, others). Consult product label information. No analgesic effects. **Role:** A good choice in conjunction with appropriate analgesia for short-term sedation of patients in whom rapid awakening is advantageous. Also a good choice to decrease elevated intracranial pressure or for short-term sedation in a general critical care population that is likely to be ready soon for ventilator weaning trials.
Ketamine	0.25 to 0.5 mg/kg bolus IV Bolus doses may be given prior to sedation with an infusion of ketamine or as a single bolus (eg, patients with burns prior to dress changes or for procedural sedation) Bolus dosing may be repeated if necessary during the procedure (maximum dose 2 mg/kg in a 30 minute period)	0.05 to 0.4 mg/kg/hour	≤1	10 to 15 (single dose)	**Advantages:** A potent dissociative sedative-anesthetic with marked analgesia that maintains cardiac output and mean arterial pressure without inhibition of respiratory drive. Does not inhibit protective reflexes. May reduce acute opioid tolerance. **Disadvantages:** Sympathetic stimulation (ie, increased heart rate and myocardial oxygen demand, elevated intracranial pressure and systemic blood pressure) may be intolerable depending upon clinical setting. Rarely, cardiorespiratory depression associated with rapid administration or higher doses. Adverse effects may include hallucinations, delirium upon withdrawal, tonic-clonic movements, dissociative experiences, unpleasant recall, hypersalivation, nausea, and vomiting. Complex metabolism includes CYP3A4, 2C9, 2B6, and non-CYP hepatic transformations and an active metabolite (norketamine), which may accumulate in renal and/or hepatic impairment or due to drug interactions. **Role:** An alternate choice for postsurgical pain management, severe agitation, or as an adjunctive analgesic in patients with severe refractory pain in clinical settings where increased myocardial oxygen demand and sympathetic tone are tolerable.
Central alpha$_2$ agonist					
Dexmedetomidine	Optional: 1 mcg/kg over 10 minutes if hemodynamically stable Usually not given	0.2 to 1.5 mcg/kg/hour Initiate at 0.2 mcg/kg/hour and titrate every 30 minutes**	5 to 10 (optional loading dose) 15 (without loading dose)	60 to 120	**Advantages:** Effective sedative sympatholytic (central alpha$_2$ agonist) with moderate anxiolysis and analgesia. Character and depth of sedation may permit critically ill, mechanically ventilated patients to be interactive or easily awakened, yet comfortable. Can be used in non-mechanically ventilated ICU patients and continued as needed following extubation. Reduces shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest. May be less likely to cause delirium than other sedative choices. **Disadvantages:** Potentially significant hypotension and bradycardia or hypertension that do not resolve quickly upon abrupt discontinuation. Metabolized hepatically by glucuronidation and CYP2A6. Dose reduction recommended with renal and/or hepatic impairment. Rapid administration of loading dose may be associated with cardiovascular instability, tachycardia, bradycardia, or heart block. Does not induce the deep sedation needed for neuromuscular blockade. **Role:** A good choice for short- and long-term sedation in critically ill patients without relevant cardiac conditions. May be useful for sedation of patients with or at high risk of developing delirium, although this has not been well established.
Benzodiazepines¶					
Midazolam¶	0.01 to 0.05 mg/kg$^{\Delta}$ (0.5 to 4 mg)¶	0.02 to 0.1 mg/kg/hour infusion (2 to 8 mg/hour)¶ with intermittent bolus dose(s) if needed. While the patient is on a continuous infusion, periodic re-bolus may be needed to maintain the sedation goal. This approach may help prevent unnecessary dose creep of the infusion.	2 to 5	30◊	**Advantages:** A potent amnestic and anxiolytic agent with an immediate onset of action and a short duration of effect when administered short term (<48 hours). It is the only IV benzodiazepine that is not delivered in propylene glycol. **Disadvantages:** Hepatically metabolized by CYP3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long term. Half-life may be prolonged in critically ill patients with hepatic or renal impairment. Risk of delirium. Also, it interacts with drugs used in the ICU (eg, some antiretrovirals, azole antifungals) that alter CYP metabolism such that excess sedation can occur with concomitant use of midazolam and drugs metabolized by CYP3A4. **Role:** A good choice for short-term anxiolysis and treatment of acute agitation. Dose adjustment and gradual titration are needed for patients with renal and/or hepatic impairment.
Lorazepam¶	0.02 to 0.04 mg/kg$^{\Delta}$ (1 to 2 mg)¶	0.02 to 0.06 mg/kg every two to six hours intermittent (1 to 4 mg)¶ **AND/OR** 0.01 to 0.1 mg/kg/hour infusion (0.5 to 10 mg/hour)¶	15 to 20	360 to 480◊	**Advantages:** Sedative, amnestic, potent anxiolysis with anticonvulsant properties. Hepatically metabolized by glucuronidation to inactive metabolites. Relatively low risk of drug interactions and safety in mild to moderate hepatic and renal impairment. **Disadvantages:** Relatively slow onset. Risk of over-sedation when titrating due to delayed response and accumulation in peripheral tissues. Risk of delirium. IV incompatibilities and risk of line precipitate. Propylene glycol solvent may accumulate with prolonged use or high dosing causing metabolic acidosis and end-organ dysfunction (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects). Long half-life, with significant risk of accumulation in older adults or in patients with significant renal or hepatic impairment. **Role:** A good choice for sedation and anxiolysis for most patients, including those who may require long-term ongoing sedation. Although intermittent bolus dosing may be preferred, a continuous infusion may be initiated for patients requiring frequently repeated higher dosing.
Diazepam¶	0.05 to 0.2 mg/kg$^{\Delta}$ (5 to 10 mg)¶	0.03 to 0.1 mg/kg every 0.5 to 6 hours	2 to 5	20 to 60◊	**Advantages:** Rapid onset with potent sedative and muscle-relaxant effects. **Disadvantages:** Hepatically metabolized by CYP2C19 and 3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long term. Half-life

		intermittent (1 to 7 mg)¶ Continuous infusion is not recommended			may be prolonged in critically ill patients with hepatic and/or renal impairment. Risk of delirium. Also, it interacts with drugs used in the ICU that alter CYP metabolism. Injection solution contains propylene glycol solvent and cannot be delivered as a continuous infusion. Injection site pain and risk of phlebitis limit usefulness of IV injections. **Role:** Seldom used for sedation of critically ill patients. May be useful for critically ill patients at risk of alcohol withdrawal or seizures due to drug overdose or poisoning.
Antipsychotics					
Haloperidol¥	0.03 to 0.15 mg/kgΔ Variable doses; refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects	0.03 to 0.15 mg/kg every 30 minutes to six hours Various regimens; refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects	5 to 20 minutes (IV)	30 to 360◊	**Advantages:** Moderately sedating dopamine$_2$ antagonist for control of positive symptoms of delirium and ICU psychoses. Minimal cardiorespiratory effects in euvolemic, hemodynamically stable patients. **Disadvantages:** Complex hepatic metabolism includes CYP3A4 and 2D6 transformations. Some experts consider certain metabolites to be active or potentially neurotoxic. Half-life becomes prolonged with repeated administration. Adverse effects include dose-dependent QT interval prolongation and hypotension. Interacts with some common ICU drugs by interference with metabolism and/or by having an additive effect, prolonging the QTc. Extrapyramidal symptoms and neuroleptic malignant syndrome are rare in critical care use. **Role:** Potential treatment for agitation and/or delirium in critically ill patients.
Olanzapine‡	Optional: 5 to 10 mg IM May repeat every two to four hours if needed (maximum total 30 mg)	Oral: Initially 5 to 10 mg once daily; increase every 24 hours as needed by 5-mg increments up to 20 mg/day	IM: 15 to 45	IM: ≥120	**Advantages:** Availability of short-acting IM formulation; less risk of extrapyramidal symptoms and QT prolongation than haloperidol. **Disadvantages:** Adverse effects include orthostatic hypotension, hyperglycemia, somnolence, QT interval prolongation, and anticholinergic effects. Undergoes extensive hepatic metabolism including non-CYP (ie, glucuronidation) and CYP1A2 transformations. Half-life may be prolonged (ie, ≥50 hours) with increased risk of accumulation in patients who are older, female, nonsmoking, and/or in the setting of hepatic or renal impairment. **Role:** Potential alternative or add-on to as-needed IV haloperidol for treatment of acute agitation and/or delirium in the ICU. Use lowest starting dose and titrate more gradually in patients with renal and/or hepatic impairment and/or other factors that predispose for slowed metabolism (see "Disadvantages" above).
Quetiapine‡	None	Oral: Initially 50 mg every 12 hours; increase every 24 hours as needed up to 400 mg/day	Oral: 60 (initial effect); ≥24 hours (full effect)	Oral: 6 to 12 hours	**Advantages:** Less risk of extrapyramidal symptoms and possibly less risk of QT prolongation than haloperidol. **Disadvantages:** Requires enteral route of administration and scheduled dosing due to slow onset of action and relatively gradual titration schedule. Adverse effects may include sedation or orthostatic hypotension, and risk of QT interval prolongation remains. Hepatically metabolized by CYP3A4 to active and inactive metabolites. **Role:** A potential choice as adjunct to as-needed IV haloperidol for treatment of agitation and/or delirium. In advanced hepatic impairment initiate with reduced dose and titrate in lower increments.
Ziprasidone†	Optional: 10 mg IM May repeat every two hours if needed (maximum 40 mg total) **OR** 20 mg IM May repeat once after four hours if needed (maximum 40 mg total)	Oral: 20 to 40 mg orally every 12 hours	IM: 30	IM: ≥90	**Advantages:** Availability of short-acting IM formulation; less risk of extrapyramidal symptoms than haloperidol. **Disadvantages:** Orthostatic hypotension, hyperglycemia, QT prolongation; undergoes extensive hepatic metabolism by hepatic non-CYP and CYP3A4 transformations to active and inactive metabolites; IM formulation contains cyclodextrin (a potential nephrotoxin), which can accumulate in renal impairment; an IV formulation is not available. Oral formulation needs to be taken in a fed state (≥500 calories) for reliable absorption. **Role:** A potential alternative or add-on to as-needed IV haloperidol for treatment of acute agitation in the ICU†. Dose reduction is needed in advanced hepatic impairment. Specific recommendations are not available. Avoid prolonged use of IM preparation in patients with renal impairment due to risk of accumulation of cyclodextrin additive.

Dosing information in this table is for critically ill adults and includes indications, dosing, duration of use, and routes of administration not listed in the US Food & Drug Administration approved product labeling. Refer to UpToDate content on managing pain, agitation, and delirium in critically ill adults, the Lexicomp drug monographs[2], and most recent product labeling for additional information.

Data provided in "Characteristics and role" on drug metabolism and the presence of active metabolite(s) are included and may be useful for assessing the potential for drug interactions and risk of drug accumulation in renal and/or hepatic organ impairment.

CYP: cytochrome P-450 metabolism; IV: intravenous; ICU: intensive care unit; HR: heart rate; MAP: mean arterial pressure; NSAIDs: nonsteroidal anti-inflammatory drugs; INR: international normalized ratio; QT: QT interval on the electrocardiogram; QTc: corrected QT interval; IM: intramuscularly.

* All doses shown are for IV administration except where otherwise noted (eg, oral or rectal acetaminophen, IM olanzapine optional initial dose).

¶ In patients who are **obese**, standard, non-weight-based initial dosing is preferred. Standard adult doses, ie, scaled to ideal body weight, are shown in parentheses following weight-based doses. A separate calculator to determine ideal body weight is available in UpToDate. For additional information, refer to UpToDate topic reviews on ICU management of the complicated postoperative bariatric surgery patient.

Δ One or more loading doses may be needed. See onset of action data for minimum time between re-dosing. Loading dose should be reduced or omitted in patients who are older, hypovolemic, having increasing vasopressor requirements, or at-risk for hemodynamic compromise.

◊ Duration of action shown is for initial dosing. Duration becomes significantly prolonged after repeated dosing or with administration as a continuous infusion due to accumulation of drug in adipose tissue.

§ As with all opioids, tolerance may require dose escalation, and withdrawal syndrome may be precipitated upon abrupt discontinuation.

¥ Dosing of haloperidol in agitated schizophrenia differs from the recommendations listed in this table for agitated delirium in the ICU and is reviewed separately. Refer to UpToDate topic reviews of emergency management of the acutely agitated or violent patient and pharmacotherapy for acute schizophrenia.

‡ The precise role of second-generation antipsychotics in the treatment or prevention of agitated delirium in ICU is not established. Quetiapine and olanzapine recommendations and data are based on limited experience and small trial results.[1,2] Some experts start at one-quarter to one-half of doses shown and titrate gradually based upon response particularly in older adults and patients with organ dysfunction.

† Ziprasidone recommendations and data are based on limited experience and small trial results in treatment of undifferentiated agitation without symptoms of delirium in non-critically ill emergency department patients.[3,4] Small trial results failed to demonstrate a benefit for scheduled oral ziprasidone in prevention of delirium in a general ICU population.[5]

** Dosing of dexmedetomidine in obese patients is typically performed according to the ideal body weight.

Special: Exam 6

Nutrition

Fluids and Electrolytes

Know the body fluid compartments and their composition
Develop an approach to managing fluid and electrolytes in patients requiring nutrition support with parenteral nutrition

Adult Maintenance IV Fluid Requirements

Most often used to calculate IV fluid requirements when patient are NPO
Approximations of 30-40 ml/kg/day can be used quickly; 35 ml/kg/day x 70 kg = 2450 ml/day
More specific calculations - Holliday-Segar Method (ex. 70 kg patient)

- 1st 10 kg = 4 ml/kg/hr x 10 kg = 40 ml/hr
- 2nd 10 kg = 2 ml/kg/hr x 10 kg = 20 ml/hr
- Kg >20 kg = 1 ml/kg/hr x 50 kg = 50 ml/hr

= 70 kg pt = 110 ml/hr x 24 h = 2640 ml/day

Factors Affecting Fluid Requirements

increasing fluid requirement: fever, sweating, hyperventilation, hyperthyroidism, burns
decreasing: chronic comorbid (HF, cirrhosis, nephrotic)
variable: extraneous losses (fistula, ostomy, drain), third spacing

Hyponatremia

<135 mEq/L; most common electrolyte abnormality in hospitalized patients (15-30%)
- caused by greater than normal body of water; "hypotonicity" primary clinical disorder
- primary cause sodium loss; secondary cause excess free water, fluctuations in ADH (Antidiuretic Hormone)

ADH, arginine vasopressin (AVP)
- synthesized hypothal, transported to posterior pituitary for release
- increased plasma osmolarity and decreased circulating volume increase ADH release
- increases water reabsorption of kidney
- pain and stress from surgery can cause sustatined release of AVP for 1-2d post-op ("hold on to fluid")

SIADH: Syndrome of Inappropriate ADH
- inappropriately HIGH levels of ADH (AVP): LOW Na, LOW plasma osmolarity
- kidneys reabsorb large volumes of water
- total body water increases and blood becomes hypo-osmolar resulting in decreased Na concentration ("dilutional effect")
- Tx: treat underlying disorder (causes: meds, tumors, cranial disorders, non-malignant lung disorders PNA)
  - fluid restriction - gradual infusion of hypertonic saline if Na <110 and/or neuro dysfunction (seizure, coma)
  - mEq Na needed = (desired Na – measured Na) x (TBW)

Hypernatremia

>145 mEq/L
- excessive water loss exceeds Na loss (dehydration) OR excessive sodium intake exceeds water intake
- sx appear when Na >160 (acute) or Na >170 (chronic); neurologic sx: lethargy, confusion, seizures, stupor, coma
- sudden contraction in ICW can lead to intracerebral hemorrhage

DI: Diabetes Insipidus
- rare; etiology: CNS (failure of ADH/AVP secretion, familial, hypothalamic injury TBI, tumors, inf), nephrogenic (failure of kidney to respond to ADH/AVP)
- sx: polyuria, polydipsia, hypernaturemia, hypotension, shock
- Tx: vasopressin

Tx Hypernaturemia
- calculate free water deficit (L) H2O deficit (L) = CF x kg body weight x [(serum Na – 140)/140] CF = 0.6Male, 0.5Female, 0.45Elderly
  Example: 70 kg male 0.6 x 70 kg x [(150 – 140)/140]; Water deficit (L) = 3L
- preferred route of water correction is via oral or feeding tube if feasible
- target is to reduce Na no more than 10 – 12 mEq/day; AVOID rapid correction
- use hypotonic fluids volume restricted to that needed to correct hypernatremia; Water – oral; D5W, 0.2% NaCl, 0.45% NaCl - intravenous

	ADH levels	Serum Na	Plasma Osmolarity
SIADH	HIGH	LOW	LOW
Diabetes Insipius	LOW	HIGH	HIGH

Na content	Water content	Serum Na (mEQ/L)
Normal	Normal	135-144
Normal	Increased	<135
Normal	Decreased	>145
Decreased	Normal	<135
Decreased	Decreased	<135, 135-144, >145
Decreased	Increased	<135 or severe at <130
Increased	Normal	>145
Increased	Increased	<135, 135-144, >145
Increased	Decreased	>145

Hyperkalemia

>5 mEq/L; Etiology: traumatic blood draws (hemolysis), excessive intake IV/PO, altered distribution (acidosis), cellular breakdown (burn, crash, IV hemolysis), impair renal excretion
EKG monitoring
Tx goals:
- stabilize the myocardium – most important! Calcium gluconate 1 gram IV over 3 – 5 minutes
- shift potassium intracellular: Insulin Regular 10 units IV push and D50W IV push (to prevent hypoglycemia from insulin administration)
- correct acidosis: Sodium Bicarbonate 50 – 100 mEq IV push
- increase potassium excretion: Sodium Polystyrene (Kayexelate) 25 – 50 grams PO once
- other medications/procedures that remove K (Loop diuretics, Hemodialysis)

Hypokalemia

<3.5 mEq/L; Etiology: kidney losses (diuretics), GI tract losses/ileus, skin losses (burn, exercising hot day), excessive insulin admin, dietary inadequate intake
Tx goals:
- PO (preferred) or IV replacement
- for each 10 mEq KCl given, raises K by 0.1
  e.g. pt with K = 3.2 was given 40 meq of KCl; K following replacement should be approximately 3.6; Do not administer more than 40 – 60 meq of KCl replacement at one time

Calcium

Essential for normal muscle contractions, nerve function, blood coagulation, and bone formation
Stored in bones and teeth: Only 1% is extracellular and 60% of it is bound to albumin
Usual IV dose – calcium gluconate 10-15 meq/day: 4.65 meq = 1 gram
Corrected Total Ca = Measured Total Ca + [0.8(4 – albumin)]

Magnesium

Functions as a coenzyme in metabolism of carbohydrates and proteins and is needed in ATP reactions
50% found in bone and 50% soft tissue
Second most abundant intracellular cation
Usual IV dose – Magnesium Sulfate 8 – 20 mEq/day; 8.12 meq = 1 gram
Attention Chocolate lovers!!! Most concentrated dietary source of Mg is dry cocoa powder

Phosphorus

Constituent of nucleic acids, phospholipid membranes, and nucleoprotein and plays a key role in macronutrient metabolism
Phosphorous levels (≤ 2) could indicate refeeding syndrome
Major component of bone and teeth
Primary intracellular cation
Usual IV dose – 20 – 40 mmol given as either sodium phosphate or potassium phosphate

Lab Values

	Normal	Parenteral Req.	Serious: ↓	Serious: ↑
Na	135-145	1-2 mEq/kg	<130	>150
K	3.5-5.0	1-2 mEq/kg	<3	>5
Cl	98-108	maintain acid-base		
HCO3	23-30	maintain acid-base	<18 (CO2)	>30 (CO2)
Ca	9-10.5	8-20 mEq/day	<1.2	>2.5
Mg	1.7-2.4	10-15 mEq/day	<2	>5.5
P	2.5-4.5	20-40 mmol/day	<4.4 ionized	>10 total

(CO2): evaluate the blood gas for actual serum pH < 7.2 severe acidemia; > 7.6 severe alkalemia
- serious electrolyte abnormalities should be corrected prior to PN starting
- if PN is causing the abnormality it may need to be stopped and an alternate fluid hung to allow for electrolyte correction

Conclusion
• Electrolyte abnormalities often correlate with fluid gains and losses
• Most abnormalities can be corrected by understanding body water composition and the selection of correct fluid and proper amount of electrolyte replacement

Worksheet: Nutrition Fluids and Electrolytes
1. Total body water (TBW) is calculated based on **60% of actual body weight**.
2. Maintenance IV fluid requirements can be approximated using **30-40 ml/kg/day**.
3. The 2 predominant electrolyte losses associated with gastric contents includes **Na and Cl**.
4. Anti-Diuretic Hormone (ADH) is released in response to **decreased** circulating volumes.
5. An increase in sodium content and decrease in water content will result in a serum sodium level of **>145**.
6. The primary goal of treating hyperkalemia is to **stabilize myocardium** with administration of **calcium gluconate 1g IV over 3-5min**.
7. Serious electrolyte abnormalities need to be corrected **before** starting parenteral nutrition.

Nutrition Support

Identify when a patient is malnourished
Utilize a systematic approach when determining between enteral or parenteral nutrition

Nutritional Screening

Nutritional status/assessment

Joint Commission mandates hospitals conduct nutrition screening within 24 hrs of admission

Nutrition screening tools vary depending on setting and population

Validated screening tools assess items such as:

- Diagnosis
- Intake history
- Weight history; comparison to IBW
- Nursing assessment (physical appearance on exam)
- Classify patients at "no risk", "at risk", or "malnourished"
- Many of the screening tools take into account gastrointestinal function and clinical status

Malnutrition Diagnosis → Evaluate GI Function

Symptoms that may preclude oral feeding: abdominal pain and distention, severe diarrhea or ostomy output
Diagnoses that may preclude oral feeding: ileus, mesenteric ischemia, small bowel obstruction, high output fistulas
Consider anticipated duration of GI dysfunction
Can the GI tract be used for feeding? If YES – consider oral nutrition support; If NO – may need to consider parenteral nutrition support

Spectrum of Nutrition Support

Nutrition Support

Enteral route preferred - "If the gut works, use it!"; maintenance of intestinal villi height and function; reduced bacterial translocation; gallbladder stimulation
Parenteral nutrition does have place in therapy for GI tract failure; however, risks: mechanical/metabolic complications, infections (secondary to vascular access)

algorithm

two factors below must be present for a malnutrition diagnosis
energy intake, weight loss, body fat loss, muscle mass wasting, fluid/edema, handgrip strength

PN Indications

Acute and/or Chronic Intestinal Failure: acute: small bowel obstruction, ileus; chronic: mesenteric ischemia (can be acute degree of ischemia), short gut syndrome
Enteral nutrition is contraindication, not feasible, or poorly tolerated with appropriate tube placement
Inability or projected inability to tolerate an oral diet for 7 – 10 days
PN initiation should be delayed in patient's with severe metabolic instability and avoided in any patient with a known source of bacteremia and/or fungemia

PN Selection

Peripheral (PPN)
- Infused into peripheral veins
- Large fluid volumes required for vein tolerance; Irritating!
- Short term (<2 wks)
- Mild to moderate malnutrition

Central (CPN) preferred
- Infused through central venous catheters
- Complete, balanced formula
- Fluid volume adjusted to patient needs and tolerance (ability to concentrate if needed)
- Prolonged duration
- Improves nutritional status

Central Venous Catheter (CVC)
Peripherally-Inserted Central Venous Catheter (PICC)
Tunneled Central Venous Catheter
Central Venous Port

Summary

• Nutrition screening tools and risk assessments help identify malnourished patients
• GI function versus GI dysfunction/failure help drive how we provide nutrition support to patients

Worksheet: Malnutrition: Intro to Nutrition Support

1. Nutrition screening must be completed within **24 hrs** in the hospital setting to remain in compliance with Joint Commission standards.
2. What are the 6 characteristics that are used to make a diagnosis of malnutrition?
   energy intake, weight loss, body fat loss, muscle mass wasting, fluid/edema, handgrip strength
3. Understanding whether the **GI tract** can be used is the most important question to ask before determining the type of nutrition support.
4. If a total enteral formula is warranted, patients will need to have an oronaso tube placed in order to transport feeds to the stomach.
5. **Enteral** parenteral nutrition is preferred over **total** parenteral nutrition so a complete and balanced formula can be provided and volume can be adjusted to meet patient needs.

Malnutrition

Understand why malnutrition matters
Describe the nutritional consequences of the injury/stress response
Discuss how malnutrition influences patient outcomes

Malnutrition

An acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function

- poor nutrition, can occur due to underweight or overweight – inadequate intake of **micronutrients**
- high prevalence of malnutrition amon hospitalized, often goes unrecognized
- has significant impact on patient outcomes; worsened outcomes leads to increased healthcare costs and higher economic burden

The 3 etiology-based nutrition diagnoses in adults:

- **Starvation-related malnutrition**
  Chronic starvation **without inflammation**; Anything that limits access to food
  Examples: Anorexia nervosa, Poverty/homelessness, Concentration camps
- **Chronic disease-related malnutrition**
  Inflammation is **chronic** and of **mild to moderate degree**; Chronic illnesses
  Examples: organ failure, pancreatic cancer, rheumatoid arthritis, Crohn's
- **Acute disease or injury-related malnutrition**
  Inflammation is **acute** and of **severe degree**; Critical illness
  Examples: sepsis, trauma, burns, respiratory failure, acute renal failure

Results in changes: Body composition, particularly Lean Body Mass (LBM); Decreased functionality

Causes of Malnutrition

Altered or decreased intake (anorexia)
Increased nutrient losses – gastrointestinal disorders:
- NVD
- fistulas – abnormal communication between 2 or more organs causing fluid/electrolyte/nutrient loss; Ex. Enterocutaneous fistula – bowel → skin

Nutrient intake may be adequate but poor utilization: Hyper- or altered metabolism (trauma); INFLAMMATION

Changes in LBM due to Starvation

Changes in LBM due to DRM

Metabolic Response to Injury

Physiologic Function	**Response**	**Nutrional Consequence**
Energy expenditure	↑↑↑	Expenditure > energy intake creating **energy (kcal) deficits**
Catabolism (protein bkdn)	↑↑↑	Breakdown in excess of intake or synthesis creating **↓ in LBM**
Protein synthesis	--/↑	Change out of proportion with catabolism
Ureagenesis (protein waste)	↑↑	**Limited tolerance to protein doses** required to offset protein catabolism
Gluconeogenesis	↑↑↑	**Glucose difficult to control**, creates worse outcomes from illness
Response to feeding	↓↓	Nutritional response dictated by injury response – **use nutrients as fuel and healing injury rather than sustaining LBM**

Inflammatory Response and Nutrition

Starvation vs. Injury/Disease Summary

	Starvation	**Trauma or Disease**
Metabolic rate	↓	↑↑
Body fuel	conserved	wasted
Body protein	conserved	wasted
Urinary nitrogen	↓	↑↑
Weight loss	slow	rapid

Consequences of Malnutrition

Decreased Lean Body Mass (LBM), Prolonged wound healing, Increased incidence of complications, Infections: pneumonia, surgical wound, UTI, Physical and mental deterioration, Functional impairment, Increased healthcare costs

Summary

- Malnutrition matters!
- Disease-related malnutrition always has an inflammatory component ranging in severity from acute to chronic
- Recognizing malnutrition and its impact on patient outcomes is important to the success of disease management

Worksheet: Malnutrition: Etiology and Impact on Outcomes

1. Malnutrition often goes unrecognized and can have a significant impact on patient outcomes and lead to increased **economic** burden.
2. The 3 etiology-based nutrition diagnoses in adults include:
   a. **Starvation-related malnutrition**
   b. **Chronic disease-related malnutrition**
   c. **Acute disease or injury-related malnutrition**
3. The difference between starvation and acute/chronic malnutrition is the absence of **inflammation**.
4. Some nutritional consequences as a result to metabolic response to injury include (↑,↓): ___ Kcal ___ Lean Body Mass ___ Glucose
5. Increased incidence of infection is more common among malnourished patients? (**True** or False)

Enteral Products

Identify appropriate candidates for enteral nutrition (EN)
Describe the various characteristics of enteral nutrition products
Select an enteral nutrition product based on the patients condition and gastrointestinal function

Summary

- Enteral nutrition is the preferred method of feeding for patients at risk for malnutrition
- Enteral nutrition products vary by caloric and protein content as well as individual nutrients modified to meet special patient characteristics or diseases
- The Standard Enteral Formulations remain the most frequently used enteral feeding formulas

Worksheet: Enteral Nutrition Products and Characteristics

1. "If the gut works, **use it**!"
2. Enteral nutrition should be initiated when inadequate oral intake is expected for **7-14 days**.
3. The majority of patients should be started on a **liquid** enteral formula.
4. Enteral nutrition products contain approximately **70-84%** water.
5. Hydrolyzed EN formulations are indicated for patients with **impaired GI digestion or absorption**.

Parenteral Products

Understand the indications for parenteral nutrition (PN)
Design parenteral nutrition formulas taking macronutrient and micronutrients into consideration
Prevent and recognize PN related complications

Indications for PN support: • Inaccessible GI tract • Short bowel syndrome • Intestinal obstruction • High output fistulas (>500 ml/day) • Ileus
PN Criteria: duration should extend >7d for nutritional benefit, venous access available, hemodynamically stable (no/taper vasopressor), tolerate fluids
Peripheral (PPN): short-term 3-7days; osmolarity 600-900 mosm/l (risk of thrombophlebitis); requires high volumes to meet needs (keep mosm <900)
Central (CPN): indefinite duration; osmolarity exceeds 1000 mosm/l; PN can be concentrated allows less fluid admin; modify CKD, HF, etc.

Macronutrients
Intravenous Lipid Emulsion (ILE) = Fat **[10 kcal/g]**
Dextrose = Carbohydrate (CHO) **[3.4 kcal/g]**
Amino Acid = Protein **[4 kcal/g]**

Macronutrient Daily Doses
Calories (*gold std; indirect calorimetry) = 20-30 kcal/kg/d (~28 kcal/kg/d)
IV Lipid Emulsion = 1 g/kg/d (~20-30% of calories); dose to prevent EFAD: 2.5% calories as linoleic acid, 1.5% as linolenic acid
Carbohydrate (dextrose) = 60-75% calories (glucose infusion rate should be <4-5 mg/kg/min)
Protein = 1-1.5 g/kg/d (~10-15% of calories)
Fluid = 30-40 ml/kg/d

Micronutrient: Electrolytes
Na (tonicity, fluid balance) = 1-2 mEq/kg
K (muscle cardiac function) = 1-2 mEq/kg
Cl/acetate (extracell acid-base) = maintain acid-base balance
Phos (energy ATP) = 20-40 mmol
Ca (bone, cardiac function) = 10-15 mEq
Mg (cardiac, GI function) = 8-20 mEq

Notes: Na and K (salts Cl, acetate, phosphate)
Mg and Ca (divalent, don't exceed 20 mEq/L d/t ILE stability)

Monitoring PN	**Initiation**	**Critically Ill**	**Stable**
Electrolytes	daily x 3	daily	1-2x/wk
Glucose (serum) Glucose (POC)	daily x 3 q6h	daily q6h	1-2x/wk
Wt, I/O	daily	daily	daily
Serum TG	day 1	weekly	weekly
Liver enzymes	day 1	weekly	weekly
CBC w diff		weekly	weekly
Nitrogen balance		weekly	weekly

Micronutrient: Vitamins/Trace Elements
Vitamins: added daily to PN ≥11yo; MVI-12, MVI-13
Trace elements: multitrace formulations: MTE-4 (Zn Cu Cr Mn), MTE-5 (+ Se); 2-5ml/d
*additional Zn added in diarrheal conditions or high output fistula (5-10mg)
*additional Se added for wound healing (40-60mcg)
*trace elements contraindication (d/t Mn accum, neurotox) when T. bili >7

Efficacy of PN
progress towards goal: how long to achieve goal rate, tolerating well, any complications, signs of improvement/wound healing?
24h urine-Nitrogen Balance (NB): NB = intake (NI) – ((UUN x 1.2) + 1) *goal = +1-4g/day NI = g AA/d divided by 6.06 UUN = urine urea nitrogen
body composition: bioelectrical impedance (body fat, lean muscle, water); hand grip test; QoL

PN-Related Complications

Mechanical: Access, line insertion, line occlusion, phlebitis
Infectious: Catheter related line infections, bacteremia, fungemia; Sepsis
Metabolic: Fluid/electrolyte, acid-base abnormalities – short and long term (Refeeding Syndrome); Glucose control (hyperglycemia) – mainly short term; Renal and Hepatic – long term; Bone diseases – long term

Refeeding Syndrome
Occurs following a prolonged starvation period (NPO status) combined with high stress
Can occur when any type of feeding is initiated (PO, enteral, PN); Within first 2-3 days of feedings; can last as long as 1-2 weeks
Results in intracellular shift of **K, Mg, Phos** in response to feeding → BG abnormalities (hyperglycemia), Pulmonary failure
Early recognition is KEY
*Must limit sources of dextrose and reduce feeding rate – go "low and slow"
*Replace electrolytes aggressively
*Increase nutrition to goal gradually

Hyperglycemia (BG>180)
Hyperglycemia is the most common PN complication
BG goal = 100 –180 mg/dl
Advance dextrose to goal based on glycemic response
May need to modify dextrose dose of PN if BG not at goal; assess pt caloric goals if dextrose modified; E.g. may need to provide more calories in the form of protein or fat to compensate
If patient has glucose intolerance at baseline
Limit dextrose to 100 g
Insulin therapy: Sliding scale insulin (SSI) outside the PN (insulin regular q 6 hrs)
Can add insulin to PN (0.1 -0.2 units of insulin per gram of dextrose)
Ex. 100 grams of dextrose→10 units of insulin; Can continuing adding 2/3 SSI requirements over 24 hrs to PN if needed
Glucose intolerance may be caused by comorbid conditions and/or medications; Sometimes the PN is not to blame! Must evaluate the WHOLE patient
Examples: Diabetes, Pancreatitis, Stress/critical illness, Obesity, Medications, Steroids, Octreotide

Hypoglycemia (BG<60)
Etiology:
Excess administration of insulin
Abrupt discontinuation of PN or PN cycling
Reasons for abrupt discontinuation: Critical illness, Infected CVC, Life-threatening complication causing electrolyte imbalance, Acute renal failure, hyperkalemia (K > 5.5)
Avoid rebound hypoglycemia
*Administer 10% dextrose at 50 ml/hr x 2 hr OR Taper PN at 50 ml/hr x 2 hr before discontinuing

Hepatobiliary
Etiology:
Excess glucose "overfeeding" for prolonged periods of time can lead to steatosis
Constant hepatic stimulation (continuously over 24 hrs)
Lack of enteral stimulation
Bacterial overgrowth of the small bowel
Transaminases: Can be seen with prolonged PN therapy (2 wks or after); Normalizes with PN discontinuation
Alkaline Phosphatase: Increased with bone disease
Bilirubin: Gallbladder sludge/stones; Jaundice

Hypertriglyceridemia
Etiology:
Pre-existing conditions, other medications in ILE (e.g. propofol)
Compounded by the delivery of intravenous lipid emulsion
Ideal serum TG level <200 mg/dl
Maximum TG on ILE – 400 mg/dl; up to 500 mg/dl with SMOFlipid
Must decrease IVFE in these situations but provide enough to prevent EFAD

Metabolic Bone Disease
Effects 40-100% of patients on chronic PN (> 1 yr); Bone pain and fractures
Caused by conditions that increase calcium excretion
High protein intake (> 1 gm/kg/day long term), High sodium load, Chronic metabolic acidosis, Excess fluid, Hyperglycemia, Aluminum contamination, Other meds: loops, OCS etc.

Vitamin Deficiencies
*Thiamine (Vitamin B1): Dry beriberi – weakness, paresthesias
*Wet beriberi – lactic acidosis, cardiac failure, Wernicke's Korsacoff syndrome
*At risk patients: Alcoholic, Post bariatric surgery, Refeeding syndrome
Others: Folic acid: hemolytic anemia, Vitamin A: night blindness, Vitamin D: osteoporosis, Vitamin C: bleeding gums (scurvy)

Trace Element Deficiencies
*Zinc (Zn): acrodermatitis enteropathica → poor wound healing, skin breakdown
*Selenium (Se): cardiomyopathy (Keshan's disease)
Others: Copper (Cu): anemia, leukopenia, Chromium (Cr): hyperglycemia, Manganese (Mn): impaired growth, reproductive dysfunction, ataxia, confusion

Summary

- PN is indicated for patients with temporary or permanent GI failure as a mode of nutrition support
- PN formulas must be designed with patient specific factors in mind
- Monitoring PN includes preventing and correcting the formula to minimize PN related complications

Worksheet: Parenteral Nutrition Products and Characteristics

1. The overarching indication for parenteral nutrition is a **non-accessible GI tract**.
2. Once PN is started, it should continue for at least **7 days** for patients to derive nutritional benefit.
3. Macronutrients are the primary energy source of PN and include **carbohydrates (dextrose), protein (amino acids), lipids**.
4. Micronutrient (electrolyte) components can include: **Na, K, Cl/acetate, Phos, Ca, Mg**
5. The most common complication associated with PN is **hyperglycemia**.
6. Electrolyte abnormalities associated with refeeding syndrome include (↑,↓): ↓Phos ↓K ↓Mg
7. What component of PN should be held when T. bili is > 7? **Trace elements** (d/t manganese accum, neurotox)

Geriatrics

Discuss specific pharmacokinetic and dynamic changes with aging and their potential affect on drug therapy
Become familiar with the 2019 Beers Criteria
Apply 2019 Beers Criteria appropriately to patient care
Discuss appropriate overall treatment goals for older adults
Apply knowledge of treatment goals to help determine rationale treatment plans for older adult patients, which follow published guidelines

Physiology of Aging
Absorption: Decreased gastric acid, Slower GI motility, Delayed gastric emptying
Distribution: Increased body fat, Decreased muscle mass, Decreased total body water
Metabolism: Impaired phase I reactions (e.g., oxidation, hydroxylation), Phase II reactions intact (e.g., conjugation)
Excretion: Reduced renal function
Reduced physiologic reserve

PK Changes

digoxin, sotalol, lithium, aspirin, H2RAs
decreased total water = ↑hydrophilic drug conc, ↓Vd

warfarin, diazepam, valproate, naproxen, ceftriaxone, phenytoin
decreased serum albumin = ↑free fraction in plasma of highly protein-bound acidic drugs

lidocaine, propranolol, chlorpromazine
increased α1-acid glycoprotein = ↓free fraction of basic drugs

warfarin, theophylline, phenytoin, triazolam, zolpidem, statins
decreased hepatic blood flow and hepatic mass = ↓first-pass metabolism; phase I slightly impaired; 3A4 function ↓ with age

digoxin, gentamicin, lithium, ACEis, antithrombotics (dabigatran)
decreased renal blood flow and GFR = impaired renal elimination of drugs

PD Changes

CCBs
reduced baroreceptor response to low BP; greater sino-atrial suppressive effect, less pronounced PR interval prolongation (dilt/verap)
therefore greater hypotensive effect, risk of OH and falls; decreased HR (dilt/verap)
rec: dose adjust based on response

Diuretics
reduced response due to impaired tubular secretion of drug and decline in GFR; impaired adaptive and homeostatic mechanisms
therefore, reduced effectiveness of conventional doses of diuretic esp with NSAIDs, increased risk of hypokalemia, hypomagnesemia, hyponatremia
rec: careful upward-titration of drug dosage; if possible, avoid NSAIDs

β-blockers
impaired signal transduction of beta-receptor and down regulation of beta-adrenergic receptors
therefore, reduced effectiveness of conventional doses of β-blockers
rec: careful upward-titration of drug dosage

antipsychotics
increased responsiveness due to impaired homeostatic mechanisms and depletion of dopamine reserve
therefore, increased anticholinergic risk, extrapyramidal side effects, OH, cerebero-vascular events
rec: dose adjust; careful assess of requirement; avoid coadmin with other anticholinergics

lithium
greater sensitivity to effects of lithium
therefore, increased risk of neurotox (delirium, confusion, weakness, memory, anxiety, gait)
rec: dose adjust based on serum lithium conc

Beers Criteria

"What do I need to know regarding Beers Criteria for exam?
The article, itself, has the medications or class of medications highlighted for what you are going to be held responsible for knowing for the exam.
These categories are vital for you to know as you do medication reconciliation or comprehensive medication reviews without having to look them up.
I have tried to be cognizant of not overdoing what you need to "memorize."
Please know, however, that if the medication is highlighted, you are also responsible for knowing the rationale and recommendation.

Table 2: Potentially Inappropriate Medication Use in Older Adults

Nitrofurantoin
Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available
-Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression

Peripheral alpha-1 blockers for treatment of hypertension: Doxazosin, Prazosin, Terazosin
High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile
-Avoid use as an antihypertensive

Central alpha-agonists: Clonidine for first-line treatment of hypertension; Other CNS alpha-agonists: Guanabenz, Guanfacine, Methyldopa, Reserpine (>0.1 mg)
High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension
-Avoid as first-line antihypertensive; Avoid other CNS alpha-agonists as listed

Digoxin for first-line treatment of atrial fibrillation or of heart failure
Use in atrial fibrillation: should not be used as a first-line agent in Afib, because there are safer and more effective alternatives for rate control supported by high-quality evidence.
Use in heart failure: evidence for benefits and harms of digoxin is conflicting and of lower quality; most but not all of the evidence concerns use in HFrEF. There is strong evidence for other agents as first-line therapy to reduce hospitalizations and mortality in adults with HFrEF. In heart failure, higher dosages are not associated with additional benefit and may increase risk of toxicity. Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in those with stage 4 or 5 chronic kidney disease.
-Avoid this rate control agent as first-line therapy for atrial fibrillation
-Avoid as first-line therapy for heart failure If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day

Antidepressants, alone or in combination: Amitriptyline, Clomipramine, Desipramine, Doxepin >6 mg/day, Imipramine, Nortriptyline, Paroxetine, Trimipramine
Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable to that of placebo
-Avoid

Antipsychotics, first (conventional) and second (atypical) generation
Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia
Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others
-Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy

Benzodiazepines, Short and intermediate acting: Alprazolam, Estazolam, Lorazepam, Oxazepam, Temazepam, Triazolam
Benzodiazepines, Long acting: Chlordiazepoxide (alone or in combo with amitriptyline), Clonazepam, Clorazepate, Diazepam, Flurazepam, Quazepam
Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia
-Avoid

Meprobamate
High rate of physical dependence; sedating
-Avoid

Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs"): Eszopiclone, Zaleplon, Zolpidem
Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (ie, Z drugs) have adverse events similar to those of benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration
- Avoid

Sulfonylureas, long acting: Chlorpropamide, Glimepiride, Glyburide
Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH
Glimepiride and Glyburide: higher risk of severe prolonged hypoglycemia in older adults
-Avoid

Metoclopramide
Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure
-Avoid, unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases

Mineral oil, given orally
Potential for aspiration and adverse effects; safer alternatives available
-Avoid

Proton-pump inhibitors
Risk of Clostridium difficile infection and bone loss and fractures

-Avoid scheduled use for >8 weeks unless for high-risk patients (eg, oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (eg, because of failure of drug discontinuation trial or H2-receptor antagonists)

Skeletal muscle relaxants: Carisoprodol, Cyclobenzaprine, Methocarbamol, Chlorzoxazone, Metaxalone, Orphenadrine

Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable

-Avoid

Table 3: Drug–Disease or Drug–Syndrome Interactions That May Exacerbate the Disease or Syndrome

Syncope

AChEIs, Nonselective peripheral alpha-1 blockers (ie, doxazosin, prazosin, terazosin), Tertiary TCAs, Antipsychotics: Chlorpromazine, Thioridazine, Olanzapine

AChEIs cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia.

Nonselective alpha-1 blockers cause orthostatic BP changes and should be avoided in older adults whose syncope may be due to orthostatic hypotension.

Tertiary TCAs and the antipsychotics listed increase the risk of orthostatic hypotension or bradycardia.

-Avoid

History of falls or fractures

Antiepileptics, Antipsychotics, Benzodiazepines, Z-hypnotics (Eszopiclone, Zaleplon, Zolpidem), Antidepressants (TCAs, SSRIs, SNRIs), Opioids

May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (ie, antiepileptics, opioid-receptor agonists, antipsychotics, antidepressants, nonbenzodiazepine and benzodiazepine receptor agonist hypnotics, other sedatives/hypnotics) and implement other strategies to reduce fall risk. Data for antidepressants are mixed but no compelling evidence that certain antidepressants confer less fall risk than others.

-Avoid unless safer alternatives are not available; avoid antiepileptics except for seizure and mood disorders Opioids: avoid except for pain management in the setting of severe acute pain (eg, recent fractures or joint replacement)

Table 4: PIMs: Drugs To Be Used With Caution in Older Adults

Aspirin for primary prevention of cardiovascular disease and colorectal cancer

Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when used for primary prevention in older adult with cardiovascular risk factors, but evidence is not conclusive. Aspirin is generally indicated for secondary prevention in older adults with established cardiovascular disease.

-Use with caution in adults ≥70 years

Dabigatran, Rivaroxaban

Increased risk of gastrointestinal bleeding compared with warfarin and reported rates with other direct oral anticoagulants when used for long-term treatment of VTE or atrial fibrillation in adults ≥75 years.

-Use with caution for treatment of VTE or atrial fibrillation in adults ≥75 years

Prasugrel

Increased risk of bleeding in older adults; benefit in highest-risk older adults (eg, those with prior myocardial infarction or diabetes mellitus) may offset risk when used for its approved indication of acute coronary syndrome to be managed with percutaneous coronary intervention.

-Use with caution in adults ≥75 years

***Antipsychotics, Carbamazepine, Diuretics, Mirtazapine, Oxcarbazepine, SNRIs, SSRIs, TCAs, Tramadol**

May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults

-Use with caution

Dextromethorphan/quinidine

Limited efficacy in patients with behavioral symptoms of dementia (does not apply to treatment of PBA). May increase risk of falls and concerns with clinically significant drug interactions. Does not apply to treatment of pseudobulbar affect.

-Use with caution

Trimethoprim-sulfamethoxazole

Increased risk of hyperkalemia when used concurrently with an ACEI or ARB in presence of decreased creatinine clearance

-Use with caution in patients on ACEI or ARB and decreased creatinine clearance

Table 5: PIMs: Drug-Drug Interactions that Should Be Avoided (Changes)

AED, AP, benzo, Z-hypnotic, TCA, SSRI, SNRI, opioid: avoid any combination of ≥3 of these CNS-active drugs

- reason for change is due to increased risk of falls; minimize number of CNS-active drugs shown to decrease risk of falls

opioids + benzos: increase risk of overdose

opioids + gabapentinoids: increased risk for severe sedation related adverse events

Table 7: Drugs with Anticholinergic Properties

Disopyramide, Amitriptyline, Amoxapin, Clomipramine, Desipramine, Doxepin (>6 mg), Imipramine, Nortriptyline, Paroxetine, Protriptyline, Trimipramine, Prochlorperazine, Promethazine, Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Dexchlorpheniramine, Dimenhydrinate, Diphenhydramine (oral), Doxylamine, Hydroxyzine, Meclizine, Clidinium-chlordiazepoxide, Dicyclomin, Homatropin (excludes ophthalmic), Hyoscyamine, Methscopolamine, Propanthelin, Promethazine, Pyrilamine, Triprolidine, Darifenacin, Fesoterodine, Flavoxate, Oxybutynin, Solifenacin, Tolterodine, Trospium, Benztropine, Trihexyphenidyl, Chlorpromazine, Clozapine, Loxapine, Olanzapine, Perphenazine, Thioridazine, Trifluoperazine, Antispasmodics, Atropine (excludes ophthalmic), Belladonna alkaloids, Scopolamine (excludes ophthalmic), Cyclobenzaprine, Orphenadrine

Factors to Direct Goals of Therapy for Older Adults

5 Guiding Principles:
- Patient Preferences
- Interpreting the Evidence
- Prognosis
- Treatment Complexity and Feasibility
- Optimizing Therapies and Care Plans

BP Goals: ACC/AHA <130/80, ACP/AAFP <150
Alzheimer's staging, MMSE/30: 24-20 mild, 10-19 moderate, <10 severe, 0 profound
Functional status: IADLs (shopping, cooking, housework, bills, laundry); ADLs (bathing, toileting, eating, climbing stairs, grooming, dressing)
The Clinical Fraility Scale (CFS): score 1-4 fit preserved function, score 5-6 loss of function, score 7-9 loss of function and altered ADL, score 9 terminally ill

Dr Emptage's Bottom Line for Treatment of Hypertension in those over 65 years old
- Mixed messages (guidelines) and lack of CONSISTENT, good evidence especially in the very old make it an art not an exact science
- Take into account risk versus benefit for the SPECIFIC PATIENT
- Determine or data gather:
  - Age – being over 75yo MAY be ONE indicator for adjusting goals of therapy
  - Cognitive ability
  - Functional status
  - Fall history, specifically
  - Concomitant illnesses which might affect therapy choice or goals of therapy
- For some individuals the goal will be <130/80 or <140/90 or possibly <150/90; always be able to back up recommendation with a GOOD rationale for your patient

deprescribing.org
PPIs, Antihyperglycemics, Benzodiazepines and "Z" Drugs, Antipsychotics, Cholinesterase Inhibitors and Memantine

Needs tapering
antidepressants, anticonvulsants, antipsychotics, benzos, beta-blockers, cholinesterase inhibitors, clonidine, steroids, memantine, PPIs, tizanidine, tramadol, Z-drug

"Dr Emptage, what do I need to know from all of this?"
- o Beers Criteria as highlighted on the Tables 1-4
- o Five Guiding Principles of Step Wise Approach
- o Factors to consider when deciding on specific goals of therapy for hypertension and diabetes in the older adult
- o Which medications/class of medications have full deprescribing algorithms on deprescribing.org
- o Common oral medications that May Need Tapering as highlighted on the table
- o Preferred agents to be used in older adults for both Hypertension and Diabetes in the older patient
- o All of these elements will help you be able to determine goals and therapy choices for both hypertension and diabetes in the older adult patient in case based questions – you will get additional practice in Small Group covering Special Populations.

Type 2 DM Older Adults

Apply overall treatment goals for older adults with diabetes
Determine appropriate drug therapy options for older adults with type II diabetes
Define deintensification of diabetes therapy in older adults
Apply techniques to de-intensify a diabetes regimen for an older adult
https://care.diabetesjournals.org/content/44/Supplement_1/S168

Patient Characteristics/Health Status	Rationale	A1c Goal	FPG	Bed BG	BP, Lipids
Healthy few coexisting chronic illnesses intact cognitive and functional status	Longer remaining life expectancy; can perform more complex tasks	<7.0-7.5%	80-130	80-180	<140/90, statin
Complex/intermediate multiple coexisting chronic illnesses or 2+ IADL impairments or mild-mod cognitive impairment	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%	90-150	100-180	<140/90, statin
Very complex/poor health LTC or end-stage chronic illnesses or mod-severe cognitive impairment or 2+ ADL dependencies	Limited remaining life expectancy makes benefit uncertain	^	100-180	110-200	<150/90, consider

^avoid reliance on A1c; prevent hypoglycemia and symptomatic hyperglycemia; goals above 8.5% are not recommended as they may expose patient to more frequent higher glucose values and the acute risk from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

General

Background: 25% of >65yo have DM; 50% have preDM
Importance of deintensifying: 31% of hospitalizations in older adults are related to ADEs; 66% of these are from warfarin, antiplatets, insulin, oral hypoglycemics
Individual goal setting: control hyperglycemia (comorbidities), prevent/treat complications (QoL), self-manage (cognitive), improve general health (life expectancy)
General Drug Therapy Considerations
- Medications with lower risk of hypoglycemia are generally preferred in this patient population
- Overtreatment of diabetes is common in older adults; The most simplified regimen should be used to achieve glycemic goals

Other considerations
- Consider costs of care and insurance coverage rules when developing treatment plans in order to reduce risk of cost-related nonadherence (12.16)
- Cost-related nonadherence: Not filling or taking (forgoing) medications because of cost related concerns
- Approximately 10 - 40% of home dwelling older adults experience cost-related nonadherence

Drug Options

Metformin	preferred agent in older adults	caution renal (CI eGFR <30), hepatic, CHF
TZDs	not considered first-line	caution CHF, risk falls/fractures; avoid combo with insulin
SU, Meg	not considered first-line	caution hypoglycemia risk; if used, glipizide preferred
DPP-4i, GLP-1	adjunctive agents	DPP-4i expensive, GLP-1 NV potential, wt loss; CVD benefit
SGLT-2i	not considered first-line	long-term experience limited; ASCVD benefit
Insulin	reasonable qday basal	caution hypoglycemia, caution MDD

Deintensification

What? Non-insulin regimens: achieved by either lowering the dose or discontinuing some medications Insulin regimens: simplifying regimens; see algorithm
When? When regimens are too complex beyond individual self-management abilities
Why? Recommended to reduce the risk of hypoglycemia, polypharmacy & disease related stress

Conclusion

- Treatment goals for older adults with type II diabetes are individualized based on co-morbidities, functional status and cognitive status
- Many considerations when choosing pharmacotherapy: Focusing on the “Compelling Need to Minimize Hypoglycemia” in the ADA Standards of Care
- Deintensification is simplifying medication regimens when they become to complex to reduce the risk of adverse events

Pediatrics

Definitions and concepts relevant to pediatric pharmacotherapy
PK/PD/efficacy/safety differences in pediatric vs. adult patients
Ways to improve medication access, efficacy, safety, adherence and health outcomes in pediatric patients

- Gestational age: FDLMP to delivery day
- Premature infant: Born <37 weeks GA
- Chronological age: Age after birth
- Corrected age: Age minus weeks <40
- ELBW<1 Kg; VLBW 1–1.5 Kg; LBW 1.5-2.5 Kg
- Neonates: Birth to 28-30 days of age
- Infants: 1 month to <2 years of age
- Children: 2 to <12 years of age
- Adolescents: 12 to 18 years of age
- Adults: 18 years and above

Early Influences
- Role modeling
- Home environment (relationships)
- Diet and exercise
- Wellness screenings and disease prevention
- Alcohol/drug abuse, smoking, risky behaviors

2D6 take longest to develop

Pediatric Drug Dosing
- Verify that mg/kg/dose is correct for the patient's age and disease being treated after calculating mg dose
- 3 major clinical factors
  - Age, body weight or surface area
  - Organ function
  - Disease being treated

Absorption
- Passive diffusion depends on gastric pH
- Premature infants do not produce adequate acid; absorption of weak acid is decreased, weak base increased
- Gastric emptying is delayed in premature infants
- Few bioavailability studies done in newborns
- IM absorption variable in newborns
- Percutaneous absorption increased in newborns
- Rectal absorption increased in newborns
- Few bioavailability studies conducted

Drug Distribution
- ECF and TBW per kg highest in the youngest
- Protein binding lowest in youngest
- Fat content lowest in youngest
- Organ systems more sensitive among neonates

Drug Metabolism in Neonates

acetaminophen

CYP Isoforms and Maturation After Birth

Theophylline Dose Requirements

Amlodipine Efficacy in HTN

Maturation of Drug Elimination After Birth

Gentamicin Dosage Regimens

Dosage Requirements (mg/kg/d) in Pediatric Population

Developmental Changes in Drug Clearance

Treatment of Cough and Cold

Acetaminophen for Fever

Ibuprofen for Fever

SSRI Treatment Update

High-Risk Medications
Medication Safety

Dose Calculations: Error Potential

Conclusions

- Significant progress made in diagnosis, prevention and treatment
- Advances and challenges continue
- Interdisciplinary programs important
- Medical home and accountable care organizations emerging

Behavioral

Understand diagnostic criteria and background information associated with Anorexia Nervosa / Bulimia Nervosa / Autism Spectrum Disorder
Identify specific target symptoms in which medication intervention can be utilized
Recommend a medication based on a target symptom
Recommend a treatment plan for a patient with Anorexia Nervosa / Bulimia Nervosa / Autism Spectrum Disorder

Eating Disorders

Anorexia Nervosa DSM-5

Restriction of energy intake, leading to significantly low body weight.
Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
Disturbance in the way one's body weight is experienced, undue influence of body weight or shape on self-evaluation, or lack of recognition of seriousness of current low body weight.

Restricting Type
• Over the last 3 months, the patient has not engaged in binging or purging behavior (self-induced vomiting or misuse of laxatives)
• Weight loss is accomplished through dieting / fasting / excessive exercise
Binge-Eating / Purging Type
• Over the last 3 months, the patient has experienced recurrent episodes of binging or purging

Epidemiology: onset adolescence/young adult, 1-2%, female 0.3-0.7%; highest females 15-19yo; 11:1 female>male; less AA
*Risk Factors:
- Obsessional traits in childhood
- Social pressures related to thinness/appearance
- Certain activities such as ballet, gymnastics, wrestling
- 1st deg relative with AN

Behavioral Interventions – Family Based Treatment (FBT)*
1st line therapy for AN
FBT is superior to individual therapies: Effective, Decreases hospitalizations
Consists of 10-20 family meetings over 6-12 months; Empowers families to take control of weight restoration of child
Weight restoration can help resolve depressive / obsessive compulsive symptoms
FBT may not be possible for everyone, individual therapy can be used

Treatment
2nd line therapy for AN
If medication used, antipsychotics are treatment of choice
Potential benefit for AN symptoms*
Evidence of atypical antipsychotics is limited although may be beneficial for delusional thinking related to body image
May also be beneficial for comorbid conditions (ex: depression augmentation)

Olanzapine (most studied): Shown to reduce anxiety, hyperactivity, and depression while *increasing* BMI
Quetiapine (alt option): improvement in delusionary body image beliefs; risperidone also studied but not used d/t risk of hyperprolactinemia

Antipsychotics in AN, Benefit vs. Risk
Positive: Patients with AN often have near delusionary thoughts about body image → Antipsychotics may improve these thoughts. Also, may cause weight gain.
Negative: Cardiac complications are associated with the starvation state → Antipsychotics can increase risk of QTc prolongation and orthostatic hypotension.

Bulimia Nervosa DSM-5

Recurrent episodes of binge eating
Recurrent inappropriate compensatory behaviors in order to prevent weight gain
The disturbance does not occur exclusively during episodes of anorexia nervosa
Self-evaluation is unduly influenced by body shape and weight
Binge eating and compensatory behaviors occur at least once a week for 3 months

Purging Type
• Regularly engages in self-induced vomiting
• Misuses laxatives, diuretics, or enemas

Nonpurging Type
• Patient does not purge
• Engages in fasting and excessive exercise

Epidemiology: onset 14022yo (may follow period of AN; rarely children), 1-1.5% young females; 10:1 female>male

Risk factors:
- Low self-esteem, depression, or social anxiety disorder
- Childhood Obesity
- Certain activities such as ballet, gymnastics, wrestling
- Childhood trauma (physical or sexual)

Clinical Course

S/s: Body type – normal to slightly overweight; Psychiatric manifestations; Signs of binge eating; Compensatory behaviors; Physical manifestations / complications
Course/severity: Average episode duration: 3 months; Mean duration of illness: 8-12 years; Mortality rate: 1% ; Early identification indicates improved outcomes

Behavioral Interventions – Cognitive Behavioral Therapy (CBT)*
1st line therapy for BN
CBT is most effective behavioral intervention
Focuses on change of thought patterns with eating: Phase 1: resist BN behaviors Phase 2: increase regularity of eating Phase 3: relapse-prevention strategies
Consists of 16-20 sessions over 4-5 months

Treatment – Fluoxetine
1st line therapy for BN
Fluoxetine is most studied
Beneficial for binge eating and purging
High dose necessary for benefit: 60-80 mg / day
First line treatment for depression / anxiety
Can trial other SSRIs if necessary but fluoxetine is gold standard

Medications + Therapy*
Fluoxetine 60 mg / day + psychotherapy x 8 weeks = decrease in binging and purging to zero and almost noneZ

Autism Spectrum Disorder

What is ASD?

Developmental condition that involves challenges in: Social interaction; Speech and nonverbal communication; Restricted/repetitive behaviors

ASD symptom severity varies within each person

ASD DSM-5

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following, currently or by history:
   1. Deficits in social-emotional reciprocity
   2. Deficits in nonverbal communicative behaviors used for social interaction
   3. Deficits in developing, maintaining, and understanding relationships

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history
   1. Stereotyped or repetitive motor movements, use of objects, or speech
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
   3. Highly restricted, fixated interests that are abnormal in intensity or focus
   4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment

C. Symptoms must be present in the early developmental period

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay

CDC Possible Red Flags for ASD

Not responding to his/her name by 12 months of age Not pointing at objects to show interest by 14 months Not playing "pretend" games by 18 months
Avoiding eye contact or preferring to be alone Getting upset by minor changes Flapping their hands, rocking their body or spinning in circles
Having unusual and intense reactions to how things smell, taste, feel and/or look

Epidemiology: 1 in 59 ASD; 4x male>female; highest incidence in whites

Risk factors:
- Shorter and longer time periods between births
- Advanced maternal or paternal Age
- Extremely premature birth
- Family member with autism

Clinical Course

S/s: Impairment in socialization; Delayed or unusual communication; Repetitive stereotyped behaviors; Restricted Interests; Behavior symptoms: Meds target behavior symptoms

Course/severity: Signs usually present by 3yo (6-12mo); most not lead to independent lives; comorbid (seizures, intellectual/language impair, GI disorders)

Behavioral Interventions – Applied Behavior Analysis (ABA)*

1st line for ASD

ABA is the most studied treatment for ASD

ABA focuses on behavior changes and positive reinforcement; Goal is to determine behavior triggers and remove such triggers

Important to also provide family education

Treatment

Medications should target a specific symptom or comorbid condition

Medications do not cure or manage core ASD symptoms

Recommend medications when social and/or daily functional impairment exists*

Irritability: Antipsychotics (risperidone, aripiprazole)
- irritability in ASD = aggression, deliberate self-injurious behavior, temper tantrums, quickly changing moods; Two FDA approved APs

ADHD/Hyperactivity: Stimulants (methylphenidate)
- patients with ASD often struggle with hyperactivity/inattention; Most studied stimulant in ASD; Initiate with low dose IR product and titrate as necessary

Repetitive Behavior: Antidepressants (fluoxetine, clomipramine), Antipsychotics (haloperidol, rispderidone, aripiprazole)
- clomipramine (TCA, more ADEs); haloperidone shows benefit but not often used bc ADEs

Sleep Disturbances: Melatonin
- sleep hygiene education; Melatonin if needed: Reduces sleep latency, Increases length of nighttime sleep, No significant ADE

<u>Summary</u>

Anorexia Nervosa Treatment
   1st line – behavioral interventions
   2nd line – antipsychotics as risk vs. benefit

Bulimia Nervosa Treatment
   1st line – behavioral interventions and fluoxetine
   2nd line – alternative SSRI

Autism Spectrum Disorder Treatment
   Medications will not cure ASD
   Medications should be used to target specific behavioral symptoms

Ophthalmology

Illustrate the pathophysiology for common ophthalmic conditions
Recall ophthalmic agents used in the treatment of glaucoma
Describe the mechanism of action and pharmacologic effects of agents used in ophthalmic disorders
Select therapeutic options based on pathophysiology and patient characteristics, with a focus on glaucoma and age-related macular degeneration
Counsel a patient on key side effects and administration of agents

Glaucoma

"Glaucoma is the build up of fluid in your eyes that puts pressure on the parts of your eye that help you see"

Glaucoma is most accurately defined as an optic neuropathy involving a characteristic atrophy of the optic nerve head, which may or may not be accompanied by elevated intraocular pressure (IOP). In open-angle glaucoma, optic nerve damage results in a progressive loss of retinal ganglion cell axons, which is manifested initially as visual field loss and, ultimately, irreversible blindness if left untreated. Treatment is directed at lowering IOP, regardless of baseline IOP. Open-angle glaucoma is largely asymptomatic.

The goal of therapy is to prevent further deterioration of vision from disease progression, which is accomplished by lowering the intraocular pressure (IOP).
Lowering IOP has been shown to reduce the risk of progression of visual field loss and/or optic disc changes
All patients with open-angle glaucoma (defined by presence of optic neuropathy) should be treated with IOP-lowering therapies, regardless of their IOP at time of dx.
↑aqueous outflow (prostaglandins, alpha adrenergic agonists, cholinergic agonists, rho kinase inhibitor)
↓aqueous production (alpha adrenergic agonists, beta blockers, carbonic anhydrase inhibitors)

Epid: 2.8M cases, 1.91% pop, 8% >80yo, 2nd leading cause of blindness; AA
Presentation: often asymptomatic; mild-mod rarely any disturbances in vision; severe: vision field changes begin to occur
Risk factors: age >50yo, race (AA), FH, DM
Pathophys: disease caused by increase in intraocular pressure (IOP) from excess aqueous humor IOP >24mmHg considered intraocular hypertension, needs tx
↑aqueous humor = ↑IOP = leads to blindness via apoptosis of retinal ganglion cells, increased pressure of optic nerve, decreased signaling to thalamus

Open-angle: Increased resistance of trabecular meshwork > decreased drainage > increased IOP - more common in Caucasian/AA
primary: generally bilateral (70% of open-angle cases)
secondary: something else blocking outflow (pigmentary dispersion syndrome, pseudoexfoliation syndrome)
Closed-angle: Blockage of trabecular meshwork > decreased drainage > increased IOP - more common in Asian
acute: rapid increase in IOP resulting in loss of vision; can be caused by trauma
chronic: gradual blockage and increase in IOP; more susceptible to sudden blockage resulting in acute closed-angle event

Treatment goals
decrease IOP; decrease aqueous humor production; increase aqueous humor clearance

Open-angle
1st: prostaglandin analog
2nd: alternative prostaglandin analog
3rd: add drug with different pharmacologic effect, based on patient comorbidities, desired IOP lowering, etc.
4th: surgical options (laser trabeculopathy)

Closed-angle, Acute
First-line: carbonic anhydrase inhibitors +/- topical beta-blocker +/- topical alpha-2 agonist
Adjunctive: hyperosmotic agent (glycerin, mannitol)
Surgery: laser peripheral iridotomy

Closed-angle, Chronic
First-line: topical prostaglandin analog +/- topical beta-blocker +/- topical alpha-2 agonist
Adjunctive: topical carbonic anhydrase inhibitors
Surgical options as well

Ophthalmic Medication Review

Prostaglandin Analogs

MoA: Mimic endogenous prostaglandins; Improve uveoscleral pathway via stimulation of collagenases and matrix metalloproteinases
Effect: Increased uveoscleral outflow of aqueous humor; increased removal of aqueous humor and decreased IOP
ADEs: Better tolerated than other classes; Altered iris pigmentation (irreversible) Hypertrichosis (reversible) Hyperpigmentation of lids/lashes (reversible)
Caution: Risk of uveitis in patients with ocular inflammatory conditions

latanoprost	1 gtt qhs	prostanoid agonist	store fridge prior to use; can be at room temp while using; available in combinations
bimatoprost	1 gtt qhs	prostamide agonist	slightly more effective at lowering IOP

Beta-adrenergic blockers

MoA: Block β-adrenergic receptors in ciliary body
Effect: Decreased production of aqueous humor by ciliary body
ADEs: Local: dry eyes, blepharitis, blurred vision (temporary) Systemic: decreased heart rate, reduced blood pressure, negative inotropic effects, bronchospasm
Caution: Use with caution in patients with asthma, sinus bradycardia, congestive heart failure, diabetes, and/or myasthenia gravis

timolol	1 gtt bid (aq)	nonselective	gel formulation 1 gtt qday, potential for lower risk of systemic absorption
levobunolol	1 gtt bid	nonselective	potentially best for IOP lowering post-cataract surgery
metipranolol	1 gtt bid	nonselective	increased stinging compared to others
carteolol	1 gtt bid	nonselective	has intrinsic sympathomimetic activity
betaxolol	1 gtt bid	*selective* β1	less systemic effects; increased stinging

Alpha-2 adrenergic agonists

MoA: Enhance α-2 adrenergic receptors in ciliary body
Effect: Decreased production of aqueous humor by ciliary body
ADEs:
Apraclonidine may cause an allergic-type reaction in roughly 30% of patients: Lip edema, eye discomfort, foreign-object sensation, itching, hyperemia
Brimonidine may cause systemic effects: Dizziness, fatigue, somnolence, dry mouth
Caution: Use is cautioned in patients with cardiovascular disease, cerebrovascular disease, renal insufficiency, and/or diabetes
Brimonidine contraindicated in infants (hypotensive reactions, apneic spells)

apraclonidine	1 gtt bid-tid	used as adjunct; considered second-line
brimonidine	1 gtt bid-tid	used as adjunct; considered-first-line; may also increase uveoscleral outflow

Carbonic Anhydrase Inhibitors

MoA: Inhibit secretion of sodium and bicarbonate ions from ciliary body to the aqueous humor
Effect: Decreased production of aqueous humor by ciliary body
ADEs: Typically well tolerated, especially compared to systemic carbonic anhydrase inhibitors; Side effects are mild and transient: blurry vision, stinging
Caution: Both agents contain sulfonamide moiety and use is cautioned in patients with sulfa allergies

dorzolamide	1 gtt bid-tid	available as solution
brinzolamide	1 gtt bid-tid	available as suspension; more blurry vision with less stinging

Cholinergic Agonists

MoA: Enhance parasympathetic activity in ciliary body
Effect: Increased outflow of aqueous humor via trabecular network
ADEs: mostly with pilocarpine: Miosis, Frontal headache, Brow ache, Periorbital pain, Eyelid twitching

pilocarpine	1 gtt bid-tid (aq)	1 gtt qhs (gel); parasympathomimetic agent of choice; darker pigmented eyes require higher doses
carbachol	1 gtt bid-tid	longer duration of action; weak inhibitor of cholinesterase

Comparison Chart

Agent	Reduction in IOP
Prostaglandin Analogs	25-35%
Beta-adrenergic blockers	20-30%
Alpha-2 adrenergic agonists	18-27%
Carbonic Anhydrase Inhibitors	15-26%
Cholinergic Agonists (pilocarpine)	20-30%

Administration: Solution/Suspension, Ointment
1) Tilt head back, have children lie down.
2) Gently grasp lower outer eyelid below lashes. Pull away from eye to create a pouch.
3) Place dropper over eye.
   Place ointment tube over eye.
4) Look up before applying.
   Place ¼ to ½ inch strip of ointment inside lower eyelid using sweeping motion. Avoid touching tip to tissue surface.
5) Release lid and gently close eye. Minimize blinking or squeezing of eyelid.

Patient counseling
Proper drug instillation is critical: Do not touch dropper to eye (no longer sterile)
Recommended to remove contact lenses: Especially before use of ketotifen or BAK containing products
When using multiple ophthalmic agents: Separate dose administration by at least 5 minutes (or longer if indicated for specific product)
Evaluating outcomes
  Acute disorder – symptom improvement within 72 hours
  Chronic disorder – worsening symptoms despite proper medication
Discard or replace eye drop bottles after 30 days of breaking seal
Check solution for color change or cloudy appearance: Some suspensions may be cloudy, solutions should not be

Age-Related Macular Degeneration

Epid: leading cause of blindness in US for those >65yo
Presentation: gradual vision loss starting with central vision ("halo" in vision)
Types:
  nonexudative ("dry"); dry is 90% of cases; gradual, progressive vision loss > often starts with near vision issues
  exudative ("wet"); majority of high severity cases; can be rapid or gradual vision loss
Risk factors: age >65yo, female, White, genetic predisposition, smoking
Pathophys
  dry: Breakdown of the retinal pigment epithelium (RPE) > drusen deposits in macula; Ultimate loss of function of the overlying photoreceptors; No cure or reversibility
  wet: Neovascularization in the choroid resulting in serous/hemorrhagic leakage; Eventual elevation of the RPE or neurosensory retina leading to drusen deposits
    Potential cessation with VEGF inhibitors (bevacizumab, ranbizumab, aflibercept)
Management
  AREDS: Age-Related Eye Disease Study
    Sponsored by the National Eye Institute
    Supplemented with high doses of oral vitamin C, vitamin E, beta-carotene, zinc, and copper
    Found that there was delay in progression for patients with mild-moderate macular degeneration
  AREDS 2
    Specifically looking at smokers
    Removed beta-carotene (association with increased risk of lung cancer)
    Added lutein, zeaxanthin, and omega-3 fatty acids
    Demonstrated similar delay in progression
AREDS recommended by AOA if mild-moderate AMD in one or both eyes OR advanced AMD in only one eye

Bacterial Conjunctivitis

Presentation: Unilateral discharge, irritation, and/or hyperemia; Mucopurulent/purulent discharge; Tearing, lid crusting
Risk factors: immunocomp, poor hygiene, children
Pathophys
  Can be from sexually transmitted disease (Neisseria gonorrhoeae)
  Maternal transmission to neonate (gonococcal and/or chlamydial)
  Most common pathogens: Staphylococcus spp (primarily S aureus), Haemophilus spp, Streptococcus pneumonia, Moraxella spp
Generally self-limiting
Antimicrobial options:
  solutions/suspensions: gentamicin, polymyxin B/neomycin (minimal vision impact)
  ointments: bacitracin, erythromycin (blurry vision after admin, less frequent dosing than solution)

Drug-Induced Dry Eye

General rule: if it causes drying of something in the body, it can cause drying of the eyes
Well-recognized effect: anticholinergics, histamine receptor antagonists, TCAs, diuretics, beta-blockers
Probable effect: Postmenopausal hormonal replacement therapy, antipsychotics, benzodiazepines, SSRI/SNRIs, levodopa
Common causative agents: antidepressants (SSRI SNRI TCA), antipsychotics (quetiapine), antihypertensives (diuretics, beta-blockers), histamine antag (DPH, lorat, ranit), oral contraceptives, decongestants (pseudo, phenylephrine)

Things to Focus On

Pathophysiology of each disease state covered
Pharmacologic effect, MOA, common side effects, and contraindications of each medication
Counseling tips for administration and side effects

Dermatology

Recall medical terminology associated with dermatological conditions
Recognize features of common dermatological conditions
Apply guidelines to common dermatological conditions
Construct treatment plans for common dermatological conditions
Topics: Dermatitis, Pediculosis and scabies, Acne vulgaris, Acne rosacea, Psoriasis, Atopic dermatitis, Hyperhidrosis
Not covered: drug-induced skin reactions, melanoma, skin infections, otc dermatology

Intro

Skin Anatomy
macules: flat lesions, diff color; papules: more superficial; nodules: palpable, deeper than papule; vesicles: blisters; plaque: raised patch, local damage; wheals: seen w allergic rxns

Description: color, thickness, location, distribution
A slightly lichenified, erythematous patch and excoriations are present in the antecubital fold.
antecubital (armfold), erythematous (red), lichenified (thickened/leathery resulting from rubbing/scratching), excoriations (skin picking)

Dermatitis

Contact Dermatitis: any irritating exposure
Treatment: remove offending agent (nail polish, tape, etc)
- topical corticosteroid; potency duration?

Poison Ivy: urushiol (plant oil)
- mild-moderate case: topical corticosteroids
- severe/widespread (eyes, face): systemic corticosteroids 2-3 weeks of treatment
  - short systemic corticosteroid leads to rebound; typically prednisone 2-3 wk and taper
  - oral AHs not helps with itching (histamine not causing itching), only sedation; do not give topical AH/lidocaine

Diaper Dermatitis
- irritant vs. candida
- treatment: topical barriers oint (white petroleum, zinc oxide), topical antifungals before barrier; no topical CS)
- prevention key; diaper free time

Aquaphor/Maalox is an has NOT been show in clinical trials to decrease the duration of diaper rash.
Aquaphor can take up 50% of its weight in water.

Summary: Dermatitis
- History of present illness
- Cornerstones of therapy:
  – Topical corticosteroids
  – Barriers
  – Prevention
- Patient education

Pediculosis and Scabies

Pediculosis aka: head/pubic lice
First-line: – Permethrin 1% lotion (re-treatment?)
Other options: Ivermectin 0.5% lotion (Sklice®), Malathion 0.5% lotion (Ovide®), Spinosad 0.9% topical suspension (Natroba®), Benzoyl alcohol 5% lotion (Ulesfia®)
Non-pharmacologic: washing bed, clothes, ettc
What's covered: http://www.partnersforkids.org/resources

Scabies
Presentation
Transmission: 20min contact time
First-line: – Permethrin 5% cream – Patient counseling
Non-pharmacologic

Summary: Pediculosis/Scabies
- OTC vs RX treatment options
- Treatment resistance
- Non-pharmacologic treatment
- Patient counseling!

Acne vulgaris

Guidelines
Epid/Etiology: 60-80% of americans
Four factors promote acne development
1. Hyperkeratinization of sebaceous follicles (overprod skin in oil glands causes obstruction of pore, black head)
2. Increased sebum production (promotes early lesion)
3. Propionibacterium acnes (P. acnes) proliferation (bacterial component)
4. Inflammation

Causes: Hormone abnormalities/fluctuations, Physical occlusion/damage, Medications (OCS, pheny, estrogens, oral contraceptives)
Clinical presentation:
– Open (blackhead) and/or closed (whitehead)
– Neonatal acne, infantile acne (no treatment, let it go away)
- Comprehensive assessment, Consider pyscho-social impact
Classification
Mild acne: few to several papules/pustules (<10) and no nodules
Mod acne: several to many papules/pustules (10-40) along with comedomes (10-40) and few to several nodules
Several acne: numerous or extensive papules/pustule and many nodules

Treatment Overview
- classification and severity guides treatment
- give patients realistic expectations, provide comprehensive treatment plan
- options: topical (antimicrobials, retinoids), oral (antimicrobials, retinoids, hormonal)
- antibacterial effects: 1. Benzoyl peroxide (BPO) 2. Topical antibiotics (AB) 3. Oral antibiotics 4. Isotretinoin
- inflammation: 1. Intralesional corticosteroids 2. Oral corticosteroids 3. NSAIDs 4. Antibiotics
- normalize pattern of follicular keratinization: 1. Tretinoin 2. Isotretinoin
- inhibit sebaceous gland function: 1. Oral contraceptives 2. Oral corticosteroids (low dose) 3. Isotretinoin 4. Spironolactone

***Mild**: topical retinoid or BPO, or topical retinoid + BPO if closer to moderate (1-2 agents)
***Moderate**: same but add oral antibiotic (might add 3rd agent)
***Severe**: oral isotretinoin

	Mild		**Moderate**		**Severe**
	Comedonal	**Papular/Pustular**	**Papular/Pustular**	**Nodular**	**Nodular**
First-line therapy	Topical retinoid or BPO	Topical retinoid + BPO or BPO/AB	Topical retinoid + BPO + oral antibiotic or BPO/AB	Topical retinoid +/- BPO + oral antibiotic or BPO/AB	Oral isotretinoin
Alternatives	BPO or AB			Oral isotretinoin	Oral antibiotic + topical retinoid + BPO or BPO/AB
Alternatives for female			Hormonal therapy + topical retinoid +/- BPO or BPO/AB	Hormonal therapy + topical retinoid +/- BPO or BPO/AB	Hormonal therapy + oral antibiotic + topical retinoid +/- BPO or BPO/AB
Maintenance therapy	Topical retinoid +/- BPO or BPO/AB		Topical retinoid +/- BPO or BPO/AB		Topical retinoid +/- BPO or BPO/AB

<u>Topical Retinoids</u>
adapalene (Differin, OTC), tazarotene (Tazorac, pregX), tretinoin (Retin-A)
- similar efficacy, limited comparisons
MoA: - Normalizes follicular hyperkeratosis, - Prevents formation of blackheads/whiteheads
Use in both inflammatory and non-inflammatory acne; First-line treatment for mild to moderate acne
Apply a thin layer to affected area once daily at bedtime
Onset of action*
- Weeks 1-4: redness, burning, peeling
- Weeks 3-6: acne may get worse or better
- Weeks >6: most improve by ninth to twelfth week

Adverse effects – Photosensitivity – Irritation, dryness, flaking of the skin

<u>azelaic acid (Azelex)</u>
Antikeratinizing, antibacterial, and antiinflammatory properties
Can be used for noninflammatory and inflammatory acne
Apply twice daily
Well tolerated, but place in therapy? failed topical retinoid (doesn't cause as much irritation/photosens)
– Comparable efficacy to tretinoin cream, benzoyl peroxide gel, and topical erythromycin

<u>benzoyl peroxide (BPO)</u>
Primary effect is antibacterial
Apply a thin layer to the entire affected area
Adverse effects – Drying, peeling, and cracking of skin
Recommend a gradual increase in frequency of use or strength of preparation
May discolor some fabrics (sheets, towels)
FDA Warning: severe adverse reactions (allergyic rxn sx)

<u>Topical Antimicrobials</u>
Reduce P. acnes present on skin
Effective in mild to moderate acne

Initial or adjunctive therapy
- Monotherapy (?), not really d/t resistance
- Combined with retinoids or benzoyl peroxide → better efficacy and less resistance

Available products: Many are alcohol-based

Topical Combination Products

Topical antibiotic + benzoyl peroxide – Benzamycin® (Erythromycin/benzoyl peroxide) – BenzaClin® (Clindamycin/benzoyl peroxide)
Topical antibiotic + topical retinoid – Ziana® (Clindamycin/tretinoin)
Topical retinoid + benzoyl peroxide – Epiduo® (Adapalene/benzoyl peroxide)

Oral Antibiotics

Primary effect is to decrease follicular populations of P. acnes
P. acnes resistance is increasing
Consider a higher dose to control acne – Use lower dose for maintenance?
Minocycline = ~~Tetracycline~~ = Doxycycline (Erythromycin? no really d/t GI SE)
Sulfamethoxazole/trimethoprim
Avoid monotherapy; use topical with it to prevent resistance

Oral Contraceptives

Recall previously learned knowledge
Useful in moderate to severe acne
Patient's most likely to respond:
- Increased facial oiliness
- Premenstrual acne flare-ups
- Inflammatory acne on mandibular line and neck

What type of oral contraceptive should you consider? Low E, anti-A activity; Four products used for acne

Oral Retinoids (isotretinoin)

Reserved for severe, nodular and inflammatory acne
Accutane, Amnesteem, Claravis, Sotret, Absorica
Dosage: 0.5 mg/kg/day, up to 1 mg/kg/day; better with high fat meal
Treat for up to 16-20 weeks, or longer?
Teratogenic, iPledge program
MoA: Effective, targets multiple acne causes
– Decreased sebum excretion
– Decreases follicular keratinization
– Reduces ductual and surface P. acnes

Monitoring: CBC, Fasting lipid panel, Liver function tests
Side effects: Cheilitis (dry skin corner mouth, use vaseline), Dry skin
SE reported, but NOT causal: Irritable bowel disease, Osteoporosis, Psychiatric effects

Postinflammatory hyperpigmentation

Acne Hygiene Tips

Wash face twice daily with mild cleanser and warm water
Patients should avoid rubbing the skin
Recommend water-based lotions, cosmetics, and hair products

Other Agents

Spironolactone (oral, topical), Salicylic acid (topical)
Clascoterone cream 1% (Winlevi, new); apply twice daily; SE: redness/dryness, itching; MoA (anti-androgenic): Decreases sebum production, Decreases inflammation

Summary: Acne vulgaris

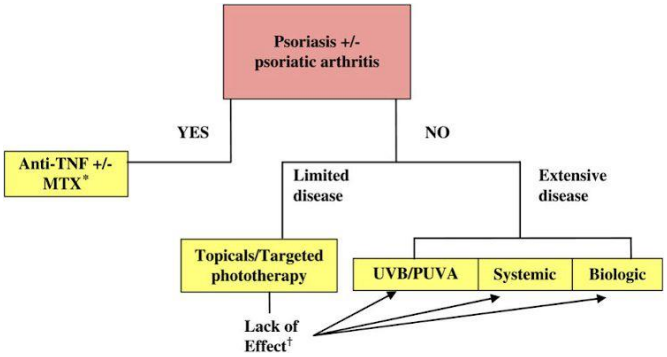
- Non-pharmacologic interventions
- Over-the-counter products
- Treatment
  – Severity guides treatment
  – Many options both topical and oral
- Patient education

Acne rosacea

Inflammatory disorder, Women (>30 years)
Treatment (Topical): Metronidazole*, Sodium sulfacetamide, Oxymetazoline
Treatment (Oral): Tetracyclines (severe)
Laser therapy can help
Topical corticosteroids should not be used

Psoriasis

Immune-mediated, multisystem, inflammatory, chronic disorder
Co-morbidities: Autoimmune disease, CVD, Psychiatric conditions
Most common classification: plaque psoriasis (Others: pustular, erythrodermic)
Associated factors: Genetic, Skin trauma, Smoking,
Medication induced (?): NSAIDs, Antimalarials, Propranolol, Lithium, Salicylates
Clinical presentation (plaque psoriasis): *Well-defined, sharply demarcated, erythematous plaques*
Treatment overview
  Topical treatment: Topical corticosteroids, Vitamin D analogs
  Systemic treatment: Methotrexate, Cyclosporine
  Others: UVB and PUVA, Biologic agents



Topical Treatment
Monotherapy (mild, less extensive disease)
Adjunctive therapy (extensive disease)
Options
  – Topical corticosteroids
  – Vitamin D analogs
  – Others
Adherence

Topical Corticosteroids
Cornerstone of therapy
Potency selection
Vehicle selection
Side effects
Duration of application?
Potency determined by vasoconstrictiveproperties
  – Vehicle
  – Strength
  – Salt form
Know where to find a table (Lexicomp, Pharmacist's Letter, UpToDate, etc)
Long-term topical corticosteroid use
  - Atrophy
  - Hypertichosis
  - Hypopigmentation
  - Topical steroid dependence

Vitamin D Analogues
Calcipotriene (Dovonex), twice daily
Vit D receptor binding → Inhibit keratinocyte proliferation
Often used in combination with topical corticosteroid, phototherapy
Side effects

Other Agents
Tazarotene (alone or in combination with TC) – 40-50% efficacy
Tacrolimus or pimecrolimus – Plaque psoriasis on the face
Salicylic acid (use after phototherapy), Anthralin, Coal tar

Methotrexate (MTX): For severe or disabling psoriasis; less efficacious than cyclosporine; Better tolerated? Folic acid?

Cyclosporine: Severe psoriasis; more efficacious than MTX Greater adverse effects? Place in therapy – Unable to tolerate other systemic or biologic agents

UVB and PUVA: Phototherapy: Benefits vs. Risks; Place in therapy

Psoriasis & Biologics
Tumor necrosis factor (TNF) inhibitors: Adalimumab (Humira) pediatric psoriasis?, Etanercept (Enbrel) pediatric psoriasis?, Infliximab (Remicade), Certolizumab (Cimzia)
Anti-IL-12/IL-23 antibodies: Ustekinumab (Stelara) pediatric psoriasis?
Anti-IL-17 receptor antibodies: Brodalumab (Siliq)
Anti-IL-17 antibodies: Secukinumab (Cosentyx), Ixekizumab (Taltz)
Anti-IL-23/IL-39: Guselkumab (Tremfya), Tildrakizumab (Ilumya)

Summary: Psoriasis
• Genetic, immune-mediated, systemic, inflammatory, chronic disorder
• Severity guides treatment
  – Many treatment options
  – Topical vs systemic vs biologic
• Patient education

Atopic dermatitis (Eczema)

Guidelines; prevalent in pediatric (20%)
Genetic factors (associated with parental atopy); Immunologic factors (early IgE prod)
Environmental factors (aeroallergens-pets,mites,pollen,molds; food allergens-cowsmilk/hens-eggs; topical irritants-soaps,detergents,nickel)
Clinical pattern: 3 stages based on age-group:
Infantile stage: Lesions on extensor surfaces and checks/scalp: - Pruritic - Red - Scaly
Childhood stage 2yo-puberty (less exudative): Lesions found on: - Hands, wrists - Feet, ankles - Antecubital regions - Popliteal regions
Adult stage: Lesions appear dry, scaly erythematous papules and plaques, often occur on: - Face, neck, arms back, hands, feet - Flexural folds
Presentation varies in severity, involves chronic relapse and remission
Affects quality of life: Nighttime itching, Social stigma
Atopy triad: atopic dermatitis, allergic rhinitis, asthma

Treatment Overview
Goal: improve symptoms and limit exposure to medications
Three parts of treatment: 1. Eliminate exacerbating factors, 2. Hydrate skin, 3. Treat inflammation and acute flare-ups
Prevent future exacerbations

1. Elimination of Exacerbating Factors
Avoid triggers (Heat, perspiration; Fragrances, detergents)
Treat skin infections, Bath time, Limit exposure to excessive sunlight

2. Hydrate Skin
Creams and ointments are preferred: – White petroleum, Eucerin, Cetaphil, Aquaphor
Avoid lotions, Avoid products that contain lanolin or fragrances
Apply 2-3x/day; Best applied after bathing or showering

3. Treatment of Inflammation
First-line: topical corticosteroids
- Mild to moderate atopic dermatitis: Low potency cream or ointment (hydrocortisone 1% or 2.5%)
- Severe atopic dermatitis: Medium potency ointment (fluocinolone 0.025% or triamcinolone 0.1%)

Vehicle is important
Apply to affected area(s) twice daily
Cautions for topical corticosteroids: Avoid potent corticosteroids on face/skin folds; Moisturizers should be applied after topical CS application
Acute flares:
Use a higher potency topical CS: up to 10 days; avoid oral CS
Step down to lower potency; provide education on proper use of higher potency topical CS

Second-line: topical calcineurin inhibitors (MoA: Suppress cellular immunity via inhibiting T-cell activation)
- Use in children >2 years - Do not cause atrophy - Useful for face, neck, and skin folds
Available topical calcineurin inhibitors: Tacrolimus (Protopic) 0.03% & 0.1% ointment, Pimecrolimus (Elidel) 0.1% cream
Apply to affected area(s) BID
Long term use?
Common side effects: Burning, pruritus, erythema
Black Box Warning: Increased risk of lymphoma and skin cancers
Avoid the following: - Topical calcineurin inhibitors in patients <2 or immunocompromised patients - Prolonged (>1 year) use - tacrolimus 0.1% use in children

Second-line: phosphodiesterase-4 inhibitor (MoA: reduces inflammation); crisaborole (Eucrisa)
Place in therapy: Second line option after topical corticosteroids
Side effects
Apply twice daily to affected area(s)

Other therapies: proactive use of topical therapies, food elimination/avoidance diets, probiotics, complementary therapies
Prevention: Hydration is important in prevention: Wet dressings; Avoid triggers, Use emollients during both flares and remission; Emollients must be reapplied q6h

Summary: Atopic Dermatitis
- Hydration, hydration, hydration
- Treatment
  – First-line: topical corticosteroids
  – Second-line: topical calcineurin inhibitors, phosphodiesterase-4 inhibitor
- Patient education

Hyperhidrosis

Sweat secretion greater than need for thermoregulation
Prevalence estimated at 1-5% of population
Treatment
– Prescription antiperspirant (e.g. Drysol 20%)
– Topical anticholinergic (e.g. Qbrexza 2.4%)
Other therapies

Ceutics

Obtain an understanding of how pharmaceutics concepts are used to facilitate optimal development and use of drugs and drug formulations in children.
Understand how variation in absorption and disposition of drugs can affect the therapeutic and/or toxic properties of drugs in children.
Discuss the main causes of inter-individual pharmacokinetic variation of drugs in children as a function of route of administration.

Absorption: the movement of a substance from the site of administration to the site of measurement
Distribution: the reversible movement of a substance to and from the site of measurement
Metabolism: conversion of a substance to another species (and vice versa)
Excretion: irreversible loss of a substance from the body
Elimination: Metabolism + Excretion

Sources of variability in drug plasma concentrations (PK variability) in children: Morphometric: Body size, Demographic: Age

Pediatric pharmacology - What's unique?
Continuous development from embryo to adolescent: "Perpetual pharmacologic moving target"; PD and PK change with time
The most profound differences occur in the first weeks through first year of life.
Descriptive pharmacology (especially for new drugs) in pediatric patients is often lacking

The "Moving Target" - Developmental Changes
- Body composition
- Organ function
- Drug metabolizing enzymes / transporters: Unique metabolic and transport pathways
- Renal function
- Receptor response
- Unique disorders
- Immune systems are different from adults', and immune responses can be different at different ages
- Extremely small margin of error for the most fragile patients: Errors can be devastating, Individual variance unpredictable

* The BSA method of calculating drug doses is widely used for two types of patient groups:
- cancer patients receiving chemotherapy: to decrease inter-individual PK variability for narrow therapeutic index drugs
- pediatric patients, with exception of neonates, usually dosed on a weight basis (per kg); multiple developmental changes in children that can affect drug ADME

- Pharmacokinetic properties of most drugs are different in children and infants compared with adults.
- Appropriate drug therapy cannot be assumed to be identical to that in adults, even when adjusted for weight or body surface area.
- Each agent is unique and requires adequate clinical studies before a drug can safely be used in children.

Appendix

Agents that reduce intraocular pressure

Class	Examples	Side effects
Agents that suppress aqueous inflow		
Beta adrenergic blockers	Betaxolol, carteolol, levobunolol, metipranolol, timolol	Ocular irritation and dry eyes. Contraindicated in patients with bradycardia, heart block, heart failure, asthma, or obstructive airway disease.
Alpha-2 adrenergic agonists	Apraclonidine, brimonidine	Red eye and ocular irritation. CNS effects and respiratory arrest in young children (brimonidine). Caution in patients with cerebral or coronary insufficiency, Raynaud phenomenon, postural hypotension, hepatic or renal impairment.
Carbonic anhydrase inhibitors	Dorzolamide and brinzolamide (topical), acetazolamide and methazolamide (oral)	Oral form can cause transient myopia, nausea, diarrhea, loss of appetite and taste, parasthesiae, lassitude, renal stones, and hematological problems. Topical forms much less likely to cause systemic side effects but can cause local irritation and redness.
Agents that increase aqueous outflow		
Prostaglandins	Bimatoprost, latanoprost, tafluprost, travoprost	Brown discoloration of iris, lengthening and darkening of eyelashes, ocular irritation and redness, macular edema or iritis in susceptible individuals
Alpha adrenergic agonists	Apraclonidine, brimonidine	Red eye and ocular irritation. CNS effects and respiratory arrest in young children (brimonidine). Caution in patients with cerebral or coronary insufficiency, Raynaud phenomenon, postural hypotension, hepatic or renal impairment.
Cholinergic agonists	Pilocarpine, carbachol	Ciliary spasm leading to headaches especially in younger patients, myopia, dim vision (small pupil). Cataracts and iris-lens adhesions in long term.
Rho kinase inhibitors	Netarsudil	Red eye and ocular irritation.

Goodman Gilman Drugs

Drug	Therapeutic Use	Clinical Pharmacology and Tips
Section I: Alkylating Agents and Platinum Coordination Complexes		
Mechanism of action: covalent modification of DNA. Adverse effects of all alkylating drugs: myelosuppression and immunosuppression; toxicity to dividing mucosal cells and hair follicles (e.g., oral mucosal ulceration, intestinal denudation, alopecia); delayed pulmonary fibrosis; reproductive system toxicity (premature menopause, sterility); and leukemogenesis (up to 5%, highest for melphalan, procarbazine, nitrosoureas).		
Nitrogen Mustards: DNA alkylation		
Mechlorethamine	• Hodgkin lymphoma • Topical: cutaneous T-cell lymphoma	• Vascular damage during injection due to vesicant properties
Cyclophosphamide	• Acute and chronic lymphocytic leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; neuroblastoma; breast, ovary, Wilms tumor; soft-tissue sarcoma • Autoimmune disease (Wegener granulomatosis, rheumatoid arthritis, nephrotic syndrome)	• Oral or intravenous administration • Active alkylating moieties generated through hepatic metabolism • Nephrotoxic and urotoxic metabolite, acrolein; severe hemorrhagic cystitis in high-dose regimens; prevented by MESNA • Provide vigorous hydration during high-dose treatment • Elimination not affected by renal dysfunction; reduce dose in patients with hepatic dysfunction
Ifosfamide	• Germ cell testicular cancer • Pediatric and adult sarcoma • High-dose chemotherapy with bone marrow rescue	• See cyclophosphamide • Can cause neurotoxicity (including seizures) • Methylene blue treatment of CNS toxicity possibly useful
Melphalan	• Multiple myeloma	• Oral and intravenous administration
Chlorambucil	• Chronic lymphocytic leukemia	• Oral administration
Bendamustine	• Non-Hodgkin lymphoma • Chronic lymphocytic leukemia	• Lacks cross-resistance with other classical alkylators
Alkyl Sulfonate: DNA alkylation		
Busulfan	• Chronic myelogenous leukemia • High-dose chemotherapy regimen with bone marrow transplantation	• Oral administration • Adverse effects: prolonged (up to years) pancytopenia; suppression of stem cells; seizures; ↑ clearance of phenytoin; hepatic VOD
Nitrosoureas: DNA alkylation		
Carmustine (BCNU)	• Malignant gliomas • Hodgkin lymphoma; non-Hodgkin lymphoma	• Vascular damage during injection due to vesicant properties • Profound and delayed myelosuppression
Streptozocin (streptozotocin)	• Malignant pancreatic insulinoma • Carcinoid	• Frequent renal toxicity, sometimes renal failure
Methylhydrazine Derivatives: Monofunctional DNA alkylation		

Procarbazine (*N*-methylhydrazine, MIH)	• Hodgkin lymphoma • Gliomas	• Greater capacity for mutagenesis and carcinogenesis than bifunctional alkylators (e.g., cyclophosphamide)
Triazenes: Methyl transfer to DNA		
Dacarbazine (DTIC)	• Hodgkin lymphoma; soft-tissue sarcomas • Melanoma	• Intravenous administration • Activation by hepatic CYPs • Adverse effects: nausa, vomiting • Rare hepatotoxicity and neurotoxicity
Temozolomide	• Malignant gliomas	• Oral administration • Combined with radiation therapy • Greater capacity for mutagenesis and carcinogenesis than bifunctional alkylators; more active in MGMT-deficient tumors
Platinum Coordination Complexes: Form covalent metal adducts with DNA		
Cisplatin	• Testicular, ovarian, bladder, esophageal, gastric, lung, head and neck, anal, and, breast cancer	• Intravenous administration • Adverse effects: • Nephrotoxicity (reduce by forced pretreatment hydration, diuresis, and use of *amifostine*) • Ototoxicity (tinnitus, high-frequency hearing loss) • Nausea and vomiting (antidote, *aprepitant*) • Peripheral sensory and motor neuropathy (may worsen after discontinuation; may be aggravated by taxane treatment) • Drug resistance due to loss of mismatch repair proteins
Carboplatin	• Same as above	• Less nausea, neuro-, oto-, and nephrotoxicity than cisplatin • Dose-limiting toxicity: myelosuppression • May cause hypersensitivity reaction
Oxaliplatin	• Colorectal, gastric, and pancreatic cancer	• Peripheral neuropathy is dose limiting • Some nausea • Efficacy not dependent on intact mismatch repair
Section II: Antimetabolites		
Folic Acid Analogues: Inhibit dihydrofolate reductase		
Methotrexate (amethopterin)	• Acute lymphocytic leukemia; choriocarcinoma; breast, head and neck, ovary, bladder and lung cancers; osteogenic sarcoma • Noncancer use: psoriasis, rheumatoid arthritis	• Oral, intravenous, or intramuscular administration • Adverse effects: myelosuppression, GI toxicity • Leucovorin can reverse toxic effects; used as "rescue" in high-dose therapy • *Glucarpidase*, a methotrexate-cleaving enzyme, is approved to treat toxicity • ↓ Dose in renal insufficiency
Pemetrexed	• Mesothelioma, lung cancer	• Similar effects and side effects as methotrexate • Attenuate toxicity with folate and Vit B12 supplementation
Pyrimidine Analogues		
5-Fluorouracil (5FU) *Thymidylate synthase inhibitor*	• Breast, colon, esophageal, stomach, anal cancer • In FOLFOX or FOLFIRINOX combination to treat pancreatic or colorectal cancer • Combined with cisplatin in head and neck cancer • Premalignant skin lesion (topical)	• Intravenous administration • Nausea, mucositis, diarrhea, myelosuppression, hand-foot syndrome • Combined with leucovorin to enhance efficacy • Enhanced toxicity with DPD deficiency; may rescue with uridine
Capecitabine *Thymidylate synthase inhibitor*	• Metastatic breast, colorectal cancer	• Orally administered prodrug of 5FU • Similar adverse effects as 5FU; hand and foot syndrome more frequent than with 5FU
Cytarabine (cytosine arabinoside) *Interferes with base pairing in DNA; inhibits DNA polymerase*	• Acute myelogenous and acute lymphocytic leukemia; non-Hodgkin lymphoma	• Intravenous administration • Myelosuppressive; can cause acute, severe leukopenia, thrombocytopenia, anemia • GI disturbances • Noncardiogenic pulmonary edema

		• Dermatitis
Gemcitabine (difluoro analogue of deoxycytidine) *Inhibits DNA polymerase; causes strand termination*	• Pancreatic, ovarian, lung, bladder cancer	• Intravenous administration • Female and elderly patients clear the drug more slowly • Myelosuppression, hepatic toxicity • Rare posterior leukoencephalopathy syndrome; sometimes interstitial pneumonitis • Radiosensitizer; should be used with caution in radiotherapy
5-Azacytidine *Inhibits DNA cytosine methyltransferase*	• Myelodysplasia	• Subcutaneous or intravenous administration • Myelosuppression and mild GI symptoms • After intravenous administration severe nausea possible
Purine Analogues and Related Inhibitors		
6-Mercaptopurine *Inhibits purine nucleotide synthesis and metabolism*	• Acute lymphocytic and myelogenous leukemia; small cell non-Hodgkin lymphoma • Noncancer: Crohn disease, ulcerative colitis	• Oral absorption incomplete, thus intravenous administration • Reduce oral dose by 75% in patients receiving allopurinol; no adjustment needed for intravenous administration • Myelosuppression; anorexia, nausea, vomiting; GI side effects less frequent in children than adults • Secondary malignancy: SCC of the skin, AML
Fludarabine *A chain terminator when incorporated into DNA; inhibits RNA function and processing*	• Chronic lymphocytic leukemia • Follicular B-cell lymphoma • Allogeneic bone marrow transplant	• Oral or intravenous administration • Frequently myelosuppression • Less frequent: nausea, vomiting; altered mental status; seizures • Secondary myelodysplasia and acute leukemias • Adjust dose for renal dysfunction
Cladribine *Incorporated into DNA, produces strand breaks; inhibits conversion of ribo- to deoxyribonucleotides*	• Hairy cell leukemia • Chronic lymphocytic leukemia • Low-grade lymphoma • CTCL, Waldenström macroglobulinemia	• Intravenous administration • Adjust dose for renal dysfunction • Myelosuppression, opportunistic infections, nausea, high fever, tumor lysis syndrome
Clofarabine (mechanism as above)	• Acute myelogenous or lymphocytic leukemia	• Intravenous administration • Adjust dose to creatinine clearance • Myelosuppression • Capillary leak syndrome: discontinue drug • Nausea, vomiting, diarrhea
Nelarabine *Incorporated into DNA, terminates DNA synthesis*	• T-cell leukemia, lymphoma	• Intravenous administration • Myelosuppression; liver function abnormalities; infrequent neurologic sequelae
Pentostatin (2′-deoxycoformycin) *Inhibits adenosine deaminase; causes immunodeficiency (T and B cells)*	• Hairy cell leukemia; chronic lymphocytic leukemia; small cell non-Hodgkin lymphoma	• Intravenous administration • Adjust dose for renal dysfunction • Myelosuppression, GI symptoms, skin rashes, opportunistic infections • Renal, neurologic, pulmonary toxicity
Section III: Natural Products		
Vinca Alkaloids: Inhibit tubulin polymerization and microtubule formation		
Vinblastine	• Hodgkin and non-Hodgkin lymphoma • Breast, bladder, lung, testicular cancer • Kaposi sarcoma, neuroblastoma • Part of ABVD combination with doxorubicin (adriamycin, bleomycin, dacarbazine) for Hodgkin lymphoma	• Intravenous administration; extravasation causes irritation and ulceration • Reduce dose in patients with impaired liver function • Least neurotoxic Vinca alkaloid • Myelosuppressive • GI side effects nausea, vomiting, diarrhea • Vinca alkaloids are substrates of the Pgp efflux pump
Vinorelbine	• Breast cancer • Non–small cell lung cancer	• Intravenous administration • Reduce dose in patients with impaired liver function • Intermediate neurotoxicity amongst the Vinca alkaloids • Myelosuppressive (granulocytopenia)

Vincristine	• Acute lymphocytic leukemia; neuroblastoma; Wilms tumor; rhabdomyosarcoma; Hodgkin and non-Hodgkin lymphoma • part of CHOP regimen: cyclophosphamide, doxorubicin (H), vincristine (O), prednisone	• Intravenous administration; extravasation causes irritation and ulceration • Reduce dose in patients with impaired liver function • Least myelosuppressive Vinca alkaloid • Dose-limiting neurotoxicity • Better tolerated by children than adults
Eribulin	• Breast cancer, liposarcoma	• Side effects overlap with vinca but less sensitive to extrusion by Pgp
Taxanes: Stabilize microtubules, inhibit depolymerization		
Paclitaxel	• Ovarian, breast, lung, prostate, bladder, head and neck cancer	• Intravenous administration • Metabolized by hepatic CYPs, ↓ dose in patients with hepatic dysfunction • Substrate of Pgp efflux pump • Myelosuppressive, alleviated by G-CSF • Peripheral neuropathy is dose limiting • Mucositis
Docetaxel	• Same as above	• No effect on doxorubicin clearance • Pharmacokinetics similar to paclitaxel's • ↓ Neutropenia, ↓ neuropathy than paclitaxel
Camptothecins: Inhibit topoisomerase I; DNA religation is inhibited: accumulation of single-strand breaks		
Topotecan	• Ovarian cancer; small cell lung cancer	• Intravenous or oral administration • Reduce dose in patients with renal dysfunction • Neutropenia, GI side effects, nausea, vomiting • Substrate for Pgp
Irinotecan	• Colorectal cancer, small cell lung cancer • Part of FOLFIRI or FOLFIRINOX combination for GI tumors	• Intravenous administration • Prodrug activated in the liver; CYP substrate • Diarrhea and neutropenia • Acetylcholinesterase inhibition results in cholinergic syndrome: treat with atropine
Antibiotics		
Dactinomycin (actinomycin D) *Intercalates between GC base pairs of DNA*	• Wilms tumor; rhabdomyosarcoma; Ewing, Kaposi, and other sarcoma; choriocarcinoma	• Intravenous administration; severe injury on extravasation • Nausea, vomiting; myelosuppression; GI side effects; erythema, inflammation of the skin
Anthracyclines **and Anthracenediones: Inhibit topoisomerase II and intercalate DNA**		
Daunorubicin (daunomycin, rubidomycin)	• Acute myelogenous and acute lymphocytic leukemia	• Intravenous administration • Impart a red color to the urine • Myelosuppression, GI side effects • Most important long-term side effect is cardiotoxicity, including tachycardia, arrhythmias, congestive heart failure • Alopecia
Doxorubicin	• Soft-tissue, osteogenic, and other sarcoma; Hodgkin and non-Hodgkin lymphoma; acute leukemia; breast, genitourinary, thyroid, and stomach cancer; neuroblastoma	
Mitoxantrone (an anthracenedione)	• Acute myelocytic leukemia; breast and prostate cancer	• Similar side effects as above • Less cardiotoxic
Epipodophyllotoxins: Inhibit topoisomerase II and religation of cleaved DNA strand		
Etoposide	• Testicular and lung cancer; Hodgkin lymphoma; non-Hodgkin lymphomas; acute myelogenous leukemia; Kaposi sarcoma	• Oral and intravenous administration • Reduce dose in patients with renal dysfunction • Leukopenia, GI side effects; hepatic toxicity after high doses • Secondary leukemia
Teniposide	• Acute lymphoblastic leukemia in children; glioblastoma, neuroblastoma	• Intravenous administration • Myelosuppression, nausea, vomiting
Drugs With Diverse Mechanism of Action		
Bleomycin *Binds to DNA, generates free radicals, and induces DNA cleavage via deoxyribose ring damage*	• Testicular cancer; Hodgkin and non-Hodgkin lymphoma; local treatment of bladder cancer • Part of the ABVD regimen (doxorubicin [Adriamycin], Bleomycin, Vinblastine, and Dacarbazine)	• IV, IM or SC administration; instilled into bladder • Reduce dose in patients with renal dysfunction

		• Most serious: pulmonary toxicity • Cutaneous toxicity (erythema, ulcerations) • Less myelosuppression than other cytotoxics
L-Asparaginase *Hydrolyzes asparagine; deprives leukemia cells that lack asparagine synthase*	• Acute lymphocytic leukemia	• IV and IM administration • Hypersensitivity reactions, anaphylaxis • Hyperglycemia, clotting abnormalities
Hydroxyurea *Inhibits RNR (conversion of ribo- to deoxyribonucleotides)*	• Chronic myelogenous leukemia; polycythemia vera; essential thrombocytosis; sickle cell disease in adults	• Oral administration • Reduce dose in patients with renal dysfunction • Myelosuppression; some GI side effects
Tretinoin (all-*trans* retinoic acid) *Promotes degradation of PML-RARA fusion protein*	• Acute promyelocytic leukemia	• Oral administration • CYP substrate • Leukocyte maturation syndrome, pulmonary distress, effusions, fever, dyspnea • Dry skin, cheilitis • Hypercalcemia and renal failure
Arsenic trioxide *Inhibits thioredoxin and generates reactive oxygen species*	• Acute promyelocytic leukemia	• Oral or intravenous administration • Leukocyte maturation syndrome as above with ATRA • QT prolongation; rare torsade de pointes

[a]

For drugs that are subject to hepatic metabolism by CYP enzymes, drug exposure of a patient can be affected by coadministration of inhibitors or inducers of CYP3A4 and can then reduce efficacy or increase side effects.

[b]

Embryo-fetal toxicity: Consider that all of these drugs can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug and for 1 month after cessation of therapy. Advise men to avoid fathering a child during the same time period. Avoid lactation during therapies.

Monitoring of Anticancer Drugs

Agent	Major Adverse Effects	Monitoring Parameters	Comments
Antimetabolites			
Capecitabine	Diarrhea, hand-foot syndrome (palmar–plantar erythema), mild nausea and vomiting, mucositis	Stool count, hands and feet for early signs of skin breakdown	Adjust dose for renal impairment Oral prodrug of 5-FU Warfarin results in increased anticoagulant effects; may require phenytoin dose reduction
Cladribine	Myelosuppression, fever (onset by day 6, persisting for about 3 days), immunosuppressive, severe opportunistic infections occur	CBC, signs of infection	Risk of opportunistic infections necessitate prophylactic antibiotics for PJP and other infections
Clofarabine	Myelosuppression, elevated liver enzymes, nausea and vomiting, TLS	CBC, liver function, uric acid	
Cytarabine and liposomal cytarabine for intrathecal use	Myelosuppression, nausea and vomiting, diarrhea, mucositis, TLS, flu-like syndrome, rash high-dose toxicities: worsening of above and cerebellar toxicity, conjunctivitis	CBC, signs of infection, renal function, neurologic examinations (signs of confusion)	High-dose infusions should be administered over 2-3 hours to decrease risk of CNS toxicity, use eye drops during treatment and for 48 hours after treatment to prevent conjunctivitis with high dose Increased high-dose neurotoxicity with impaired renal function
Fludarabine	Myelosuppression, including decreased T cells; diarrhea; rare CNS toxicity; somnolence; peripheral neuropathy; hearing and visual changes; altered mental status; seizures; pulmonary toxicity; TLS	CBC, signs of infection, renal function, neurologic examinations	Adjust dose for renal impairment Risk of opportunistic infections necessitate prophylactic antibiotics for PJP and HSV
Fluorouracil	Mucositis, diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting, hyperpigmentation, photosensitivity, ocular toxicity, myocardial ischemic symptoms	CBC, stool count, hands and feet for early signs of skin breakdown	Deficiency of DPD correlates with increased toxicity Drug interaction with warfarin: increased anticoagulant effect
Gemcitabine	Myelosuppression, flu-like syndrome, rash, elevations in liver transaminases, nausea and vomiting	CBC, liver function	Rash may respond to topical steroids, fevers may respond to acetaminophen
6-Mercaptopurine	Myelosuppression, dry skin, rash, photosensitivity, hepatotoxicity, jaundice and hyperbilirubinemia, nausea and vomiting	CBC, liver function	Allopurinol increases the toxicity of mercaptopurine by interfering with metabolism Mercaptopurine reduces anticoagulant effects of warfarin
Methotrexate	Myelosuppression, mucositis, renal failure at high doses, nausea and vomiting, CNS toxicity (more severe with IT administration), hepatotoxicity	CBC, liver function, renal function, urine pH and methotrexate drug levels with high-dose therapy	Adjust dose or avoid use with renal impairment, avoid drugs that decrease renal excretion of methotrexate (eg, NSAIDs, PPIs, sulfas, and penicillins) Distributes readily into third-space fluids (ascites, pleural effusions), prolonging exposure and increasing toxicity; may be contraindication for use Monitor methotrexate levels with high-dose administration; these must include leucovorin rescue to prevent excessive myelosuppression; sodium bicarbonate also given for high-dose therapy to prevent nephrotoxicity (maintain urine pH >7) Use preservative-free preparations for IT and high-dose administration
Pemetrexed	Myelosuppression, stomatitis, pharyngitis, rash, desquamation	CBC, renal function, skin examinations	Avoid with renal impairment Avoid NSAIDs during administration Supplement with folic acid (400 mcg daily starting 1 week before first dose, continued days after last dose) and vitamin B_{12} (1,000 mcg IM during week before first dose and even cycles thereafter) to decrease myelosuppression Premedicate with dexamethasone (day before, the day of, and day after) to decrease incidence of rash
Trifluridineand tipiracil	Anemia, neutropenia, thrombocytopenia, asthenia/fatigue, decreased appetite, diarrhea, nausea and vomiting, abdominal pain, pyrexia	CBC, renal function	Consider dose modifications for moderate renal impairment
Microtubule-Targeting Drugs			
Cabazitaxel	Myelosuppression, infection, hypersensitivity reactions, diarrhea, asthenia, renal failure, nausea and vomiting	CBC, signs of infection, stool count, renal function, signs of hypersensitivity reactions, liver function	Avoid with hepatic impairment Premedicate with H_1 and H_2 antagonist plus dexamethasone to decrease risk of hypersensitivity

Docetaxel	Myelosuppression, fluid retention and edema, pleural effusions, ascites, alopecia, rash, peripheral neuropathy, hypersensitivity reactions	CBC, fluid status, liver function	Contraindicated with hepatic impairment (hyperbilirubinemia, elevated transaminases, or elevated alkaline phosphatase) Premedicate with dexamethasone to lower risk of fluid retention
Paclitaxel and nab-paclitaxel	Myelosuppression, infection, hypersensitivity reactions, peripheral neuropathy, myalgias or arthralgias, mucositis, cardiac arrhythmias, alopecia	CBC, signs of infection, signs of hypersensitivity reactions, liver function	Avoid or adjust dose with hepatic impairment Premedicate with dexamethasone, diphenhydramine, and ranitidine 30 minutes before paclitaxel; nab-paclitaxel is associated with minimal risk of hypersensitivity reactions and does not require premedication Neurotoxicity may require discontinuation Products are not interchangeable
Vinblastine and vinorelbine	Myelosuppression, mucositis, neurotoxicity (less common than with vincristine), myalgias, SIADH (rarely), vesicant	CBC, liver function	Adjust dose with elevated bilirubin Treat extravasation injury with warm soaks and injection of hyaluronidase
Vincristine	Peripheral neuropathy (highest of vinca alkaloids); motor, sensory, autonomic, and cranial nerves may be affected (paresthesias, ileus, urinary retention, facial palsies) and can be irreversible; SIADH; vesicant	Signs of neurotoxicity (tingling in extremities, constipation, CNS toxicity); liver function	Adjust dose with elevated bilirubin Treat constipation aggressively to prevent ileus Doses are commonly capped at 2 mg to minimize neurotoxicity LETHAL if administered IT Treat extravasation similar to vinblastine
Eribulin	Myelosuppression, peripheral neuropathy, asthenia, alopecia, nausea, constipation	CBC, liver function, renal function, potassium and magnesium levels	Dose reduce for Child-Pugh class A or B hepatic impairment and moderate renal impairment May cause QT prolongation in patients with electrolyte or congenital abnormalities (avoid other drugs that may prolong QT interval)
Ixabepilone	Myelosuppression, peripheral neuropathy, hypersensitivity reactions, asthenia, arthralgias, alopecia	CBC, signs of infection, signs of hypersensitivity reactions, liver function	Avoid or adjust dose with hepatic impairment CYP3A4 substrate, levels may be effected by inducers or inhibitors, avoid use or dose adjustment to ixabepilone may be necessary Premedicate with H_1 and H_2 antagonist
Topoisomerase Inhibitors			
Irinotecan and liposomal irinotecan	Diarrhea: acute (during or immediately after infusion, related to cholinergic effects) and delayed (>24 hours after administration, usually after the second or third dose), nausea and vomiting, myelosuppression (neutropenia), alopecia, fatigue, increased liver enzymes, pulmonary toxicity: diffuse infiltrates, fever, dyspnea	CBC, GI symptoms (bowel movements), fluid and electrolytes	Acute diarrhea is best treated or prevented with atropine, delayed diarrhea is managed with antimotility agents Consider dose adjustment with elevated total bilirubin or UGT1A1 deficiency Products are not interchangeable and have different indications
Topotecan	Myelosuppression (neutropenia and thrombocytopenia), mucositis, reversible increased liver enzymes	CBC, liver function, renal function	Adjust dose for renal impairment
Daunorubicin and liposomal daunorubicin	Myelosuppression (dose related); mucositis; nausea and vomiting; alopecia; vesicant: severe extravasation injury; cardiac toxicities: acute—not related to cumulative dose, arrhythmias, pericarditis; chronic—cumulative injury to myocardium (total dose >550 mg/m^2)	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely Liposomal form: decreased risk of cardiac and vesicant toxicity
Doxorubicin and liposomal doxorubicin	Similar to daunorubicin, cardiac toxicity associated with cumulative doses >450-550 mg/m^2, radiation recall reactions	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely May discolor urine (red-orange) Liposomal form: decreased risk of cardiac and vesicant toxicities
Epirubicin	Similar to daunorubicin, cardiac toxicity associated with cumulative doses >900 mg/m^2	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely
Etoposide	Myelosuppression; nausea and vomiting: may be worse with oral and high-dose regimens; alopecia; mucositis; hypotension (infusion rate–related); hypersensitivity reactions	CBC, blood pressure	Adjust dose for renal impairment Requires large volumes of fluid for IV administration because of limited solubility (maximum concentration 0.4 mg/mL) Available orally in liquid-filled gelatin capsules; ~50% bioavailability but absorption is variable and greater at lower oral doses
Idarubicin	Similar to daunorubicin Total cumulative dose not well established; >150 mg/m^2 reported to be associated with decreased LVEF	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely

Mitoxantrone	Myelosuppression, nausea and vomiting, mucositis, alopecia, less cardiotoxic than the anthracyclines	CBC, LVEF, liver function	Not a vesicant (may cause vein irritation but not associated with severe tissue injury such as anthracyclines) May discolor urine blue-green
Alkylating Agents			
Bendamustine	Myelosuppression, infection, dermatologic reactions including Stevens-Johnson syndrome, TLS, infusion reactions	CBC, signs of infection, signs of dermatologic toxicity, uric acid	Not studied in renal impairment Allopurinol may increase risk for Stevens-Johnson syndrome
Busulfan	Myelosuppression, skin hyperpigmentation, pulmonary fibrosis, gynecomastia, adrenal insufficiency High (HSCT) dose toxicities: seizures; hepatic venoocclusive disease; severe nausea and vomiting	CBC, pulmonary status, liver function, signs of edema (weight gain, fluid status)	Bone marrow recovery may be delayed (3-6 weeks), pulmonary fibrosis associated with >3-year exposure, prior chest radiation Seizure prophylaxis with HSCT doses Pharmacokinetic monitoring is required with IV busulfan IV and oral preparations are not interchangeable, put tablets in gelatin capsules for easier administration with high-dose administration
Carboplatin	Myelosuppression (thrombocytopenia), nausea and vomiting (acute and delayed), risk of hypersensitivity reactions at higher cumulative doses (frequently results in cross-hypersensitivity to cisplatin)	CBC, renal function	Calvert formula used to dose carboplatin Lower incidence of nephrotoxicity, neurotoxicity, nausea and vomiting than cisplatin
Chlorambucil	Myelosuppression, increased liver enzymes, skin rash, menstrual irregularities, pulmonary toxicity, risk of secondary malignancies, causes infertility and sterility, teratogenic	CBC, liver function, pulmonary function	Administer on an empty stomach, food decreases absorption May be dosed in low daily-dosing regimens or in higher dose, “pulse,” or intermittent dosing schedules administered biweekly or monthly; pulse dosing may require patients to take several tablets (eg, 10-20 tablets) per dose
Cisplatin	Nephrotoxicity, potassium and magnesium wasting, severe nausea and vomiting (acute or delayed onset), peripheral neuropathy that is cumulative and dose related, ototoxicity, anemia seen with chronic dosing	Renal function, potassium and magnesium levels, GI symptoms (nausea and vomiting)	Avoid with renal impairment IV hydration required before and after administration; ensure good urine output; potassium and magnesium sulfate in IV fluid to replace losses; consider carboplatin with impaired renal function Aggressive antiemetics required pretreatment and for 3-5 days after to prevent delayed nausea and vomiting Doses should not exceed 100 mg/m^2 (maximum single dose and per-cycle dose)
Cyclophosphamide	Hemorrhagic cystitis; nausea and vomiting (acute and delayed); myelosuppression; alopecia; SIADH: typically with high doses (>2 g/m^2); risk of secondary malignancies; causes infertility and sterility	CBC, renal function, urinalysis	Adjust dose for renal impairment Hydration needed to prevent hemorrhagic cystitis (oral or IV); mesna may be required with high-dose regimens (see ifosfamide) Instruct patients to take oral tablets in the morning to allow for elimination of toxic metabolite; absorbed through skin: avoid spills Drug interactions: CYP450 inducers (eg, barbiturates) may increase formation of toxic metabolites; CYP450 inhibitors (eg, cimetidine) may increase myelosuppression
Ifosfamide	Hemorrhagic cystitis; nephrotoxicity; myelosuppression; CNS effects: somnolence, confusion, disorientation, cerebellar symptoms that are dose-related; nausea and vomiting (acute and delayed); alopecia	CBC, urinalysis, renal function	Adjust dose for renal impairment 3-4 L/day fluid for hydration; potassium, magnesium, and phosphate may be required to replace losses Mesna is always given (typically 60%-100% of ifosfamide dose); may be delivered in same IV bag CNS toxicity, nausea, and vomiting may be more severe with rapid infusion Methylene blue is controversial for CNS toxicity
Mechlorethamine	Myelosuppression, severe nausea and vomiting, vesicant, secondary malignancies, sterility and infertility	CBC, GI symptoms (nausea and vomiting)	Antidote for extravasation is sodium thiosulfate
Nitrosoureas (carmustine and lomustine)	Myelosuppression, severe nausea and vomiting, cumulative nephrotoxicity, pulmonary fibrosis, facial flushing during infusion	CBC, renal function, pulmonary function	Bone marrow recovery may require 6-8 weeks Carmustine is a vein irritatant; facial flushing may be related to alcohol vehicle; also available in wafer form for implantation into brain tumor cavities after resection Lomustine is administered orally

Oxaliplatin	Pharyngolaryngeal dysesthesias; peripheral neuropathy >50% patients: acute form: <14 days, rapid onset, reversible, exacerbated by cold; chronic form: onset >14 days and may be permanent; nausea and vomiting; anaphylaxis risk	CBC, renal function, acute and chronic neuropathies	Adjust dose for renal impairment Magnesium and calcium controversial for prevention of neuropathies Avoid exposure to cold
Procarbazine	Myelosuppression, diarrhea, neurotoxicity, neuropathy, flu-like syndrome, infertility and sterility, secondary malignancies	CBC	Administer as a single daily dose on an empty stomach MAOIs that interact with tyramine-rich foods and may precipitate hypertensive crisis; drug interactions: TCAs and SSRIs, sympathomimetics, disulfiram-like reaction with alcohol
Thiotepa	Myelosuppression, nausea and vomiting, mucositis, pruritus and dermatitis	CBC, dermatologic toxicities	Most commonly used in HSCT preparative regimens
Trabectedin	Myelosuppression, rhabdomyolysis, hepatotoxicity, nausea and vomiting, diarrhea or constipation, cardiomyopathy	CBC, CPK, liver function	Extravasation may lead to tissue necrosis
Triazenes (dacarbazine and temozolamide)	Myelosuppression, severe nausea and vomiting, increased liver enzymes, flu-like syndrome (may last for several days after dacarbazine administration), facial flushing, photosensitivity	CBC, liver function	Dispense in a light-proof bags Temozolamide crosses the blood–brain barrier, may cause lymphosuppression and requires PJP prophylaxis when given with radiation therapy
Miscellaneous Agents			
Arsenic trioxide	Differentiation syndrome (pulmonary infiltrates, respiratory distress, fever, and hypotension); QT prolongation; electrolyte abnormalities (hypokalemia, hyperkalemia, hypomagnesemia); hyperglycemia; rash; lightheadedness; fatigue; musculoskeletal pain	ECG and serum electrolytes (calcium, magnesium, potassium) before each course; renal function	Differentiation syndrome must be treated promptly with corticosteroids Do not give if QTc >500 msec Replace electrolytes before therapy
Bleomycin	Anaphylaxis and hypersensitivity reactions, fever and flu-like symptoms, mucositis, pulmonary fibrosis	Obtain PFTs before use and if signs of pulmonary toxicity develop; monitor for anaphylactic reactions	Adjust dose for renal impairment Test dose (1 unit) is recommended but controversial; premedicate for subsequent doses with acetaminophen Pulmonary toxicity associated with cumulative dose >400 units and pre-existing pulmonary disease
Hydroxyurea	Myelosuppression, rash, skin hyperpigmentation, TLS, secondary leukemias	CBC, uric acid	Dose may need to be adjusted with renal impairment (use with caution) Used to decrease white blood cell counts rapidly to prevent adverse effects of leukocytosis
Mitomycin C	Myelosuppression (delayed and prolonged), mucositis, nausea and vomiting, vesicant, pulmonary fibrosis, hemolytic anemia and uremic syndrome	CBC, renal function, pulmonary function	Apply ice or cold packs to site for extravasation
Omacetaxine	Myelosuppression (thrombocytopenia including increased risk of hemorrhage, anemia, neutropenia); diarrhea; nausea; fatigue; asthenia; injection site reaction; pyrexia; infection; lymphopenia; hyperglycemia	CBC, blood glucose	
Retinoids			
Bexarotene	Peripheral edema, insomnia, headache, fever, increased triglycerides and cholesterol, hypothyroidism, leukopenia and anemia, dry skin, increased liver enzymes, pancreatitis, photosensitivity	CBC, liver function, cholesterol and triglyceride levels, thyroid function	Avoid gemfibrozil to treat elevated triglycerides Limit vitamin A supplements May cause hypoglycemia in patients receiving insulin, sulfonylureas, or metformin Teratogenic, contraindicated in pregnancy, female patients should be educated about proper contraceptive measures
Tretinoin (ATRA)	Headache; differentiation syndrome; “ATRA syndrome” consisting of pulmonary symptoms, fever, hypotension, and pleural effusions; dry skin and mucous membranes; mucositis; increases in liver enzymes and bilirubin	CBC, liver function, signs of differentiation syndrome	Differentiation syndrome must be treated promptly with corticosteroids Teratogenic, contraindicated in pregnancy, female patients should be educated about proper contraceptive measures
ALK Inhibitors			
Alectinib	Fatigue, bradycardia, hepatotoxicty, anemia, constipation, edema, myalgia, visual disturbances	CBC, liver function, heart rate, CPK	Administer with food
Brigatinib	ILD and pneumonitits, hypertension, bradycardia, visual disturbances, creatinine phosphokinase elevation, pancreatic enzyme elevation, hyperglycemia	HR, BP, pulmonary symptoms, CPK, pancreatic enzymes	Dose escalation required to decrease early-onset pulmonary symptoms Avoid strong CYP3A inhibitors and inducers; may affect hormonal contraceptives

Ceritinib	Gastrointestinal toxicity, increases in liver enzymes, fatigue, visual disturbances, QT prolongation, bradycardia, hyperglycemia	CBC, renal function, liver function, blood glucose, pancreatic enzymes, cardiac monitoring, electrolytes	Administer on an empty stomach
Crizotinib	Nausea and vomiting, diarrhea, constipation, fatigue, increases in liver enzymes, visual disorders, edema, ILD, QT prolongation, bradycardia	CBC, renal function, liver function, HR, BP, cardiac monitoring, electrolytes, pulmonary symptoms	Visual disorders (visual impairment, blurred vision, and photopsia) occur in approximately half of patients
Lorlatinib	Hepatotoxicity, CNS toxicity, hyperlipidemia, atrioventricular block, ILD and pneumonitits	Liver function, lipids, ECG	Strong CYP3A inducers contraindicated, avoid strong CYP3A4 inhibitors and certain CYP3A4 substrates
B-Cell Lymphoma-2 Inhibitor			
Venetoclax	TLS, myelsosuppression, diarrhea, upper respiratory tract infection	CBC, chemistries	Ramp-up dose required Premedicate with antihyperuricemics and ensure adequate hydration Contraindicated with strong CYP3A inhibitors during initiation and ramp-up Avoid strong and moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic Avoid live-attenuated vaccines Administer with a meal
BCR-ABL Inhibitors			
Bosutinib	Nausea and vomitin, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, rash, diarrhea, increased liver enzymes, hypophosphatemia	CBC, liver function, electrolytes, Philadelphia chromosome levels, signs of edema	Adjust dose for hepatic impairment Avoid antacids and PPIs Maintenance dose based on CBC Administer with food
Dasatinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, fatigue, rash, diarrhea, increased liver enzymes, QT prolongation, hypophosphatemia and hypocalcemia	CBC, liver function, electrolytes, signs of edema, Philadelphia chromosome levels	Avoid antacids, H_2 antagonists, and PPIs Maintenance dose based on CBC
Imatinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, rash, diarrhea, increased liver enzymes, hypophosphatemia	CBC, liver function, electrolytes, Philadelphia chromosome levels, signs of edema	Dose adjustments should be considered with severe liver and moderate renal impairment May increase warfarin effects Maintenance dose based on CBC Take with meals and a full glass of water
Nilotinib	Nausea and vomiting, edema, myelosuppression, increased lipase, hyperglycemia, arthralgias, rash, diarrhea, increased liver enzymes, QT prolongation	CBC, liver function, serum lipase, serum glucose, electrolytes, Philadelphia chromosome levels	Adjust dose for hepatic impairment Take on an empty stomach CYP3A4 substrate: avoid inhibitors Maintenance dose based on CBC Avoid PPIs, stagger administration with H_2 antagonists and antacids if use is necessary
Ponatinib	Myelosuppression, hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, pyrexia, thromboembolic events, hepatotoxicity, congestive heart failure, pancreatitis, hemorrhage (secondary to thrombocytopenia), fluid retention	Cardiac monitoring (CHF, arrhythmias), BP, pancreatic enzymes, fluid retention, CBC, liver function	May need to decrease or hold therapy if hepatotoxicity develops Avoid antacids and drugs that decrease gastric pH
BRAF Inhibitors			
Dabrafenib	Papilloma, arthralgia, alopecia, fatigue, headache, HFSR, pyrexia	CBC, serum glucose, electrolytes, renal function, dermatologic evaluations	Take on an empty stomach
Encorafenib	Cutaneous and noncutaneous malignancies, tumor promotion, hemorrhage, uvetis, QT prolongation	Visual symptoms, opthamalogic evaluations, ECG, electrolytes	Avoid strong and moderate CYP3A inhibitors, strong inducers, and sensitive CYP3A substrates Use nonhormonal contraceptives
Vemurafenib	Papilloma, arthralgia, alopecia, fatigue, headache, photosensitivity reaction, hypersensitivity reactions, QT prolongation	Liver function, electrolytes, cardiac monitoring, dermatologic evaluations	Radiation sensitization/recall
BTK Inhibitor			
Acalabrutinib	Infections (including opportunistic and hepatitis reactivation), secondary primary malignancies, atrial flutter and fibrillation	CBC, cardiac monitoring	Avoid strong CYP3A inhibitors, strong CYP3A inducers Avoid PPIs, stagger administration with H_2 antagonists and antacids if use is necessary
Ibrutinib	Diarrhea, fatigue, musculoskeletal pain, nausea, rash, atrial fibrillation, hemorrhage, TLS, bone marrow suppression	CBC, renal function, liver function, uric acid levels, electrolytes, cardiac monitoring	Reduce dose with hepatic impairment
CDK Inhibitor			

Abemaciclib	Diarrhea, neutropenia, hepatotoxicity, venous thromboembolism	CBC, electrolytes, liver function	Avoid moderate and strong CY3A inducers Dose reduce with moderate and strong CYP3A inhibitors Reduce dose with severe hepatic impairment
Palbociclib	Thromboembolic events, infection, bone marrow suppression, gastrointestinal toxicity	CBC, infection	Administer with food
Ribociclib	QT prolongation, hepatobiliary toxicity, neutropenia	ECG, electrolytes, liver function, CBC	Avoid drugs known to prolong QT interval; strong CYP3A inhibitors; strong CYP3A inducers; sensitive CYP3A substrates
DNA Methyltransferase Inhibitors			
Azacitidine and decitabine	Myelosuppression and infection, constitutional symptoms, musculoskeletal symptoms (arthralgias), cough, dyspnea	CBC, infection	
EGFR Inhibitors			
Afatinib	Rash, diarrhea, ILD, keratitis	Liver function, renal function, dermatologic evaluations, electrolytes, LVEF in patients with cardiac risk factors, pulmonary symptoms	Administer on an empty stomach
Dacominitinb	ILD, diarrhea, dermatologic toxicity	Pulmonary symptoms, skin	Avoid PPIs and sensitive CYP2D6 inhibitors Initiate use of moisturizers and appropriate measures to limit sun exposure
Erlotinib	Rash, diarrhea, ILD, hepatic and renal failure reported	Liver function, renal function, electrolytes, pulmonary symptoms, dermatologic evaluations	Dose reductions or delays may be required for rash but supportive care should be attempted first Major interaction with warfarin (may lead to increased bleeding risk) H_2 antagonists, PPIs, and antacids may decrease drug levels Administer on an empty stomach as food increases absorption and possibly toxicity
Gefitinib	Similar to erlotinib	Liver function, renal function, electrolytes, pulmonary symptoms, dermatologic evaluations	Similar precautions and drug interactions as with erlotinib
Lapatinib	Diarrhea, rash, nausea, vomiting, fatigue, decreases in LVEF, hepatotoxicity, QT prolongation, ILD	Liver function, cardiac monitoring (LVEF, QT, MUGA), electrolytes, pulmonary symptoms	Adjust dose for severe hepatic impairment Administer on empty stomach Avoid strong CYP3A4 inhibitors (if unavoidable, consider dose reduction); avoid strong CYP3A4 inducers (if unavoidable, consider gradual dose increases)
Neratinib	Diarrhea, hepatotoxicity	Liver function, electrolytes	Use prophylactic antidiarrheal Lower starting dose for hepatic impairment Avoid PPIs, strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and sensitive P-gp substrates
Osimertinib	Gastrointestinal toxicity, dermatologic toxicity, ILD/pneumonitis, pneumonia, pulmonary embolism, cardiomyopathy, QT prolongation	Cardiac monitoring (LVEF, QT), pulmonary symptoms, dermatologic evaluations	Avoid strong CYP3A4 inhibitors and inducers
Fibroblast Growth Factor Receptor (FGFR) Inhibitor			
Erdafitinib	Ocular disorders, hyperphosphatemia, stomatitis, creatinine increased, HFSR, elevated liver enzymes	Ophthalmological exams, phosphate levels	Avoid strong CYP2C9 or CYP3A4 inhibitors and inducers Increased phosphate levels are a pharmacodynamic effect
FMS-Like Tyrosine Kinase-3 (FLT3) Inhibitors			
Gilteritinib	PRES, QT prolongation, pancreatitis, hypersensitivity	ECG, electrolytes	Avoid dual P-gp and CYP3A inducers and strong CYP3A inhibitors
Midostaurin	Pulmonary toxicity	ECG	Administer with food Avoid strong CYP3A inducers
Hedgehog Inhibitors			
Glasdegib	QT prolongation, teratogenic effects	Pregnancy status, ECG	Boxed warning for severe birth defects and embryo-fetal death; advise females to use contraception during treatment and for 20 months after the last dose; advise males to use condoms during treatment and for at least 8 months after the last dose; do not donate blood during treatment and for 30 months after the last dose; do not donate sperm during treatment and for 8 months after the last dose
Sonidegib	Fatigue, alopecia, amenorrhea, musculoskeletal toxicity, teratogenic effects	Pregnancy status, CPK, renal function, liver function	Boxed warning for severe birth defects and embryo-fetal death; advise females to use

			contraception during treatment and for 20 months after the last dose; advise males to use condoms during treatment and for at least 8 months after the last dose; do not donate blood during treatment and for 20 months after the last dose; do not donate sperm during treatment and for 8 months after the last dose Avoid strong and moderate CYP3A modulators; moderate CYP3A inhibitors may be used for short term
Vismodegib	Muscle spasms, alopecia, dysgeusia, fatigue, nausea and vomiting, diarrhea, decreased appetite, constipation, arthralgias, teratogenic effects	Pregnancy status	Boxed warning for severe birth defects and embryo-fetal death; patients should not donate blood or blood products while receiving vismodegib and for at least 7 months after the last dose; verify pregnancy status within 7 days prior to treatment initiation; do not donate sperm during treatment and for 3 months after the last dose
Histone Deacetylase Inhibitors			
Belinostat	Pyrexia, nausea, fatigue, anemia, hepatotoxicity, infection, TLS	Liver function, renal function, CBC, electrolytes, uric acid levels	
Panobinostat	Cardiotoxicity, nausea, vomiting, diarrhea, hemorrhage, infection, hepatotoxicity	Cardiac monitoring, electrolytes, CBC, liver function, pregnancy status	Boxed warnings for cardiovascular events and gastrointestinal events
Romidepsin	Neutropenia, lymphopenia, thrombocytopenia, infection, nausea and vomiting, fatigue, anorexia, anemia, ECG T-wave changes	CBC, cardiac monitoring (ECG), electrolytes	Monitor INR with concurrent use of warfarin
Vorinostat	Diarrhea, fatigue, nausea, thrombocytopenia, anorexia, dysgeusia, thromboembolic events, hyperglycemia	CBC, electrolytes, serum glucose, renal function	Avoid or adjust dose for hepatic impairment Increase in INR with concomitant warfarin Severe thrombocytopenia and GI bleeding have been reported with concomitant use with vorinostat and other HDAC inhibitors (eg, valproic acid)
Isocitrate Dehydrogenase (IDH) Inhibitors			
Enasidenib	Differentiations syndrome, TLS, myelosuppression, hepatotoxicity, nausea and vomiting	CBC, electolytes	
Ivosidenib	Differentiation syndrome, QT prolongation, Guillain-Barré Syndrome, TLS	CBC, chemistries, CPK, ECG, electrolytes	Reduce ivosidenib dose with strong CYP3A4 inhibitor Avoid strong CYP3A inducers; sensitive CYP3A substrates; drugs that prolong QT interval
JAK Inhibitor			
Ruxolitinib	Thrombocytopenia, anemia, bruising, dizziness, headache, infections, cardiovascular abnormalities	CBC, renal function, liver function, cardiac monitoring	Consider dose adjustment for renal and hepatic impairment
MEK Inhibitor			
Binimetinib	Cardiomyopathy, venous thromboembolism, ILD, hepatotoxicity, rhabdomyolysis, hemorrhage, ophthalmic events	LVEF, ophthalmologic evaluation, liver function, CPK, renal function	Reduce dose for moderate and severe hepatic impairment
Cobimetinib	Dermatologic toxicity, nausea and vomiting, pyrexia, hemorrhage, new primary malignancies, cardiomyopathy, ophthalmic events, hepatotoxicity, rhabdomyolysis	CBC, liver function, dermatologic evaluation, ophthalmologic evaluation, LVEF, CPK, electrolytes	Avoid coadministration with strong or moderate CYP3A inducers or inhibitors
Trametinib	Diarrhea, lymphedema, hemorrhage, venous thromboembolism, febrile reactions, cardiomyopathy, dermatologic toxicity, hyperglycemia, hypertension, ophthalmic events	CBC, liver function, LVEF, ophthalmologic evaluation, dermatologic evaluation, BP	Capsules are stored refrigerated Administer on an empty stomach
mTOR Inhibitors			
Everolimus	Rash, asthenia, stomatitis, nausea, edema, anorexia, anemia, pneumonitis, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypophosphatemia, elevated liver enzymes, elevated Scr, lymphopenia, thrombocytopenia, leukopenia, infection	Metabolic toxicities, CBC, renal function, liver function, electrolytes, pulmonary symptoms	Adjust dose for hepatic impairment Initiation or increase in cholesterol or diabetic medications often needed CYP3A4 and Pgp substrate; may require dose adjustment based on concurrent medication
Temsirolimus	Similar to everolimus with addition of infusion-related reactions	Similar to everolimus, infusion reactions	Adjust dose for hepatic impairment Requires diphenhydramine premedication
Multikinase Inhibitors			
Axitinib	Diarrhea, rash, HFSR, bleeding, thrombotic events, hypertension, hepatotoxicity, hypothyroidism,	CBC, liver function, BP, thyroid function, urine protein,	Adjust dose for hepatic impairment

	proteinuria, GI perforation, fatigue, rare reports of progressive multifocal leukoencephalopathy	neurologic evaluation, dermatologic evaluation	Substrate of CYP3A4, may require dose adjustment based on concurrent medication administered
Cabozantinib	Diarrhea, stomatitis, HFSR, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, constipation, increased liver enzymes, proteinuria, lymphopenia, neutropenia, thrombocytopenia, hypocalcemia, hypophosphatemia, GI perforations and fistulas and hemorrhage have been reported	BP; urine protein, CBC, liver function, thyroid function; electrolytes; dermatologic evaluation	Administer on an empty stomach CYP3A4 substrate, monitor for drug interactions
Lenvatinib	Hypertension, fatigue, diarrhea, proteinuria, stomatitis, HFSR, hypothyroidism, hepatotoxicity, thromboembolic events, renal toxicity, hypocalcemia	Liver function, renal function, thyroid function, BP, electrolytes	Adjust dose for severe hepatic and renal impairment
Pazopanib	Diarrhea, hypertension, hair/skin hypopigmentation, nausea, anorexia, vomiting, decreased weight, fatigue, musculoskeletal pain, dysguesia, dyspnea, hypothyroidism, proteinuria, fatal hepatotoxicity, thromboembolic events	Liver function, cardiac monitoring (ECG), BP, thyroid function, urine protein, dermatologic evaluation	Adjust dose for hepatic impairment Take on empty stomach Reduce dose when administered with strong CYP3A4 inhibitors, avoid CYP3A4 inducers, concomitant use with simvastatin increases liver enzymes
Regorafenib	Asthenia, fatigue, decreased appetite, HFSR, diarrhea, mucositis, weight loss, infection, hypertension, dysphonia, hepatotoxicity, hemorrhage	Liver function, BP, dermatologic evaluation	Administer with food (low-fat breakfast that contains <30% fat) Monitor INR closely with concomitant warfarin because of an increased risk of hemorrhage
Sorafenib	Diarrhea, rash, HFSR, fatigue, hypertension, prolonged QT interval, cardiac events (including MI), hepatitis	BP, liver function, cardiac monitoring, electrolytes, dermatologic evaluation	Administer on an empty stomach May increase the anticoagulation effects of warfarin
Sunitinib	Diarrhea, rash, bleeding, CHF and cardiac effects, QT prolongation, fatigue, hypertension, hepatotoxicity, thyroid dysfunction	CBC, liver function, BP, thyroid function, cardiac monitoring (CHF, ECG), electrolytes	CYP3A4 substrate, may require dose adjustment based on concurrent medication administered
Vandetanib	Diarrhea, rash, acne, nausea, hypertension, headache, fatigue, upper respiratory tract infections, decreased appetite, abdominal pain, QT prolongation, torsades de pointes and sudden death, ILD, hemorrhage, increased liver enzymes	Liver function, electrolytes, cardiac monitoring (ECG), BP, pulmonary symptoms, dermatologic evaluation	REMS program for QT prolongation/sudden death; avoid other medications that prolong the QT interval Adjust dose for renal impairment Advise patients to wear sunscreen and protective clothing when exposed to sun
Neurotrophic receptor tyrosine kinase (NTRK) Inhibitor			
Larotrectinib	Neurotoxicity; hepatotoxicity	Liver function	Avoid strong CYP3A inhibitors and inducers; avoid sensitive CYP3A substrates Reduce starting dose in moderate-to-severe hepatic impairment
PARP Inhibitor			
Niraparib	Myelodysplastic syndrome, acute myeloid leukemia, myelosuppression, cardiovascular toxicity	CBC, BP, HR	
Olaparib	Fatigue, musculoskeletal pain, dermatitis, nausea and vomiting, upper respiratory infections, anemia, pneumonitis, secondary malignancies (MDS/AML)	CBC, pulmonary symptoms	Tablets and capsules are not bioequivalent Reduce dose for renal impairment
Rucaparib	Myelodysplastic syndrome, acute myeloid leukemia, nausea and vomiting	CBC	
Talazoparib	Myelodysplastic syndrome/acutem myeloid leukemia, myelosuppression	CBC	Reduce starting dose for renal impairment Reduce dose for certain P-gp inhibitors
PI3K Inhibitor			
Alpelisib	Dermatologic reactions, severe diarrhea, pneumonitis, hyperglycemia, severe hypersensitivity reactions	Blood glucose, dermatologic evaluation, pulmonary symptoms	Avoid strong CYP3A inducers, closely monitor with concurrent CYP2C9 substrates (eg, warfarin)
Copanlisib	Infections, hyperglycemia, hypertension, pneumonitis, neutropenia, dermatologic reactions	CBC, blood glucose, BP	Reduce dose with strong CYP3A inhibitors Avoid strong CYP3A inducers Consider PJP prophylaxis
Duvelisib	Infections, neutropenia, fatal/serious diarrhea, dermatologic reactions, pneumonitis, hepatotoxicity	CBC, liver function, dermatologic evaluation, pulmonary symptoms	Avoid strong CYP3A inducers Reduce moderate and strong CYP3A inhibitors PJP prophylaxis required; considered antiviral prophylaxis for cytomegalovirus
Idelalisib	Fatal/serious diarrhea, intestinal perforation, hepatotoxicity, pneumonitis, infections, neutropenia, dermatologic reactions, anaphylaxis	Liver function, CBC, dermatologic evaluation, pulmonary symptoms	PJP prophylaxis required
Proteasome Inhibitors			

Bortezomib	Fatigue or malaise, nausea and vomiting, diarrhea, anorexia, constipation, myelosuppression (especially thrombocytopenia), hyponatremia, hypokalemia, peripheral neuropathy (cumulative and dose-related), fever	CBC, thyroid function, symptoms of neuropathy, electrolytes	Adjust dose for hepatic impairment Administer IV or subcutaneous (subcutaneous administration has been shown to decrease neuropathies) Increased risk of severe neuropathy with pre-existing neuropathy Coadministration with strong CYP3A4 inhibitors can increase bortezomib concentrations
Carfilzomib	Fatigue, anemia, thrombocytopenia, nausea, diarrhea, dyspnea, pyrexia, infusion-related reactions, rare reports of cardiac arrest, CHF, and MI	Pulmonary symptoms, CBC, liver function, cardiac monitoring, infusion reactions	Premedicate with dexamethasone before all cycle 1 doses then as needed for future cycles to reduce the incidence of infusion reactions
Ixazomib	Gastrointestinal toxicity, thrombocytopenia, peripheral neuropathy, edema, cutaneous reactions, hepatotoxicity	CBC, liver function, dermatologic evaluation	Administer on an empty stomach Reduce starting dose for hepatic or renal impairment Avoid use with strong CYP3A4 inducers Consider antiviral prophylaxis
Radiopharmaceuticals			
Ibritumomab tiuxetan	Prolonged hematologic toxicity, infusion-related reactions, cutaneous and mucocutaneous reactions, development of leukemia and myelodysplastic syndrome	Infusion-related reactions, CBC, extravasation	Must consider toxicities of rutiximab Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure
Iobenguane I 131	Radiation exposure, myelosuppression, secondary malignancies, hypothyroidism, hypertension, renal toxicity, pneumonititis	CBC, thyroid function, BP, renal function	Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure Premedications include antiemetics, hydration, and thyroid blockade Administer dosimetric and therapeutic dose Avoid drugs that affect catecholamine uptake or stores
Lutetium Lu 177 dotatate	Myelosuppresion, renal toxicity, hepatotoxicity, secondary malignancies, neuroendocrine hormonal crisis	CBC, renal function, liver function	Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure Administer with short- and long-acting octreotide and amino acid solution
Radium Ra 223 dichloride	Myelosuppresion, increased fractures	CBC	Radiopharmaceutical; prepared and administered only by personnel trained in radiopharmaceuticals; patients must be trained in precautions to decrease radiation exposure
Miscellaneous Small Molecule Inhibitors			
Lanreotide	Abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hypertension, hypo- and/or hyperglycemia, gallstones, hypothyroidism (mild)	HR, BP, blood glucose, thyroid function, gall bladder ultrasonography	
Lenalidomide	Teratogen, fatigue, peripheral neuropathy, neutropenia and thrombocytopenia, thromboembolic events	CBC, signs of thrombosis, signs of peripheral neuropathies, pregnancy status	REMS program for fetal toxicity Adjust dose for renal impairment Prophylactic anticoagulation may be required
Pomalidomide	Teratogen, neutropenia, hepatotoxicity, thromboembolic events	Same as for lenalidomide	REMS program for fetal toxicity Adjust dose for renal and hepatic impairment Prophylactic anticoagulation may be required
Thalidomide	Teratogen, somnolence, constipation, dizziness or orthostatic hypotension, rash, peripheral neuropathy, thromboembolic events, increased HIV viral load	Same as for lenalidomide; HIV viral load	REMS program for fetal toxicity Prophylactic anticoagulation may be required
Monoclonal Antibodies that Target CD20			
Obinutuzumab	Infusion reactions, myelosuppression, nausea, diarrhea, Progressive Multifocal Leukoencaphalopathy, HBV reactivation	CBC, hepatitis B screening at baseline, renal function, electrolytes, infusion reaction, fluid status	Antimicrobial, antiviral, and antifungal prophylaxis in select patients Antihyperuricemic prophylaxis and hydration if risk for TLS Premedicate with acetaminophen, an antihistamine, and a glucocorticoid
Ofatumumab	Neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, upper respiratory infection	Infusion-related reactions, CBC, hepatitis B screening at baseline	Premedicate with acetaminophen, antihistamine, and corticosteroid Infusion rate-escalation required
Rituximab	Hypersensitivity reactions and infusion-related reactions, TLS (especially with large tumor	Infusion-related reactions, CBC, neurologic examination,	Patients should be screened for Hepatitis B before therapy initiation

	burden), myelosuppression and infection, rare reports of progressive multifocal leukoencephalopathy, severe skin reactions, myalgias, tachycardia	hepatitis B screening at baseline, electrolytes, HR, BP	Infusion-related reactions may be severe; increase rate of infusion gradually and premedicate with acetaminophen and diphenhydramine; rituximab and hyaluronidase available for subcutaneous injection
Monoclonal Antibodies that Target CD52			
Alemtuzumab	Myelosuppression and immunosuppression, autoimmune conditions, infection, infusion-related reactions, nausea and vomiting, fever, hypotension, rash, headache, fatigue, secondary malignancies	CBC, infusion-related reactions, CMV, $CD4^+$counts, HR, BP, autoimmune symptoms, symptoms of infection	Restricted distribution through REMS program to mitigate risks of autoimmune conditions, infusion reactions, and secondary malignancies Patients should be started on antiviral and PJP prophylaxis during and 6 months posttreatment
Monoclonal Antibodies that Target CD38			
Daratumumab	Infusion-related reactions, pyrexia, fatigue, upper respiratory tract infection, nausea, myelosuppression	CBC, acute or delayed infusion-related reactions	Type and screen patients prior to starting treatment as daratumumab may interfere with cross-matching and red blood cell antibody screening Premedicate with corticosteroids, antipyretics, and antihistamines; administer postinfusion medications
Monoclonal Antibodies that Target Chemokine Receptor			
Mogamulizumab-kpkc	Dermatologic reactions, infusion reactions, infections, autoimmune complications, complications of allogeneic HSCT	Infusion reactions	Administer diphenhydramine and acetaminophen for the first infusion
Monoclonal Antibodies that Target GD2 Receptor			
Dinutuximab	Infections, infusion reactions, hypokalemia, hypotension, capillary leak syndrome, neurological ocular toxicity, pain, bone marrow suppression, hemolytic uremic syndrome	CBC, electrolytes, renal function, BP, infusion reaction	Premedicate with IV analgesics (such as morphine), an antihistamine, acetaminophen, antiemetics, and IV hydration
Monoclonal Antibodies that Target PDGFR-α			
Olaratumab	Infusion-related reactions	Infusion reactions	Premedicate with diphenhydramine and dexamethasone prior to the first dose
Monoclonal Antibodies that Target SLAMF7			
Elotuzumab	Fatigue, pyrexia, diarrhea or constipation, respiratory infections, peripherial neuropathy, hepatotoxicity, infusion-related reactions, second primary malignancies	Liver function, infusion-related reactions, infections	May interfere with the assay used to monitor M-protein which can impact the determination of complete response Premedicate with dexamethasone, diphenhydramine, ranitidine, and acetaminophen
Monoclonal Antibodies that Target EGFR			
Cetuximab, necitumumab, and panitumumab	Rash, paronychial cracking in fingers or toes, asthenia, abdominal pain, nausea, constipation, diarrhea, infusion and hypersensitivity reactions, electrolyte wasting, cardiopulmonary arrest	Electrolytes, infusion reactions, dermatologic evaluation	Dose reductions or delays may be required for rash but supportive care should be attempted first Decreased risk of infusion-related reactions to panitumumab and does not appear to be cross-reactive (ie, a patient may receive panitumumab if they react to cetuximab)
Monoclonal Antibodies that Target HER2			
Pertuzumab	Diarrhea, nausea, alopecia, rash, neutropenia, fatigue, peripheral neuropathy, embryo and fetal toxicity, left ventricular dysfunction, infusion-related reactions	LVEF, infusion reactions, pregnancy status	
Trastuzumab	Cardiac toxicity: congestive cardiomyopathy (usually reversible with medical management); infusion-related reactions; pulmonary toxicity; embryo and fetal toxicity	Infusion-related reactions, cardiac monitoring (LVEF)	Do not administer with anthracyclines because of increased cardiotoxicity Trastuzumab and ado-trastuzumab ematansine are NOT interchangeable; trastuzumab and hyaluronidase available for subcutaneous injection
Monoclonal Antibodies that Target VEGFR			
Bevacizumab	GI bleeding or perforation, impaired wound healing, hypertension, proteinuria, thrombotic events, rare severe pulmonary hemorrhage, rare reports of progressive multifocal leukoencephalopathy	BP, urine protein, neurologic examination, signs of GI perforation, symptoms of thromboembolism	
Ramucirumab	GI bleeding or perforation, impaired wound healing; hypertension, proteinuria, thyroid dysfunction, thromboembolic events, hemorrhage	BP, urine protein, thyroid function, liver function	
Bispecific T-Cell Engagers			
Blinatumomab	Infusion reactions, cytokine release syndrome, neurologic toxicities, infections, fever, headache, peripheral edema, rash, TLS, hepatotoxicity, bone marrow suppression	CBC, liver function, neurological examination, uric acid levels, electrolytes	Premedicate with dexamethasone prior to the first dose of each cycle; prior to a step dose or when restarting therapy after an interruption >4 hours Administered as a continuous intravenous infusion over 28 days

Antibody-Drug Conjugates			
Ado-Trastuzumab ematansine	Cardiac toxicity, thrombocytopenia, hemorrhage, hepatotoxicity, infusion reactions, peripheral neuropathy, ILD, embryo-fetal toxicity	CBC, liver function, pregnancy status, cardiac monitoring (LVEF), pulmonary symptoms	Ado-Trastuzumab Ematansine and Trastuzumab are NOT interchangeable
Brentuximab vedotin	Neutropenia, peripheral neuropathy, fatigue, nausea or vomiting, anemia, diarrhea, rash, thrombocytopenia, infusion-related reactions, TLS, rare reports of progressive multifocal leukoencephalopathy	CBC, symptoms of neuropathy, infusion-related reactions, uric acid levels, electrolytes	Adjust dose for renal and hepatic impairment
Gemtuzumab ozogamicin	Hypersensitivity, infusion-related reactions, hemorrhage	Infusion reactions	Premedicate with a corticosteroid, antihistamine, and acetaminophen
Inotuzumab ozogamicin	Myelosuppression, infusion-related reactions, QT interval prolongation, hepatotoxicity	CBC, ECG, infusion reactions, liver function	Premedicate with a corticosteroid, antipyretic, and antihistamine
Polatuzumab vedotin	Peripheral neuropathy, infusion-related reactions, myelosuppression, infections, TLS, hepatotoxicity	CBC, symptoms of neuropathy, infusion-related reactions, uric acid levels, electrolytes, liver function	Premedicate with an antihistamine and antipyretic
Immune Checkpoint Inhibitors			
Ipilimumab	Fatigue, diarrhea, pruritus, rash, immune-mediated reactions (eg, enterocolitis, dermatitis, neuropathy, endocrinopathy, hepatitis)	Thyroid function, electrolytes; liver function; renal function; dermatologic evaluations; gastrointestinal symptoms	Treat severe immune-related adverse events with corticosteroids
Atezolizumab; avelumab; cemiplimab; durvalumab, nivolumab, and pembrolizumab	Fatigue, immune-mediated toxicities (eg, pneumonitis, colitis, hepatitis, nephritis, thyroid dysfunction)	Liver function, renal function, thyroid function, GI symptoms	Treat severe immune-related adverse events with corticosteroids For avelumab, premedicate with an antihistamine and acetaminophen prior to the first 4 infusions
Miscellaneous Monoclonal Antibodies			
Denosumab	Arthralgia, headache, nausea, hypocalcemia, hypophosphatemia, osteonecrosis of the jaw	Dental evaluations, electrolytes	A dental examination prior to initiation of therapy
Siltuximab	Pruritis, weight gain, hyperuricemia, infection, GI perforation	CBC, uric acid levels, cytokine release reactions	Do not administer live vaccines while being treated with siltuximab HIV-positive and HHV-8-positive patients excluded from the clinical trials
Cytokines			
Interferon-alfa	Flu-like symptoms; fatigue; serious or fatal neuropsychiatric (eg, depression and suicide); autoimmune, ischemic, and infectious complications; pulmonary symptoms; thyroid disorders; hyperglycemia	Neurological evaluation, infection, pulmonary and cardiac monitoring, blood glucose, thyroid function	Fatigue and flu-like symptoms tend to decrease with duration of therapy Exists in a pegylated form that has a prolonged half-life
Interleukin-2	Flu-like syndrome: fevers, chills, malaise; vascular or capillary leak syndrome: hypotension, pulmonary and peripheral edema; nausea and vomiting; diarrhea; nephrotoxicity; myelosuppression (thrombocytopenia and leukopenia); bacterial infections; CNS: somnolence and confusion; arrhythmias; rash; itching	Intense monitoring required, electrolytes, liver function, renal function, CBC, thallium stress test, pulmonary function tests, cardiac monitoring during interleukin-2 administration, BP, HR	Vasopressor support and fluid resuscitation may be necessary during treatment because of hypotension Pulmonary edema can be managed with cautious use of diuretics; short courses of albumin may also be beneficial Itching may respond to treatment with antihistamines; emollient skin creams or occlusive agents are effective for dry, peeling skin Avoid corticosteroids because they may counteract the antitumor effects of interleukin-2 Patients on beta-blockers will need to be tapered off before initiation of aldesleukin
Enzymes			
L-asparaginase	Hypersensitivity reactions (fever, hypotension, rash, dyspnea in 25%); much lower risk with polyethylene glycol form and asparaginase *E. chrysanthemi;* pancreatitis; decreased synthesis of proteins, clotting factors; lethargy	Pancreatic enzymes; liver function; coagulation parameters (fibrinogen, PT, PTT); hypersensitivity reactions; blood glucose; CBC	Skin test before administration of *E. coli*–derived asparaginase; anaphylaxis precautions Pegaspargase complexes with polyethylene glycol to decrease immunogenicity and prolong duration of action Asparaginase *E. chrysanthemi*was developed for patients who have developed hypersensitivity to *E. coli*–derived asparaginase
Fusion Proteins			
Denileukin diftitox	Pyrexia, nausea, fatigue, rigors, vomiting, diarrhea, headache, peripheral edema, cough, dyspnea, pruritus, infusion reactions, capillary leak syndrome, loss of visual acuity	Infusion reactions, fluid status, BP, serum albumin, ophthalmologic evaluation	Serum albumin should be ≥3 g/dL (30 g/L) before initiating therapy Premedicate with an antihistamine and acetaminophen
Moxetumomab pasudotox	Renal toxicity, infusion-related reactions, electrolyte abnormalities, hemolytic uremic syndrome	Renal function, electrolytes, infusion reactions	Premedicate with acetaminophen, an antihistamine, and an H_2 antagonist

			Consider low-dose aspirin on days 1-8 of each cycle
Ziv-aflibercept	Neutropenia, diarrhea, proteinuria, increases in liver enzymes, stomatitis, fatigue, thrombocytopenia, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, increased serum creatinine, headache, hemorrhage, GI perforation, compromised wound healing, arterial thromboembolic events, fistula formation	BP, urine protein, signs and symptoms of hemorrhage, CBC, liver function, renal function	Should be held at least 4 weeks before elective surgery and restarted at least 4 weeks after major surgery and until the surgical wound is fully healed
Vaccines			
Sipuleucel-T	Infusion reactions; chills; fatigue; back pain; nausea; joint ache; headache; thromboembolic events have occurred	Infusion reaction	Physicians and patients must be registered Premedicate with an antihistamine and acetaminophen For autologous use only
Talimogene laherparepvec	Fatigue, chills, pyrexia, nausea, influenza-like illness, injection-site pain, cellulitis, risk of herpetic infection	Herpetic infections, injection-site complications, immune-mediated events	Administered directly into the cutaneous, subcutaneous, and/or nodal lesion(s) Precautions for accidental exposure of healthcare works and close contacts Acyclovir and other antiviral medications may interfere with the efficacy of talimogene leherparepvec
Chimeric Antigen Receptor Therapies			
Axicabtagene ciloleucel and tisagenlecleucel	Hypersensitivity, myelosuppression, hypogammaglobulinemia, secondary malignancies, neurologic toxicities, cytokine release syndrome	CBC, infection, cytokine release syndrome	For autologous use only REMS program to mitigate the risk of cytokine release syndrome and neurological toxicities

[a]Only approximate guidelines can be given. Consult current references before dispensing as not all dose adjustments and monitoring parameters are provided in the table.

5-FU, fluorouracil; AML, acute myeloid leukemia; ATRA, all-trans-retinoic acid; BP, blood pressure; CBC, complete blood count; CHF, congestive heart failure; CMV, cytomegalovirus; CNS, central nervous system; CPK, creatinine phosphokinase; CYP, cytochrome P450 isoenzyme; DPD, dihydropyrimidine dehydrogenase; ECG, electrocardiogram; GI, gastrointestinal; H_1 and H_2, histamine 1 and 2; HBV, hepatitis B virus; HDAC, histone deacetylase; HFSR, hand-foot skin reaction; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; HR, heart rate; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; ILD, interstitial lung disease; IM, intramuscular; INR, international normalized ration; IT, intrathecal; IV, intravenous; LVEF, left ventricular ejection fraction; MAOI, monoamine oxidase inhibitor; MDS, myelodysplastic syndrome; MI, myocardial infarction; mTOR, mammalian target of rapamycin; MUGA, multigated acquisition scan; NSAID, nonsteroidal anti-inflammatory drug; PFT, pulmonary function tests; Pgp, P-glycoprotein; PJP, Pneumocystis jiroveci pneumonia; PPI, proton pump inhibitor; PRES, posterior reversible encephalopathy syndrome; PT, prothrombin time; PTT, partial thromboplastin time; REMS, risk evaluation and mitigation strategy; Scr, serum creatinine; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TLS, tumor lysis syndrome; UGT1A1, Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase).