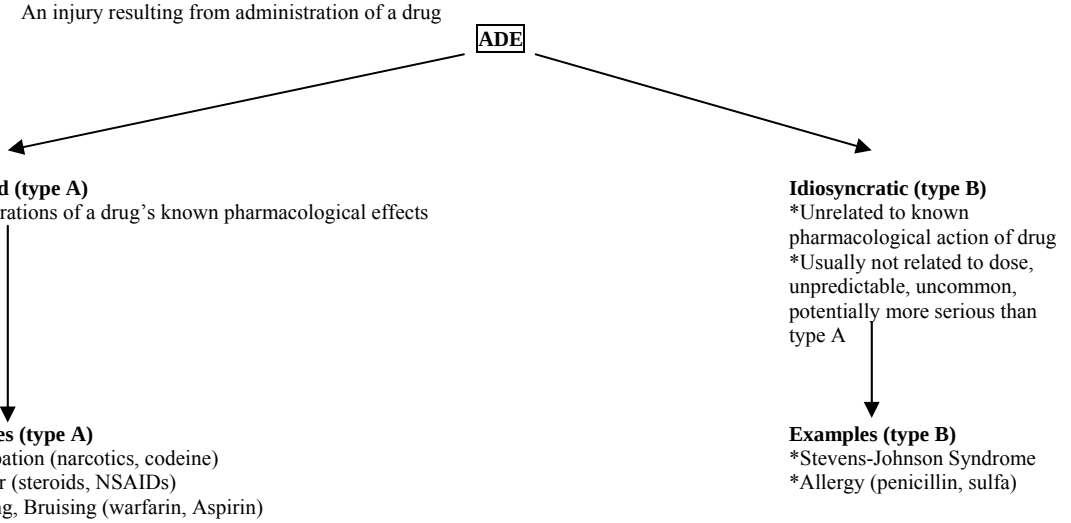
ADVERSE DRUG REACTIONS
Adapted from Wil Edwards, PharmD

Report Adverse Drug Reactions to FDA via Medwatch: www.fda.gov/medwatch

Definitions

Adverse Drug Reaction:
- Any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy

Adverse Drug Event:
- An injury resulting from administration of a drug



Variables

- Age
- Sex
- Genetics
- Concurrent diseases (diabetes, renal failure, cirrhosis)
- Drug route, formulation, duration

Drug-Induced Diseases

Pancreatitis
- Ethanol (heavy and prolonged)
- Estrogens
- ACE Inhibitors
- Statins
- Valproic Acid
- Oncological agents

Nephrotoxicity
- Aminoglycosides
- NSAIDs
- Amphotericin B
- Oncology agents (cisplatin)

Pulmonary
- Amiodarone (pulmonary fibrosis)
- β-blockers (bronchial constriction)
- Bleomycin (pulmonary fibrosis)

Drug-Induced Photosensitivity
- Antibiotics (tetracyclines, sulfa drugs, quinolones)
- Cardiovascular (thiazides, amiodarone)
- Antipsychotics (phenothiazines e.g. prochlorperazine)
- Analgesic Agents (NSAIDS)
- Skin Agents (Retin-A, Accutane 5%-10%)

Drug-Discoloration of Urine
- Yellow-Brown (nitrofurantoin)
- Yellow-Orange (phenazopyridine)
- Red-Orange (phenazopyridine)
- Red or Pink (phenazopyridine, doxorubicin, rifampin)
- Red-Brown (heparin/warfarin—hematuria), phenazopyridine)

Orthostatic Hypotension
- α-blockers
- β-blockers
- Nitrates
- Phosphodiesterase Inhibitors
- ACE Inhibitors

- Antidepressants

ALLERGIC RHINITIS
Adapted from Terri Levien, PharmD

Treatment Guidelines

- University of Michigan Health System Clinical Guideline. Allergic Rhinitis in Adults and Children. **http://cme.med.umich.edu/iCME/allergicrhinitis/Defaults.asp**
- The Allergy Report: Science Based Findings on the Diagnosis and Treatment of Allergic Disorders. American Academy of Allergy, Asthma, and Immunology. **http://www.theallergyreport.org/**
- Diagnosis and Management of Rhinitis: Parameter Documents of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 1998 November 81(5): 463-518.

Most Common Symptoms

- Seasonal: sneezing, rhinorrhea, itching
- Perennial: congestion, post-nasal drip, cough

Classification

- Intermittent: symptoms no more than 4 days per week or less than 4 weeks at a time
- Persistent: symptoms more than 4 days per week AND for more than 4 weeks at a time

- Mild: Normal sleep AND no impairment of daily activities AND normal work/school function AND no troublesome symptoms
- Moderate/Severe: abnormal sleep OR impairment of daily activities OR abnormal work/school function OR troublesome symptoms

Non-pharmacological Management

- Acarosan (benzyl benzoate) kills dust mites in carpeting
- HEPA filters
- Avoid allergens

Pharmacological Management

- Systemic Antihistamines
  - Role: first-line therapy for sneezing, rhinorrhea, itching, conjunctivitis
  - Best results when taken regularly
- Nasal Corticosteroids
  - MOA: decrease inflammation
  - Indications: sneezing, rhinorrhea, itching, congestion, cough, conjunctivitis
  - Role: First-line therapy, especially when inflammatory component
  - Onset: 4-12 hrs for initial relief, but 2 weeks or longer for maximum benefit
  - **Fluticasone and mometasone have lowest bioavailability = lower potential for systemic side effects
  - SE = stinging, dryness, sneezing, bleeding
- Leukotriene Antagonists
  - Indication: seasonal allergic rhinitis in patients <2 years—relieves congestion, rhinorrhea, sneezing, may reduce ocular symptoms
  - Inferior to oral antihistamines and nasal steroids
  - SE = headache, upper respiratory infection
  - Give HS if using for asthma as well, otherwise can give anytime
- Systemic Decongestants
  - MOA: constrict nasal blood vessels via α-agonism
  - Precautions: closed-angle glaucoma, hypertension, cardiovascular disease, urinary retention/BPH, MAOI, hyperthyroidism, diabetes
  - SE = hypertension, restlessness, tremor, insomnia, headache, urinary retention, palpitations
- Topical Decongestants
  - More rapid and effective than systemic decongestants with fewer side effects
  - SE = rebound congestion occurring after ~5-10 days of therapy
  - **Limit use to 3 to 5 days
- Nasal Mast Cell Stabilizers
  - MOA: inhibits mast cell degranulation
  - Role: prevention of nasal symptoms before exposure to allergen
  - Effects last 4-8 hrs after administration
- Intranasal Antihistamines
  - Role: sneezing, rhinorrhea, nasal itching
  - SE: bitter taste, sedation
- Intranasal Ipratropium
  - Role: rhinorrhea only
  - SE: nasal dryness, bleeding
- Immunotherapy
  - When to consider: allergen exposure is unavoidable, allergic response occurs all year or most of the year, allergies are difficult to treat pharmacologically, AND there is the potential for significant benefit
  - Process: start with 1-2 weekly allergen injections, then taper to once monthly for 3-5 years
  - Efficacy: relieves symptoms for up to 3 years after discontinuing injections

Preferred Agents

- Intermittent mild AR: antihistamine, decongestant
- Intermittent moderate/severe AR: antihistamine, decongestant, intranasal corticosteroids, antileukotriene
- Persistent mild AR: antihistamine, decongestant, intranasal corticosteroid, cromolyn
- Persistent moderate/severe AR: intranasal corticosteroid 1st, then decongestant, nasal ipratropium, antihistamine as needed

Specific Medications to Treat Allergic Rhinitis

Drug Name		Ind.	Dose	
Generic	**Trade**		**Adults**	**Children**
Oral nonsedating antihistamines				
Cetirizine HCl	Zyrtec 5 & 10 mg tabs Zyrtec Syrup 1 mg/mL	a, b, c	5 - 10mg QD	12 yrs and older: same as adult 6-11 yrs: 5 - 10mg QD 2-5 yrs: start with 2.5mg QD; may increase to 5mg QD or 2.5mg BID
Desloratadine	Clarinex 5 mg tablets Clarinex 5 mg Reditabs	a, b, c	5mg QD	12 yrs and older: same as adult
Fexofenadine HCl	Allegra 60 mg capsules 30, 60, 180 mg tablets	a, c	60mg BID OR 180mg QD	12 yrs and older: same as adult 6-11 yrs: 30 mg BID
Loratadine (OTC)	Claritin Tablets 10 mg Claritin Reditabs 10 mg Claritin Syrup 1 mg/mL generics	a, c	10mg QD	12 yr and older: same as adult 6-11 yrs: 10mg QD 2-5 yrs: 5mg QD
Oral nonsedating antihistamine-decongestant combinations				
Fexofenadine/Pseudoephedrine HCl	Allegra-D	a	1 tablet (60mg/120mg) BID	12 yrs and older: same as adult
Loratadine/Pseudoephedrine HCl	Claritin-D 12 hour Claritin-D 24 hour	a	1 tablet (5mg/120mg) BID 1 tablet (10mg/240mg) QD	12 yrs and older: same as adult
Oral less sedating antihistamine-decongestant combinations				
Acrivastine/Pseudoephedrine HCl	Semprex-D Cap	a	1 capsule (8mg/60mg) q4-6h	12 yrs and older: same as adult
Oral sedating antihistamines				
Chlropheniramine (OTC)	Chlor-Trimeton, others Chewable tablets, tablets, extended release tablets	a, b, d	4mg q4-6h 8mg extended release q8-12h 12mg extended release q12h 16mg extended release (Efidac) q24h	12 yrs and older: same as adult 6-11 yrs: 2 mg q4-6h OR 8 mg extended release HS
Diphenhydramine (OTC)	Benadryl, tablets, capsules, chewable tablets, liquids	a, b, c, d	25-50mg q4-6h	12 yrs and older: same as adult 6-11 yrs: 12.5-25 mg q4-6 h
Intranasal antihistamines				
Azelastine HCI	Astelin Nasal Spray	a, d	2 sprays (137 mcg/spray) each nostril BID	12 yrs and older: same as adult 5-11 yrs: 1 spray/nostril BID
Oral decongestants				
Pseudoephedrine (OTC)	Various, drops 7.5 mg/0.8 mL, liquids 3 & 6 mg/mL, 30 & 60 mg	e	60 mg q4-6h OR 120 mg extended release tablet q12h OR 240 mg	12 yrs and older: same as adult 6-11 yrs: 30 mg q4-6h (max 120 mg/24 hrs)
Intranasal decongestants*				
Naphazoline (OTC)	Privine 0.05%	e	2 drops or sprays per nostril q4-6 h	12 yrs and older: same as adult
Oxymetazoline (OTC)	Afrin, Allerest, Dristan, others 0.025% & 0.05%	e	2 or 3 drops or sprays each nostril BID	6 yrs and older: same as adult 2-5 yrs: 2 or 3 drops (0.025%) BID
Phenylephrine (OTC)	Neo-Synephrine, others 0.125%,0.16%,0.25%, 0.5%, & 1 %	e	2 or 3 drops or sprays each nostril; may repeat q3-4h (0.25% &	12 yrs and older: same as adult 6-11 yrs: 2 or 3 drops or sprays (0.25%) in each nostril; may repeat after 3-4 hrs
Tetrahydrozoline	Tyzine 0.05% & 0.1%	e	2-4 drops (0.1%) each nostril q3-4h prn OR 3-4 sprays (0.1 %) each	6 yrs and older: same as adult 2-6 yrs: 2 or 3 drops (0.05%) each nostril q4-6h prn
Xylometazoline (OTC)	Otrivin 0.05% & 0.1 %	e	2-3 drops or sprays (0.1 %) each nostril q8-10h	12 yrs and older: same as adult 2 - 11 yrs: 2 or 3 drops (0.05%) each nostril q8-10h
Intranasal mast cell stabilizers				
Cromolyn Sodium (OTC)	Nasalcrom	a, b	I spray (5.2 mg/spray) each nostril 3-6 times daily at regular 4-6 hr	6 yrs and older: same as adult
Intranasal anticholinergics				
Ipratropium bromide	Atrovent Nasal Spray 0.03%, generics	f	2 sprays (21 meg/spray) each nostril 2-3 times/day	6 yrs and older: same as adult
Intranasal corticosteroids				

Beclomethasone dipropionate	Beconase, Vancenase	a, b, d, g	1 inhalation (42 mcg) each nostril 2-4 times/day; often 1 inhalation/nostril TID	12 yrs and older: same as adult 6 - 11 yrs: 1 inhalation/nostril TID
	Beconase AQ	a, b, d, g	1-2 sprays (42 mcg/spray) each nostril BID	12 yrs and older: same as adult 6 - 11 yrs: 1 spray/nostril BID; may increase to 2 sprays/nostril if needed
	Vancenase AQ 84 mcg	a, b, d, g	1-2 sprays (84 mcg/spray) in each nostril QD	6 yrs and older: same as adult
Budesonide	Rhinocort Nasal Inhaler	a, b	2 inhalations (32 mcg/actuation) each nostril 2 times/day OR	6 yrs and older: same as adult
	Rhinocort Aqua Nasal Spray	a, b	start at 1 spray (32 mcg/spray) per nostril QD; may increase to 4	12 yrs and older: same as adult 6 - 11 yrs: start at 1 spray/nostril QD; may increase to 2 sprays/nostril QD
Flunisolide	Nasalide, Nasarel	a, b	2 sprays (25 meg/spray) per nostril 2 times/day may increase to 2	14 yrs and older: same as adult 6 - 13 yrs: 1 spray/nostril TID OR 2 sprays/nostril BID
Fluticasone propionate	Flonase Nasal Spray	a, b	2 sprays (50 mcg/spray) each nostril QD OR I spray/nostril BID	4 yrs and older: start 1 spray/nostril QD; may increase to 2 sprays/nostril QD
Mometasone furoate monohydrate	Nasonex Nasal Spray	a, b	2 sprays (50 mcg/spray) each nostril QD	12 yrs and older: same as adult 3 - 11 yrs: 1 spray/nostril QD
Triamcinolone acetonide	Nasacort Nasal Inhaler	a, b	2 inhalations (55 mcg/actuation) each nostril QD	12 yrs and older: same as adult 6 - 11 yrs: 2 sprays/nostril QD
	Nasacort AQ Nasal Spray	a, b	2 sprays (55 mcg/spray) each nostril QD	12 yrs and older: same as adult 6 - 11 yrs: 1 spray/nostril QD; may increase to 2 sprays/nostril QD

Indications: (a) seasonal allergic rhinitis; (b) perennial allergic rhinitis; (c) chronic idiopathic urticaria; (d) vasomotor rhinitis; (e) nasal congestion due to common cold, allergies, or sinusitis (f) rhinorrhea associated with allergic or nonallergic perennial rhinitis; (g) prevent recurrence of nasal polyps following surgical removal

*Limit intranasal therapy to 3-5 days

Specific Ophthalmic Medications to Treat Allergic Conjunctivitis

Drug Name		Ind.	Dose	
Generic	**Trade**		**Adults**	**Children**
Mast cell stabilizers				
Cromolyn	Crolom 4%, generics	a, b, c	1-2 drops 4-6 times QD	4 yrs and older: same as adult
Lodoxamide tromethamine	Alomide 0.1%	a, b, c	1-2 drops QID	3 yrs and older: same as adult
Nedocromil sodium	Alocril 2%	d	1-2 drops BID	3 yrs and older: same as adult
Pemirolast	Alamast 0.1%	d	1-2 drops QID	3 yrs and older: same as adult
Antihistamines				
Emedastinde difumarate	Emadine 0.05%	d	1 drop up to 4 times/day	3 yrs and older: same as adult
Levocabastine HCl	Livostin 0.05%	d	1 drop QID	12 yrs and older: same as adult
Antihistamine/mast cell stabilizer				
Azelastine HCl	Optivar	d	1 drop BID	3 yrs and older: same as adult
Epinastine HCl	Elestat 0.05%	d	1 drop BID	3 yrs and older: same as adult
Ketotifen fumarate	Zaditor 0.025%	d	1 drop q8-12 hrs	3 yrs and older: same as adult
Olopatadine HCl	Patanol 0.1%	d	1-2 drops BID; 6-8 hr interval	3 yrs and older: same as adult
Decongestants				
Naphazoline (OTC)	Allerest, others, 0.012%, 0.02%, 0.03%, 0.1% (Rx)	e	1-2 drops q3-4 hrs, to QID	6 yrs and older: same as adult
Tetrahydrozoline (OTC)	Murine Plus, Visine, others, 0.05%	e	1-2 drops QID	6 yrs and older: same as adult
Decongestants/Antihistamines				
Antazoline/naphazoline (OTC)	Vasocon-A	d	1-2 drops up to QID	6 yrs and older: same as adult
Pheniramine/naphazoline (OTC)	Naphcon-A, Opcon-A, Visine-A	d	1-2 drops up to QID	6 yrs and older: same as adult
NSAIDs				
Ketorolac tromethamine 0.5%	Acular	d, f	1 drop QID	12 yrs and older: same as adult

Corticosteroids				
Dexamethasone	Decadron, generics	g	1 drop TID-QID	
Fluorometholone	FML, generics	g	1-2 drops BID-QID	2 yrs and older: same as adult
Loteprednol etabonate	Alrex 0.2% Lotemax 0.5%	d g	1 drop QID	
Medrysone	HMS	b,d,h,i	1 drop up to q4 hrs	
Prednisolone	Pred Forte, generics	g	1-2 drops BID-QID	

Indications: (a) vernal keratoconjunctivitis; (b) vernal conjunctivitis; (c) vernal keratitis; (d) allergic conjunctivitis; (e) redness due to minor irritation; (f) postoperative inflammation following cataract extraction; (g) steroid responsive inflammatory conditions; (h) episcleritis; (i) epinephrine sensitivity

ANEMIAS
Adapted from Carol Lyn Vanevenhoven, PharmD

Characteristics of Different Anemias

	RBC	HGB	HCT	MCV	MCH	MCHC	Retic.	Common Lab Tests with Anemias (Normal Values Indicated)
Iron Deficiency Anemia (microcytic)	⇓	⇓	⇓	⇓	⇓	⇓	⇒ ⇓	Red Blood Cells: M 4.3-5.9 x10^6/mm^3 F 3.5-5.0 x10^6/mm^3; Hemoglobin: M 14-18 g/dl F 11.5-15.5 g/dl; Hematocrit: M 39-49% F 33-43%; Mean Cell Volume: 76-96 fL; Mean Cell Hemoglobin: 27-33 pg; Mean Cell Hemoglobin Concentration: 33-37 g/dL; Reticulocyte count: 0.5-2.5% (has to be corrected if the person has lost a lot of blood b/c they will have a larger % of new red blood cells); Serum Iron: M 65-175 μg/dL F 50-170 μg/dL (draw in morning); Total Iron Binding Capacity: 250-400 μg/dL; Serum Ferritin: 15-200 ng/ml; Percent Transferrin Saturation: 33%; Folic Acid: 1.8 -16 ng/mL; B_{12}: 100-900 pg/mL (varies with assay); Schilling Test detects presence of intrinsic factor; Coombs Test detects anti-RBC antibodies; Stool sample of occult blood
Folate Deficiency Anemia (macrocytic)	⇓	⇓	⇓	⇑	⇑	⇒	⇒ ⇓	
B12 Deficiency anemia (macrocytic)	⇓	⇓	⇓	⇑	⇑	⇒	⇒ ⇓	

Iron Deficiency Anemia

- Causes
  - Diet
  - Chronic Illness
  - Inflammatory Conditions
  - Malabsorptive Syndromes
  - Pregnancy
  - Blood loss
  - Endurance sports
- Signs and Symptoms
  - Easy fatigability
  - Tachycardia/palpitations
  - Koilonychia (spooning of fingernails)
  - Glossitis (smooth tongue)
  - Pica (crave ice, ashes, clay, etc)
  - Angular cheilitis (chapping at corners of mouth)
- Treatment **symptoms should resolve within 2 months, iron stores will be replenished in the next 4 months
  - Dietary supplementation: meat, fish, poultry
  - Ferrous salts: 100-200 mg elemental iron/day divided BID-TID for 3-6 months
    - Best absorption on empty stomach or with orange juice (something acidic)
    - Titrate slowly e.g. 1 tab QD X 1 week, 1 tab BID X 1 week, then 1 tab TID
    - Dilute liquid formulations in water/juice and drink through straw to avoid staining teeth
    - **Keep iron out of reach of children
    - SE = GI cramping, constipation, black stools
    - Hemoglobin should increase 1 gm/week of therapy while reticulocytes will increase between day 4-7 and peak on day 10

Oral Iron Salt	Dosage Form	Elemental Iron Content
Ferrous sulfate **cheapest	300 mg tab 325 mg tab	60 mg 65 mg
Ferrous sulfate exsiccated	200 mg tab	65 mg
Ferrous gluconate	300 mg tab 325 mg tab	37 mg 39 mg
Ferrous fumarate	100 mg tab	33 mg
Iron polysaccharide (Niferex) **tolerated best	150 mg cap 50 mg tab	150 mg 50 mg

  - Parenteral Iron (useful if no oral meds, malabsorption, high-dose antacid therapy)
    - Iron dextran (DexFerrum®, InFed®; elemental iron = 50 mg/ml)
      - Usual dose: 100 mg IV daily over 1-6 hrs (dilute in 250-1000 ml normal saline)
      - May give up to 1000 mg/dose—not possible with other IV irons
      - Can give IM using Z-track method
      - **Must give test dose: 25 mg IV over 30 min; wait 1 hr for anaphylaxis
      - SE = hypotension, headache, flushing, fatigue
    - Ferric gluconate (Ferrlecit®; elemental iron = 12.5 mg/ml)
      - Usual dose: 125 mg in 100 ml NS over 1 hour

        - Larger doses and IM dosing not recommended
        - Twice as expensive as iron dextran
        - Test dose not required
        - SE = hypotension, fatigue, flushing, lightheadedness
        - **Avoid in neonates (contains benzoyl alcohol)
    - Iron sucrose (Venofer®; elemental iron = 20 mg/ml)
        - Usual dose: 100 mg in 100 ml NS IV over 15 min 1-3 times/week
        - Larger doses and IM dosing not recommended
        - Test dose not required
        - Most expensive IV iron
        - SE = hypotension, cramps, diarrhea, headache, nausea, vomiting

Vitamin B_{12} Deficiency Anemia

- Causes
    - Inadequate intake (strict vegetarians)
    - Decreased intrinsic factor production (pernicious anemia, gastrectomy, congenital IF dysfunction)
    - Intestinal resection
    - Competition for cobalamin (bacterial overgrowth, fish tapeworm)
    - Drugs (colchicines, neomycin)
    - Decreased transcobalamin
- Signs and Symptoms
    - Extremity paresthesia (glove and stocking)
    - Romberg sign (lose balance when eyes closed)
    - Babinski sign (big toe reflex not coordinated with other toes)
    - Dementia/psychosis
    - Sore tongue (smooth, beefy red)
- Treatment **patient should regain strength in 1-3 days, anemia should resolve within 4 weeks
    - Oral: 1000-2000 mcg B_{12} QD
    - IM: 100 mcg/day X 2-3 weeks, 800-1000 mcg/day X 1-2 weeks, then 100 mcg monthly for life
    - **Treatment only stops progression of symptoms—usually doesn't reverse damage

Folic Acid Deficiency Anemia

- Causes
    - Inadequate Intake (alcoholics, teenagers, infants)
    - Increased Demand (pregnancy, infancy, malignancy, hemodialysis)
    - Malabsorption (Crohn's, phenytoin, barbiturates, celiac disease)
    - Impaired metabolism (alcohol, methotrexate, triamterene, trimethoprim, oral contraceptives, sulfasalazine)
- Signs and Symptoms = same as B_{12} deficiency anemia
- Treatment
    - Folic acid 0.5 – 5 mg PO QD for ~4 months
    - **Always use B_{12} concomitantly
    - Dietary sources = green leafy veggies, citrus fruits, yeast, mushrooms, liver, bread
    - HCT should increase within 2 weeks and normalize within 2 months

Anemia of Chronic Disease

- Causes: infections, inflammatory diseases, cancer
- Treatment
    - **Anemia usually resolves once underlying disorder is corrected (if possible)
    - Erythropoietin (Epogen®, Procrit®)
        - Renal failure: 50-100 units/kg 3 times/week
        - Cancer: 150 units/kg 3 times/week (titrate to 300 units/kg); may use 40,000-60,000 units weekly
        - HIV: 100 units/kg 3 times/week (titrate to 300 units/kg)
        - Surgery: 300 units/day X 10 days before and 4 days after or 600 units/kg weekly X 3 weeks before and 1 dose after surgery
        - **Must give supplemental iron for EPO to work
    - Aranesp®
        - Dose: 0.45 mcg/kg
        - Like EPO, but has longer half-life
    - RBC Transfusions: best to limit use

APPETITE STIMULANTS
Adapted from Louise Achey, PharmD

Megestrol Suspension 400-800 mg daily

- Indicated for AIDS wasting syndrome
- **Suspension is not equivalent to tablets
- May suppress HPA axis with chronic use—consider glucocorticoid supplementation

Dronabinol 2.5-10 mg BID with lunch and dinner

- Avoid in patients with history of schizophrenia
- Kinetics = lipid soluble so increased absorption with high fat meal, excreted in breast milk, long half-life (~24 hrs)
- SE = drowsiness, confusion, dry mouth, depression

Off-label Appetite Stimulants

- Atypical antipsychotics
- Tricyclic antidepressants

ASTHMA
Adapted from Greg Matsuura, PharmD, BCPS

Clinical Guidelines = National Asthma Education and Prevention Program Expert Panel Report
http://www.nhlbi.nih.gov/guidelines/asthma/index.htm

Measuring Lung Function

- Peak flow meters
  - Measure maximum forced expiratory flow rate with fully inflated lungs
  - Measures airway obstruction—not specific for asthma
  - Personal best
    - Patient must be stabilized with consistent therapy
    - Usually obtained in early afternoon
    - Personal best estimated after peak expiratory flow rate recorded for 2-3 week period
    - Reassess every 6 months in children because growth affects personal best
  - Monitoring with peak flow meters
    - 80-100% of personal best = Green Zone
    - 50-79% of personal best = Yellow Zone
    - <50% of personal best = Red Zone
    - Use best reading after three tries
- Spirometry
  - Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1)
  - More consistent evaluation than peak expiratory flow rate
  - FEV_1/FVC ratio <0.7 suggests expiratory disease

Drug Therapy for Asthma

- Short-acting β_2-agonists
  - Use: acute exacerbation, exercise-induced asthma, and temporary bronchoprotection
  - Potential Adverse Effects
    - Tachycardia
    - Headache
    - Nervousness
    - Arrhythmia
    - Skeletal muscle tremor
    - Hyperglycemia
    - CNS stimulation
    - Hypertension/hypotension
    - Hypokalemia
    - Angina
    - Insomnia
    - Increased lactic acid
    - Paradoxical bronchoconstriction

Inhaled Short-Acting β-agonists

Generic (Brand)	Dosage Forms Available	Adult Dose (children>12)	Pediatric Dose
Albuterol (Proventil, Ventolin)	MDI: 90 mcg/puff	2 puffs q4-6 hrs	1-2 puffs q4-6 hrs
	Nebulizer: 5 mg/ml and 2.5 mg/3ml solutions	1.25-5 mg q4-8 hrs (diluted)	0.05 mg/kg q4-6 hrs (children >2)
	Oral: 4mg tablet and 2mg/5ml oral syrup	2-4 mg/dose 3-4 times/day	0.1-0.2 mg/kg/dose PO TID (2-6yo; max of 12 mg/day) 2 mg/dose 3-4 times/day (6-12 yo)
Levalbuterol (Xopenex)	Nebulizer: 0.63 mg/3ml and 1.25 mg/3ml solutions	0.63-2.5 mg q4-8 hrs	0.25 mg/kg (6-11 yo; max of 1.25 mg q4-8 hrs)
Bitolterol (Tornalate)	Nebulizer: 2 mg/ml solution	0.5-3.5 mg q4-8 hrs (diluted; max 8mg/day)	Not established
	MDI: 370 mcg/puff	2 puffs q4-6 hrs	
Metaproterenol (Alupent)	MDI: 650 mcg/puff	2-3 puffs q3-4 hrs (max 12 puffs/day)	Not established
	Nebulizer: 50 mg/ml solution	0.2-0.3 ml q4-6 hrs (diluted)	0.01 ml/kg q4-6 hrs (6-12 yo)
Isoetharine (Bronchometer)	Nebulizer: 10 mg/ml solution	4 inhalations (diluted)	Not established
Pirbuterol (Maxair)	MDI: 200 mcg/puff	2 puffs q4-6 hrs	Not established <12 yo

- Long-acting β_2-agonists
  - Use: long-term inhaler, exercise-induced asthma
  - Dry Powder Inhalers:
    - Salmeterol (Serevent) = 1 inhalation BID
    - Formoterol (Foradil) = 1 cap q12 hrs
- Anticholinergics—ipratropium bromide (Atrovent)
  - Use: acute bronchospasm in addition to short-acting β_2-agonist
  - Does not block exercise-induced asthma and has slower onset than short-acting β_2-agonists
  - Dosage forms
    - Metered-dose inhaler 2-4 puffs QID
    - Nebulizer: 500 mcg q4-6 hrs
- Theophylline
  - Use: long-term management and prevention of symptoms

- Dose: 10 mg/kg/day up to 300 mg max starting dose
  - Target serum concentration 5-15 mcg/ml
- Adverse effects
  - Insomnia
  - GI upset
  - Tachycardia
  - Hyperglycemia
  - Hypokalemia
  - Seizures
  - Hematemesis

- Systemic Corticosteroids
  - Use: chronic management, relieve acute exacerbations, hospitalizations

Relative Potencies of Systemic Corticosteroids

Hydrocortisone	1
Prednisone	4
Methylprednisolone	5
Dexamethasone	25

  - Indications
    - Chronic Management: prednisone (or equivalent) 7.5-60 mg qd or qod
    - Acute exacerbations (outpatient): prednisone 1-2 mg/kg/day in 1-2 doses for 3-10 days
    - Hospitalizations: prednisone 120-180 mg in 3-4 divided doses for 48 hrs, then 60-80 mg/day until patient at 70% of predicted PEF
- Inhaled corticosteroids
  - Use: persistent asthma to decrease inflammation/remodeling and frequency of attacks
  - Counseling: rinse mouth after use, does not abort existing attacks, SE = cough, thrush, voice change
- Cromolyn sodium or Nedocromil
  - Not used much because no spirometry improvement—even in children
- Leukotriene Inhibitors (zafirlukast, montelukast, zileuton)
  - Use: long-term control (esp for mild symptoms or children), potentially steroid-sparing
  - Dose:
    - Montelukast: 10 mg PO QD (peds 5 mg PO QD if 6-14 yo; 4 mg PO QD if 2-5 yo)
    - Zafirlukast: 20 mg PO BID on empty stomach (peds 10 mg PO BID if 7-11 yo)
    - Zileuton: 600 mg PO QID (not used much because QID and increases LFTs)
- Omalizumab
  - Use: moderate to severe asthma in addition to existing treatment, in patients over 12 yo and positive reactivity to perennial allergen
  - Mechanism: binds IgE, which prevents activation of mast cells and basophils
  - Dose:150-375 mg SQ every 2-4 weeks (based on weight and serum IgE)

Classification of Asthma Severity: Clinical features before treatment.

	Symptoms	Lung Function
Step 1 Mild intermittent	Daytime ≤ 2 times/wk Asymptomatic between episodes Exacerbation brief (few hrs to days) Nocturnal episodes ≤ 2 times.mo	FEV_1 or PEF ≥ 80% PEF variability < 20%
Step 2 Mild persistent	Daytime > times/wk but < 1 time/day Exacerbations may effect activity Nocturnal episodes > 2 times/mo	FEV_1 or PEF ≥ 80% PEF variability < 20% to 30%
Step 3 Mod persistent	Daily symptoms Daily inhaled short-acting β_2-agonists, ADL effected Exacerbations >2times/wk	FEV_1 or PEF > 60% to < 80% PEF variability > 30%
Step 4 Severe Persistent	Continual symptoms Limited ADL's, Frequent exacerbations Frequent nocturnal episodes	FEV_1 or PEF ≤ 60% PEF variability >30%

FEV_1 = forced expiratory volume in 1 second PEF = peak expiratory flow rate

Step down: Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.
Step up: If control is not maintained, consider step up. First: review patient medication technique, adherence, and environmental control.

A STEPWISE APPROACH TO ASTHMA DRUG THERAPY AND EDUCATION

Long Term Control	Quick Relief	Education
Step 1 • *None needed*	• Short-acting bronchodilator: **inhaled ß2-agonists** prn for symptoms.	•Inhaler/spacer holding chamber technique •Roles of medications •Self management plan •Action plan for when and how to take rescue actions •Environmental control to avoid allergens and irritants

Step 2 ***Daily medication:*** • **Anti-inflammatory:** either **inhaled corticosteroid (low-doses) or cromolyn, or nedocromil.** Sustained release theophylline to serum concentration of 5-15 mcg/ml is an alternative. Leukotriene modifiers considered for patients ≥ 12 years.	• Short-acting bronchodilator: **Inhaled ß2-agonists** PRN symptoms.	• Step 1 actions plus: • Teach self monitoring • Refer to group education if available • Review and update self management plan
Step 3 ***Daily medication:*** Either • **Anti-inflammatory: inhaled corticosteroid (medium dose) - OR-** • **Inhaled corticosteroid (low-medium dose)**, and add a long-acting bronchodilator, especially for nighttime symptoms: either **long-acting inhaled ß2-agonist**, sustained release theophylline, or long acting ß2-agonist tablets. If needed • Anti-inflammatory: **inhaled corticosteroids (medium-high dose)** AND • **Long-acting bronchodilator**, as stated above.	• Short-acting bronchodilator: **Inhaled ß2-agonists** as needed for symptoms.	• Step 1 actions plus: • Teach self monitoring • Refer to group education if available • Review and update self management plan
Step 4 ***Daily medications:*** • **Anti-inflammatory: inhaled corticosteroid (high dose) –AND-** • Long-acting bronchodilator: **either long-acting inhaled ß2-agonist**, sustained release theophylline, and/or long-acting ß2-agonist tablets or syrup -AND- • Corticosteroid tablets or syrup long term (2mg/kg/day, NTE 60mg/day).	• Short-acting bronchodilator: **inhaled ß2-agonists** as needed for symptoms.	• Steps 2 and 3 actions plus: • Refer to individual education/counseling

CONSTIPATION
Adapted from Semra Stanley, PharmD

Background

- Constipation is not a disease but a symptom based on the frequency, consistency, or difficulty of stools
- Patients should know their baseline bowel habits
- Causes: dietary inadequacy, GI disorders, metabolic disorders, pregnancy, neurogenic, psychogenic, drug induced (OPIATES, CCBs, antacids, diuretics, anticholinergics, iron), old age

Treatment

- Non-pharmacologic
  - Assess for underlying disease
  - Dietary modification- increase fiber (14g/day x 1 month) and water intake
  - Increase physical activity
  - Modify bowel habits
- Pharmacologic
  - Stool softeners – results in 1-3 days
    - Bulk forming agents – must take with lots of water; increase bulk and water retention
      - Methylcellulose – 4-6g/day
      - Polycarbophil – 4-6g/day
      - Psyllium – varies with product
    - Emollients – especially with opiate therapy or post-surgery; may increase absorption of other drugs
      - docusate sodium - 50-360 mg/day
      - docusate calcium - 50-360 mg/day
      - docusate potassium - 100-300 mg/day
    - Lubricants- mineral oil (15-30ml, short-term only!); systemic absorption, aspiration, decreased fat-soluble vitamin absorption
    - Osmotic agents- lactulose (15-30ml), sorbitol (30-50 g/day)
  - Stimulants – results in 6-12 hours; for short-term use only
    - Bisacodyl – 5-15mg
    - Cascara sagrada
    - Senna
  - Evacuants – results in 1-6 hours
    - Saline cathartics- magnesium citrate/hydroxide/sulfate, sodium phosphates
    - Castor oil – not used because metabolized to ricinoleic acid
    - Glycerin suppository – especially for children
    - Polyethylene glycol solutions

PRESCRIPTION CONTRACEPTION
Adapted from Louise Achey, PharmD

Resources on the Web
A Pocket Guide to Managing Contraception: www.managingcontraception.com/managingcontraception.pdf
Emergency Contraception: www.not-2-late.com or www.opr.princeton.edu

Mechanism of Action
- Estrogens: suppress FSH and LH release from pituitary
- Progestins: suppress LH release, thicken cervical mucus, disrupt ovum transport, inhibit penetration of ovum by sperm, interfere with implantation

Estrogens and Progestins Used in Contraceptives
- Semi-synthetic Estrogens
  - Mestranol
    - Older drug; converted to ethinyl estradiol in liver
    - Dose: 50 mcg – higher doses in older OCs caused breast cancer, lower doses not effective
  - Ethinyl Estradiol: in most oral contraceptives
- Progestins: some are more androgenic than others
  - Norethindrone (in Ortho-Novum, Norinyl, Ovcon)
    - Most common progestin in US combined OC market
  - Norethindrone acetate (in Loestrin, Micronor)
    - Increased androgenic activity
  - Ethynodiol diacetate (Demulen)
    - Decreased androgenic activity
  - Norgestrel (Ovral, Lo-Ovral, Ovrette)
    - More potent progestin and androgen activity
  - Levonorgestrel (Levlen, Nordette)
  - Desogestrel (Desogen, Orthocept)
    - Most potent progestin, but minimal androgenic activity
    - Concerns about increased risk for DVT
    - Active metabolite etonogestrel in Nuva-Ring
  - Norgestimate (Ortho Cyclen, Ortho Tri-Cyclen)
    - Active metabolite norelestromin in Ortho-Evra patch
  - Drospirenone (Yasmin)
    - Anti-aldosterone action (unique among progestins)
      - Can cause potassium retention
      - Not likely to cause cyclic water retention
    - Anti-androgenic action similar to physiologic progesterone
    - Commonly thought to decrease weight gain, but evidence lacking

INDICATIONS FOR COMBINED ORAL CONTRACEPTIVES	INDICATIONS FOR PROGESTIN ONLY CONTRACEPTIVES	**ABSOLUTE** contraindications to use of combined oral contraceptives	**RELATIVE** contraindications to use of combined oral contraceptives
▪ Contraception ▪ Acne ▪ Dysmenorrhea ▪ Recurrent ovarian ▪ cysts ▪ Premenstrual ▪ syndrome ▪ Post-coital birth control	▪ Contraception ▪ Dysmenorrhea ▪ Endometriosis ▪ Post-coital birth control	▪ Thrombophlebitis or history of thromboembolic disorder ▪ CVA or history of CVA ▪ Known, strongly suspected, or history of breast cancer/reproductive organ cancer ▪ Known or suspected pregnancy ▪ Benign hepatic adenoma or carcinoma ▪ Markedly impaired liver function/acute hepatitis	▪ Over 35 years and heavy smoker ▪ Migraine that starts after OC initiated ▪ HTN ▪ DM with smoking ▪ Undiagnosed abnormal vaginal/uterine bleeding ▪ Active gallbladder disease ▪ Patients over 50 years old ▪ First 10-14 days of delivery of term pregnancy (hypercoagulable state) ▪ Unable to reliably take pills daily

Common Side Effects of Combined Oral Contraceptives

Estrogenic Excess	Progestin Excess	Androgenic Effects
Nausea Increased breast size Thromboembolic complications Cyclic weight gain (fluid retention)	Acne Depression Fatigue	Depression, fatigue, tiredness Acne, oily skin Increased LDL levels Decreased HDL levels Diabetogenic effects
Estrogen Deficiency	Progestin Deficiency	
Atrophic vaginitis Continuous bleeding Early or mid-cycle spotting Hypomenorrhea Vasomotor symptoms	Dysmenorrhea Hypermenorrhea Late-cycle spotting **from excess estrogen in combo OC	**To adjust dose for symptom relief, increase or decrease the estrogen or progesterone concentration (by adjusting the ratio of estrogen/progestin or increasing the amount)

Patient Counseling Points

Danger signs of thrombotic events	**Important Points of Contraceptive Therapy**
Abdominal pain? Yellow skin or eyes? **C**hest pain? **H**eadaches that are severe **E**ye problems: blurring or loss of vision? **S**evere leg pain or swelling (calf or thigh)?	▪ Side effects are less pronounced with dosage forms other than oral (injection, patch, vaginal ring) ▪ It takes at least 3 months for body to adapt to any new hormonal contraceptive method ▪ Emergency contraception must be initiated within 72 hours of unprotected intercourse ▪ Progestin only pills must be taken at same time every day—no placebos

Selecting a Contraceptive Agent

- Empiric: 0.5/35, 1/35, or any triphasic
- Empiric Low Dose: 0.5/30 or 1/30
- Acne: 0.5/35, Demulen 1/35, or ANY combined OC
- Concomitant Anticonvulsant Therapy: 1/50 (controversial)
- Lactation: progestin-only products like Micronor, NorQD
- Post-Coitus: Plan B, Ovral (fewest tablets per dose)
- Menses every 3 months: Seasonale or 4 packs of monophasic OC

Missed Pills

- Combined OCs
  - One pill missed: take as soon as remember, continue taking rest of packet
  - Two pills missed: take both as soon as remember, continue rest of packet
  - Three or more missed: use backup for rest of cycle
- Progestin Only OCs
  - One pill missed: take as soon as remember, use backup for rest of cycle
  - Two pills missed: take both as soon as remember, use backup for rest of cycle
  - Three pills missed: use backup for rest of cycle and perform pregnancy test, consider Depo-Provera

Non-Oral Forms of Birth Control

Drug	Advantages	Disadvantages	Special Counseling
Depo-Provera (medroxyprogesterone)	▪ Once every 3 months ▪ Can be given after childbirth ▪ No effect on breast-feeding ▪ Amenorrhea ▪ Very low failure rates	▪ Weight gain (up to 10 lb/year) ▪ Irregular bleeding ▪ Cannot just stop medication ▪ Amenorrhea	▪ Must have injection q12 weeks ▪ If more than 91 days from last injection, must get pregnancy test before next dose
OrthoEvra (ethinyl estradiol plus norelgestromin)	▪ Change patch every week ▪ No need for back-up contraception if off <24 hrs	▪ Not effective in women over 198 lb (90kg)	▪ Do not apply to breast tissue ▪ One patch for 7 days X 3 patches, then 7 days off
NuvaRing (ethinyl estradiol plus etonogestrel)	▪ One ring every month	▪ If out >3 hrs, must use 7 days of back-up method	▪ If expelled, rinse off and reinsert ▪ Wear for 3 weeks, then 1 week off

COPD
Adapted from Angela Stewart, PharmD, BCPS

Clinical Guidelines = 2004 updated Executive Summary at www.goldcopd.com

COPD Diagnosis

- Chronic cough: present intermittently or daily, usually persists throughout day, rarely nocturnal
- Chronic sputum production
- Dyspnea: progressive, persistent, worse with exercise/respiratory infections
- History of exposure to risk factors: SMOKING, occupational exposure to dust/chemicals
- Patients may be "pink puffers" (emphysema) or "blue bloaters" (chronic bronchitis), or a little of both
- Diagnosis confirmed with spirometry: $FEV_1/FVC < 70\%$

Emphysema – "*pink puffers*"

- Main complaint: dyspnea, often severe, usually presenting after age 50. Cough is rare with scant, clear, mucoid sputum. Patient appears uncomfortable with evident use of accessory muscles for respiration. Chest is quiet without adventitious sounds, no peripheral edema.
- Pathophysiology
    1. Imbalance between protective protease inhibitors and active proteases
    2. Reduced surface area for gas exchange
    3. Reduced elastic recoil of lung tissue
    4. Compression of distal airways during exhalation
    5. Loss of distal capillary network

Chronic bronchitis – *"blue bloaters"*

- Main complaint: chronic cough, productive of mucopurulent sputum, w/ frequent exacerbations due to chest infections. Often presents in late 30's-40's. Dyspnea usually mild, though pts may note limitations to exercise. Pts frequently overweight & cyanotic, but seem comfortable at rest. Peripheral edema common. Chest is noisy w/ rhonchi invariably present, wheezes common.
- Pathophysiology
    1. Mucous gland, goblet cell hypertrophy
    2. Smooth muscle hypertrophy
    3. Cartillage atrophy
    4. Inflammation
    5. Repeated respiratory infections

Asthma vs. COPD

	COPD	Asthma
Airflow Limitation	Persistent	Intermittent
β-agonist response	Moderate	Dramatic
Steroid response	Lower	Higher
Anticholinergic response	No blunting with chronic use	Decreased effect with chronic use
Patient age	Older	Younger

COPD Management Goals:

1. Prevent progression of disease
    a. Smoking cessation (80-90% of COPD patients are smokers)
2. Improve exercise tolerance/health status
3. Symptomatic relief: doesn't improve lung function
    a. Bronchodilators, oxygen
4. Prevent complications/exacerbations
    a. Immunizations (pneumococcal, influenzae)
5. Reduce mortality

Maintenance Therapy

- Anticholinergics
    - Ipratropium (2-6 puffs qid)
        - First-line therapy for stable COPD
        - Onset 1.5-2 hours, duration 4-6 hours
        - Also available as nebulizer solution
    - Tiotropium (18 mcg q 24 hr)
        - Dry powder inhaler
        - Onset 30 min, peak 1-4 hr, duration 24 hr
    - Atropine (0.025-0.05 mg/kg injectable or ophthalmic solution diluted to 2-4 ml given via nebulizer)
        - Not recommended because systemic absorption leads to side effects
- β_2-agonists
    - Many options—longer-acting agents preferred
    - Alternative to ipratropium for chronic use
    - Save combination inhalers like Duoneb® or Combivent® for severe COPD

- Theophylline (10 mg/kg to start)
  - May be more beneficial for COPD than asthma because increases respiratory drive
  - Target levels 10-20 mcg/ml
- Inhaled corticosteroids
  - Benefits: decreased respiratory symptoms, exacerbations, increased quality of life
  - Use: Stage III and IV COPD with repeated exacerbations
  - Withdrawal of inhaled corticosteroids can precipitate an exacerbation
  - Combinations with β_2-agonists: salmeterol/fluticasone and budesonide/formoterol
- Systemic corticosteroids
  - Only if inhaled route unavailable and taper to lowest effective dose
- Respiratory stimulants: medroxyprogesterone, doxapram, almitrine, acetazolamide rarely used

Stepwise Approach to COPD Management

<table>
<tr><th>COPD Stage</th><th>0: At Risk</th><th>I: Mild</th><th>II: Moderate</th><th>III: Severe</th><th>IV: Very Severe</th></tr>
<tr><td rowspan="5">Treatment Modifications</td><td colspan="5">Avoidance of risk factors; influenza, pneumococcal vaccinations</td></tr>
<tr><td rowspan="4"></td><td colspan="4">Add short-acting bronchodilator for emergencies</td></tr>
<tr><td rowspan="3"></td><td colspan="3">▪ Add regular treatment with one or more long-acting bronchodilators
▪ Add rehabilitation to maximize gas exchange</td></tr>
<tr><td rowspan="2"></td><td colspan="2">Add inhaled corticosteroids if repeated exacerbations</td></tr>
<tr><td></td><td>▪ Add long-term oxygen if chronic respiratory failure
▪ Consider surgery</td></tr>
</table>

Managing Exacerbations

- Oxygen administration
  - Goal PaO2 60-80 mmHg, O2 saturation > 90%
  - Monitor PCO2, signs and symptoms of hypercapnea
  - Dose: start with low FiO2 (24%) and titrate carefully—could cause paradoxical respiratory collapse
- Maximize inhaled therapies
  - Ipratropium every 4-6 hours
  - Albuterol every 30-60 minutes
- Systemic steroid therapy
  - Methylprednisolone 0.5-1.0 mg/kg up to 125 mg IV q 6 h x 48-72 hours
  - When stable convert to oral prednisone 40-60 mg qd
  - 8 week course no more effective than 2 weeks
- Antibiotics
  - Usual organisms: S. pneumo, H. flu, M. cat.
  - Appropriate agents include:
    - Augmentin
    - $2^{nd}/3^{rd}$ generation cephalosporins
    - Septra
    - Doxycycline
    - Azithromycin/Clarithromycin
- Maximize therapy for heart failure
- DVT prophylaxis: heparin 5000 units SQ q 8-12 hrs, or enoxaparin 30 mg SQ BID

CYSTIC FIBROSIS
Adapted from Jon Reynolds, PharmD

Definition: an inherited disease of the exocrine glands leading to thick, sticky mucus production, primarily affecting the respiratory and GI systems

Causes: CF is caused by an abnormality in the function of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein which is important in transporting chloride ions across epithelial cells in many organs. There is no cure since CF is due to genetic abnormality.

Diagnostic triad: increased sweat chloride, chronic pulmonary disease, pancreatic insufficiency

Respiratory Complications

- Repeated infections
- Recurrent bronchitis
- Chronic cough
- Bronchiectasis (chronic airway dilation)
- Pneumothorax (collapsed lung)
- Hemoptysis (coughing blood)
- Digital clubbing (enlarged fingers and toes)
- Cor pulmonale (enlarged right heart)
- Sinusitis
- Allergic bronchopulmonary aspergillosis
- Nasal polyps

Treatment of Respiratory Symptoms

- Chest percussion and postural drainage is cornerstone of therapy:
  - Performed 5x daily
  - More effective when preceded by exercise
  - Often followed by nebulizer therapy
- Nebulizer Treatment options
  - Sterile water or normal saline
  - Bronchodilators: (albuterol or ipratropium)
  - Mucolytic agents
    - Pulmozyme® (dornase alfa or DNase)
      - Selectively cleaves DNA in patients' mucus, thereby decreasing viscosity
      - Decreases frequency of respiratory infections and increases lung function
      - Given as one ampule (2.5 mg) in nebulizer daily
      - Must use specific nebulizer
      - Store in refrigerator—only good for 24 hours at room temp
    - Acetylcysteine (Mucomyst) Breaks sulfide bonds in mucus
    - Sodium bicarbonate
  - Mast-cell stabilizers (cromolyn)
- Anti-inflammatory agents
  - Oral corticosteroids for short-term use
  - Inhaled corticosteroids
  - NSAIDs—not recommended because increased bleeding risk
- Annual influenza vaccine
- Amantadine (Tx of influenza A)

Pulmonary Infection

- Signs of pulmonary infection: Increased respiratory rate, changes in breath sounds (rales), decline in pulmonary function tests, fever, leukocytosis, weight loss, new infiltrate on chest X-ray
- Common pathogens found in sputum
  - ***Pseudomonas***
  - *Staphylococcus*
  - *Haemophilus influenzae*
  - *Burkholderia cepacia*
  - *Stenotrophomonas maltophilia*
- Selection of antibiotics
  - Double-coverage is warranted—preference will vary with practice site
  - Usually given at higher doses and longer durations
  - Aminoglycoside + extended-spectrum PCN
  - E.g. = Zosyn + AG, Cipro + AG, Cefepime/Ceftazidime + Ag, Imipenem + AG
  - TOBI ® (Inhaled tobramycin)
    - Often given if patient has *P. aeruginosa*
    - Given as 300mg BID dose in 28 day cycles
    - Do not mix with Pulmozyme and administer after all other nebulized medications
    - Store vials in refrigerator out of light

Pancreatic and GI Complications

- Poor weight gain
- Delayed growth
- Steatorrhea
- Reduced bicarb secretions
- Meconium ileus
- Distal intestinal obstruction
- Abdominal discomfort
- Insulin deficiency/glucose intolerance
- Rectal prolapse

**In CF patients most of the pancreatic tissue is destroyed due to disturbed ion transport, causing pancreatic dysfunction, and eventually leading to obstruction in both the small and large intestine.

Treatment of GI Complications

- Pancreatic enzyme supplementation (see Table), taken every meal including snacks.
  - Prescribed according to Lipase content
  - Products are not interchangeable
  - Infants = 2000-4000 lipase units/120ml formula
  - 1-6 yrs = 4000-8000 lipase units /dose q meal or snack
  - >6 yrs = 4000-16000 lipase units /dose q meal or snack
  - Adolescent = 4000-48000 lipase units /dose q meal or snack
  - High doses of some pancreatic enzymes may lead to colonic stricture, occurs when doses approach 24,000 U/kg
- Vitamin Supplementation: Multivitamin to supplement water soluble vitamins and Vit A, D, E, K
- High calorie, low fat and high protein diet
- H2 Blockers (Ranitidine, Famotidine)
  - Reduce stomach acid to create a more alkaline environment so pancreatic enzymes can function
  - May help break up undigested food causing an intestinal obstruction

Pancreatic Enzyme Products

Trade Name	Enzyme Content (Units)			
	Lipase	***Protease***	***Amylase***	***Form***[a]
Cotazym	8000	30,000	30,000	C
Cotazym-S	5000	20,000	20,000	ECM
Creon	8000	13,000	30,000	ECM
Ilozyme	11,000	30,000	30,000	T
Ku-Zyme	8000	30,000	30,000	C
Pancrease	4000	25,000	20,000	ECM
Pancrease MT 4	4000	12,000	12,000	ECM
Pan crease MT10	10,000	30,000	30,000	ECM
Pancrease MT16	16,000	48,000	48,000	ECM
Pancrelipase	4000	25,000	20,000	ECM
Protilase	4000	25,000	20,000	ECM
Ultrase MT12	12,000	39,000	39,000	ECM
Ultrase MT20	20,000	65,000	65,000	ECM
Ultrase MT24	24,000	78,000	78,000	ECM
Viokase	8000	30,000	30,000	T
Viokase	16,800	70,000	70,000	P[b]
Zymase	12,000	24,000	24,000	ECM

[a]Dosage form: C=capsule; ECM=enteric coated microsphere or beads; T=tablet; P=powder. [b]Viokase powder, units of enzyme per 700mg.

Additional Complications of CF

- Hepatobiliary System
  - Liver disease including fatty liver and focal biliary fibrosis
  - Prolonged natal jaundice
  - Portal hypertension which can cause esophageal varices
- Reproductive Tract
  - Delayed puberty probably due to nutritional inadequacies
  - Male infertility due to obliterated vas deferens
  - Female fertility problems due to the effect of chronic lung disease on the menstrual cycle
- Sweat Glands
  - abnormally high levels of salt caused by defective salt reabsorption

DERMATOLOGIC DISORDERS
Adapted from Mark Garrison

Atopic Dermatitis (Eczema)

- Signs/Symptoms
  - PRURITIS, erythema, dry skin, small papules
  - Strong link to food allergies
  - Location is age-related
- Management – break the itch-scratch cycle
  - Goal: eliminate causative factor
  - Baths – tepid water, oatmeal (Aveeno) or coal tar baths
  - Wet dressing if oozing lesions - Burrow's Solution (aluminum acetate) 1:20 for 20-60 minutes
  - Topical steroids/antibiotics for severe cases
    - Initiate with higher potency x 7-10 days, taper and treat several more weeks
    - Long-term use of potent (fluorinated) corticosteroids → thins skin, atrophy, telangiectasis
    - Ointments are better occlusive emollients
  - Systemic agents- antihistamines, oral corticosteroids/antibiotics, immunomodulators (cyclosporine, tacrolimus)

Contact Dermatitis

- Two forms:
  - Irritant: direct toxic effect of substances on skin tissue (non-immune mediated)
  - Allergic: delayed hypersensitivity to substances on skin (immune-mediated)
- Signs/Symptoms
  - Acute stages- erythema, edema, papules, vesicles/bullae, severe itching
  - Chronic stage- 2° lesions occur (cracked skin, scaly plaques)
- Management
  - Goal: Remove/minimize exposure to causative allergen/irritant
  - Topical/systemic corticosteroids
    - Acute: significant blisters/edema: oral prednisone 1 mg/kg/day x 7-14 days – taper
    - Weeping lesions: compresses, baths, Burrow's soln
    - Less severe or chronic: topical hydrocortisone
    - Significant lichenification – overnight occlusion increases steroid penetration
  - Systemic antihistamines – questionable value, sedation may be beneficial
  - Avoid topical antihistamine, anesthetics, calamine

Urticaria (hives)/Angioedema

- Signs/symptoms
  - Lesions: wheals associated with intense itching/stinging
  - Angioedema- not typically pruritic, involves swelling (face, tongue)- can progress to CV/pulmonary symptoms, anaphylaxis
- Management
  - Systemic antihistamines – 65-70% respond, give on schedule
  - Corticosteroids
    - Topical corticosteroid plus oral antihistamine
    - More severe cases: prednisone 20-30 mg/day x 5 days
  - Misc- tricyclics (doxepin), short-term prednisone, β-agonist (terbutaline), calcium channel blockers (nifedipine)

Acne Vulgaris

- Signs/symptoms
  - Primary lesions (comedones) mostly involving face, neck, back, and chest
  - Commonly progresses to inflammatory lesions: papules, pustules, nodules, cyst
    - Management
  - Goal: prevention of new acne lesions, stress importance of compliance to patient (chronic therapy takes time!)
  - Mild Cases:
    - Topical benzoyl peroxide 2.5% to 5% daily then BID as tolerated
  - Mild-Moderate (and as adjunct for more severe nodulocystic acne)
    - Topical Antibiotics: clindamycin, erthyromycin, tetracycline
  - Moderate-Severe:
    - Drug of Choice: Oral tetracycline/minocycline, alternatives: erythromycin, TMP/SMX
  - Comedonal Acne (non-inflammatory)
    - Drug of Choice: topical tretinoin (Retin-A) or Retin-A derivatives (Differin, Tazorac)
  - Nodulocystic Acne & Severe Cases
    - Accutane: start at 0.5 - 1 mg/kg/day PO then increase as tolerated after 4-8 weeks, total 16-20 weeks
    - Significant toxicities: TERATOGENIC, increased LFTs, suicide, mucocutaneous effects
  - Hormonal Therapy
    - Triphasic oral contraceptives for use in women with acne

Scaly dermatoses (Dandruff, Seborrhea, Psoriasis)

- Signs/Symptoms
  - Occurs in conjunction with acne

- Scales vary: dry flakes with little erythema → oily scales/crusts on erythematous base
- Psoriasis involves erythematous plaques with silvery scales

- Management
  - Dandruff/Seborrhea
    - Shampoos with sulfur, salicylic acid (Sebulex), coal tar (Denorex), 1% selenium sulfide (Selsun Blue) and zinc pyrithione (Head & Shoulders)
    - Allow shampoo to penetrate for 5 minutes then rinse
    - If lesions inflammatory/pruritic – 1% hydrocortisone cream or 0.025% triamcinolone
    - For other areas, apply 2% ketoconazole cream
    - Blepharitis: avoid topical steroids, use hot compress and ketoconazole shampoo +/- ointment if lids inflamed
    - Infants: avoid coal tar products and steroids – use 2% ketoconazole
  - Psoriasis
    - Therapy involves stepwise approach
    - Emollients
      - Hydrates the skin, decreases water loss/cracking/scale formation
      - Apply 3-4 times/day (may increase acne)
    - Humectants (glycerin, urea) can be added to help increase water retention
    - Keratolytics
      - Reverses hyperkeratosis, removes scales
    - Salicylic acid (2-10%)
      - 6% salicylic acid/ 60% propylene glycol/ 20% ethyl alcohol (overnight occlusion)
      - 2-6% salicylic acid plus coal tar (cream, lotion, shampoos)
      - ADR: skin irritation and soreness, contact dermatitis
    - Tar Products: antimitotic effect?
      - Thins the epidermis
      - 2-10% creams, ointments, gels, lotions, shampoos, solutions
      - Compliance an issue
      - Used in combo with UVA
      - ADR: long-term use carcinogenic?, photosensitivity, folliculitis
    - *Topical Corticosteroids*
      - Decreases inflammation so other agents can work better
      - High potency steroids used initially (except face) then switched to less potent agents
      - Avoid applying to large areas (increased absorption)
      - ADR: striae/atrophy, telangiectasis, abnormal pigmentation, thinning of skin, decreased healing
    - Calcipotriol
      - Vitamin D analog that inhibits keratin proliferation
      - Good alternative to steroids
      - BID ointment x 8 weeks – typically see improvement by week 2
      - ADR: burning, itching, irritation, can sometimes worsen psoriasis
    - Retinoids
      - Vitamin A analogs that have anti-inflammatory and anti-proliferative effects
      - Reserved for refractory cases of psoriasis due to toxicities
    - Anthralin
      - Anti-proliferative effect (used more in UK/Europe)
      - Lassar's paste (anthralin + salicylic acid 0.2-0.4%) used for large plaques
        - Tar bath, apply Lassar's paste x 8-12 hours (overnight), remove with mineral oil
        - Requires increasing concentration of anthralin as plaque resolves (0.1% - 1%)
      - Alternative: higher concentration of anthralin can be used for 30-60 minutes BID
    - Systemic Antibiotics
      - Guttate psoriasis frequently occurs after Group A infections
      - Oral rifampin plus penicillin (or erythromycin) may be effective
    - Phototherapy
      - Used for patients unresponsive to topical therapy or have widespread lesions
      - UVB monotherapy (at 313 nm) and UVA + psoralen (PUVA) is beneficial
      - UVB plus 1-5% crude coal tar, Ingram method (Lassar's paste)
      - PUVA: oral dose of psoralen, 2 hrs later UVA
    - Other Systemic Therapy
      - Methotrexate: inhibits proliferation
        - Reserved for refractory cases of psoriasis
        - 10-20 mg/week, taper to lowest effective dose after lesions under control
        - 75-80% respond within 4 weeks with persistent remission
      - Hydroxyurea
        - Not approved for psoriasis
        - Less effective than methotrexate but less liver toxicity
        - Suppressive effects on bone marrow
      - Cyclosporin

- Only used in severe cases, increased costs/toxicity
- 2.5-5.0 mg/kg/day provides good results after 4-8 weeks

DIARRHEA
Adapted from Semra Stanley, PharmD

Background

- Diarrhea is a normal defense mechanism to remove harmful substances from the body
- Infants, young children, and elderly are at most risk for complications from diarrhea
- Almost any medication can cause diarrhea
- Pathophysiology
  - Secretory – bowels secrete more water and electrolytes than they absorb
  - Altered transit – change in intestinal motility
  - Osmotic – increase in luminal osmolarity
  - Exudative – mucosal inflammation/ulceration

Treatment

- Prevention is key: hand washing, proper food handling, etc.
- Goals – prevent fluid/electrolyte imbalance, symptom relief, treat underlying causes
- Non-pharmacologic management
  - Dietary – stop solid foods for 24 hrs, avoid dairy, BRAT diet = bananas, rice, apples, toast (rich in pectin)
  - Fluid/electrolyte management
- Drug therapy
  - Antimotility
    - diphenoxylate/atropine – 5 mg qid (NTE 20 mg/day)
    - loperamide – 4 mg initially then 2 mg after each BM (NTE 16 mg/day)
    - paregoric – 5-10 ml up to qid
    - opium tincture – 0.6 ml qid
    - atropine – 0.4-0.6 mg q 4-6 h
  - Adsorbents-
    - kaolin-pectin 30-120 ml after each BM
    - polycarbophil – 2 tabs after each BM up to 12 tabs/day
  - Antisecretory- bismuth subsalicylate
    - Especially for traveler's diarrhea because anti-inflammatory and antibacterial
    - SE = salicylate toxicity, black tongue/stools, gout
  - Enzymes- lactase
  - Bacterial replacement- lactobacillus
  - Octreotide 50 mcg SQ 1-2 times daily, titrate up to 600mcg/day

DRUG INTERACTIONS
Adapted from Wil Edwards, PharmD

Overview

- Drug interactions are based on multiple patient factors:
  - Age, gender, BMI, ethnicity
- Drug interactions can be experienced outside the patient and inside the patient
  - Outside: iv compatibility
  - Inside: ADME, protein binding

Patients with multiple drugs are at an increased risk of experiencing a drug interaction

Definitions

Pharmacokinetic drug interaction:
- Interactions affecting absorption, distribution, metabolism, elimination of a drug

Pharmacodynamic drug interaction:
- Interactions between agonists and antagonists at drug receptors
- Usually more severe

Drugs Affecting Absorption

Drugs that may chelate with Mg, Ca, etc
- Tetracyclines, macrolides, quinolones, bisphosphonates

Drugs that alter pH
- H2 antagonist, PPI, anatacids, Coca-Cola

Drugs that alter GI transit time
- Usually of little consequence

Antibiotics alter gastrointestinal flora
- Affects warfarin, oral contraceptives, digoxin levels

Drugs that inhibit p-glycoprotein and increase GI absorption or decrease renal excretion
- Cyclosporin, quinidine, verapamil, itraconazole, clarithromycin, amiodarone, cimetidine

Drugs Affecting Metabolism

CYP450 Inducers
- Oral anticoagulants
- Quinidine
- Corticosteroids*
- Theophylline
- Nevirapine
- Effavirenz
- Chronic ethanol consumption*
- Rifampin*
- Carbamazepine*
- Isoniazid
- St. John's Wort*

*autoinducer

CYP450 Inhibitors
- CYP 1A2: cimetidine, amiodarone, quinolones, ticlodipine
- CYP2B6: ticlodipine
- CYP2C19: cimetidine, fluoxetine, ketoconazole, ticlodipine, topiramate
- CYP2C9: amiodarone, fluconazole, paroxetine
- CYP2D6: amiodarone, cimetidine, fluoxetine, paroxetine, ritonavir, terbinafine
- CYP3A4: protease inhibitors, amiodarone, cimetidine, macrolides (except azithromycin) diltiazem, azole antifungals, grapefruit juice, verapamil

Drug Interactions You Should Know

Sildenafil AND Nitrates
- Sildenafil potentiates the hypotensive effects of nitrates
- Must wait 24 hours if taken sildenafil before taking the nitrate!

Grapefruit juice AND Statins
- Grapefruit juice inhibits the breakdown of atorvastatin, simvastatin and lovastatin, which can lead to rhabdomyolysis
- Pravastatin, rosuvastatin, and fluvastatin don't interact

Warfarin Interactions
- Amiodarone
- Sulfonamides
- Metronidazole
- Herbals starting with G: garlic, ginkgo, ginseng
- Anything and Everything

Oral Contraceptives and Antibiotics
- Coadministration of antibiotics may decrease the pharmacological effects of oral contraceptives

Metronidazole and Ethanol
- Causes a disulfiram-like reaction
- Inhibits aldehyde dehydrogenase, cause a build up of acetaldehyde
- Counsel patients to avoid alcohol (mouth wash, cold syrups) during therapy and for at least 2 days after last dose

NSAIDS and ACE Inhibitors

- Can cause acute renal failure

Drugs that prolong QT interval

- Amiodarone
- Cisapride
- Dofetilide
- Gatifloxacin
- Procainamide
- Quinidine
- And many, many others!

DRUGS OF ABUSE
Adapted from Colleen Terriff, PharmD and Andreea Tofan RPh

Alkyl Nitrites: (amyl nitrite, butyl/isobutyl nitrite, poppers, rush, liquid gold)

- How used: Inhaled (never ingest or pour on skin), glass ampule/capsule is 'popped' to release vapor – can be used with Viagra and/or alcohol
- Chemistry: Dilates coronary vasculature and decreases afterload; relaxes smooth muscles
- Good Effects: Rush, mild euphoria, feeling of fullness in head, giddiness, muscle relaxant, lightheadedness, time alteration
- Bad Effects: Decreased BP, panic attacks, dizziness, severe HA, nausea and vomiting, chills, reflex tachycardia and palpitations, - Not for use in heart disease, asthma/COPD

Amphetamines: (Ritalin)

- How used: Ingested, snorted, injected – Binders in the tablets can cause Ritalin Lung as well as abscesses under the skin

Anabolic Steroids: (Roids)

- How used: Ingested, injected – **Stacking** is when 3 or more kinds of steroids are used at one time – **Cycling** is when a person alternates the use of steroids for 4 – 18 weeks during intense training with breaks lasting weeks to months
- Chemistry: Analogs of testosterone
- Good effects: Increase in muscle mass and tone, increased confidence and aggression, mild euphoria
- Bad effects: Feminine characteristics in men (breast development), impaired sexual function, masculine characteristics in women (facial hair, decreased breast size), "roid rage", withdrawal symptoms

Barbiturates/Benzodiazepines:

- How used: Ingested with other CNS depressants; alcoholics/heroin addicts use to decrease withdrawal, cocaine addicts use to decrease excessive stimulation
- Chemistry: Potentiate GABA in the cerebellum, cerebral cortex and limbic system
- Good Effects: Similar to effects of alcohol intoxication, lowered inhibitions, muscle relaxation, memory loss, euphoria
- Bad Effects: Anterograde amnesia, loss of consciousness, rebound anxiety/agitation, depressed respiratory drive, paradoxical aggression and excitability

Carisoprodol: (Soma):

- Chemistry: Structurally related to meprobamate
- Good Effects: Can cause effects similar to alcohol or barbiturate intoxication

Cocaine: (coke, crack, snow, free-base)

- How used: Snorted, Injected, Smoked
- Chemistry: Increases catecholamine release (epinephrine, DA, NE), increases acetylcholine, increases 5-HT release
- Good Effects: Euphoria, rush, increased self esteem, increased sexual desire, increased confidence and energy, relaxation, anorexia, decreased need for sleep
- Bad Effects: Binging, exhaustion, lethargy, anhedonia, muscle tremors, memory lapses, mental confusion, paranoia and psychosis, contraction-band necrosis of the heart, stroke, MI, seizures, dental erosions, sexual dysfunction, aggression, hypertension, weight loss, depression, anxiety, irritability, hyperthermia

Cyclobenzaprine: (Flexeril)

- Chemistry: Structurally related to TCA
- Good Effects: Can cause drowsiness, delirium, relaxation, hallucinations, disorientation

Dextromethorphan (DM, Robitussin, Coricidin, Nyquil, "robo-tripping")

- How used: Ingested - a full 6 oz bottle needs to be ingested

Ecstasy: (methylenedioxymethamphetamine, MDMA, E, x-TC)

- How used: Available as powder, tabs, caps – ingested, smoked, snorted, "bumped" – can be combined with LSD, ketamine, pot or "smart drinks"
- Chemistry: Increases levels of serotonin (5-HT) by stimulating release, blocking reuptake and blocking metabolism.
- Good Effects: Psychedelic effects, increased tactile sensation, euphoria, relaxation, empathy, closeness to others, suppresses appetite/thirst/sleep, mild hallucinogenic effects
- Bad Effects: Increased HR/RR/BP, nausea, jaw clenching, blurred vision due to papillary dilation, agitation, paranoia, hyperthermia, tremor, symptomatic hyponatremia, seizures

GHB: (gamma-aminobutyric acid, liquid ecstacy, liquid X, G)

- How used: Oral solution mixed with water – can be combined with alcohol and Ecstacy – considered a date rape drug
- Chemistry: Precursor of GABA and stimulated release of DA by interacting with GABA receptors.
- Good Effects: Similar to alcohol and are dose related, relaxation, in coordination, drowsiness, dizziness, euphoria, increased dreaming, hallucinations, delusions
- Bad Effects: decreased HR/RR, deep sleep similar to coma, hypothermia, amnesia, memory impairment, seizures, respiratory depression

Heroin: (opium, morphine, black tar heroin)

- How used: Ingested, smoked, snorted, injected. – can be combined with cocaine, meth, marijuana, alcohol, benzodiazepines, clonidine – these combinations are called "speedballs"
- Chemistry: Blunts release and effects of substance P, stimulates mu, delta, kappa and sigma receptors which stimulate various dopaminergic pathways, mimics endorphins, enkephalins and dynorphins
- Good Effects: Euphoria, deadening of emotions, decreased anxiety, drowsiness, sense of serenity
- Bad Effects: Decreased HR/RR/BP, insensitivity to pain signals, pinpoint pupils, dry skin and itching, slurred speech, suppression of cough, blood vessel collapse, abscesses and infections, endocarditis, co-infections with hepatitis and HIV, cotton fever, nausea, vomiting

Ketamine: (special K, K, kit kat, super acid, jet)

- How used: Available as powder or liquid – powder is ingested or snorted, liquid is injected, smoked or dipped in cigarettes
- Chemistry: Prevents glutamate activation, inhibits reuptake of NE/DA/5-HT, indirectly acts at muscarinic, nicotinic cholinergic and opioid receptors
- Good Effects: out of body experience, visual hallucinations, analgesia at low doses
- Bad Effects: Increased HR/BP, arrhythmias, respiratory depression and apnea, high doses cause amnesia, used as a 'date rape' drug due to loss of consciousness and anterograde amnesia

LSD: (Lysergic acid diethylamide, acid, blotter, illusion)
- How used: Blotter paper, Gelatin capsules
- Chemistry: Sudden release of NE which enhances alertness
- Good Effects: Light trails, euphoria, sensory distortions (seeing sounds, feeling smells, hearing colors), dreaminess, impaired concentration and motivation, awareness of inner self, introspection
- Bad Effects: Increased HR/BP/body temp, dilated pupils, sweating, depersonalization, paranoia, insomnia, anxiety, difficulty expressing oneself verbally, delusions, depression, bad trips, memory flashbacks

Marijuana: (cannabis, hemp, hash, hashish, pot, dope, herb, grass)
- How used: Smoked, ingested
- Chemistry: Cannabinoid receptors found in limbic system and other parts of the brain, reduce cAMP and protein kinase A activity which reduce K^+, Ca^{2+} channel activity = less neurotransmitters released
- Good Effects: Relaxation, increase in appetite, decreased intra-ocular pressure and nausea, aloof feeling, distortions in time, color and sound, visual illusions, hallucinations and delusions
- Bad Effects: Paranoia, psychosis, short-term memory impairment, decreased concentration

Methamphetamine: (meth, speed, crystal meth, ice, crank, glass)
- How used: Available as powder/crystals - snorted, injected, smoked, ingested – can be combined with pot/heroin/Ecstasy
- Chemistry: Increases levels of catecholamines (Epinephrine, NE, DA) by stimulating the release, blocking reuptake and blocking metabolism.
- Good Effects: Euphoria, sense of well being, energy, alertness, mimics sexual gratification, appetite/thirst suppression, confidence, decreased need for sleep, dilation of bronchial vessels
- Bad Effects: Increased HR/RR/BP, sleep deprivation, cardiovascular disease, malnutrition, paranoia, decrease in sexual drive/performance, aggression, convulsions

Opioids: (morphine, oxycodone, hydrocodone, etc.)
- How used: Ingested, snorted, injected, transdermal

PCP: (phencyclidine, angel dust, peep, crystal KJ, ozone)
- How used: Available as liquid mixed with formaldehyde or powder – ingested, injected, inhaled or smoked – can be dipped into cigarettes, joints or mushrooms.
- Chemistry: Distorts sensory messages sent to the central nervous system
- Good Effects: (Low to moderate doses of 2 – 10mg), separation of mind and body, sensory impairment, disinhibition, decreases pain, hallucinations
- Bad Effects: (high doses >20mg), increased BP, nystagmus, confusion, retrograde amnesia, aggressive/violent behavior, depersonalization, robotic movements, paranoia, agitation, catatonia, coma, convulsions, hyperthermia, "PCP flashback"

Rohypnol: (flunitrazepam, ruffies, R-2, roche, date rape drug)
- How used: Ingested, snorted or injected
- Chemistry: Intermediate to long acting benzo that is structurally related to clonazepam. Increases GABA mediated Cl^- conduction, which prolongs hyper-polarization and decreases synaptic transmission
- Good Effects: Effects similar to alcohol intoxication, relaxation, sleepiness, disinhibition, in coordination, euphoria
- Bad Effects: Anterograde amnesia, dizziness, nightmares, confusion, tremors, decreased BP, paradoxical aggression and excitability

Signs/Symptoms of Withdrawal and Overdose and How to Treat

Barbiturates/Benzodiazepines
- Signs of withdrawal: Anxiety/agitation, loss of appetite, increased heart rate, excessive sweating, abdominal cramps, tremors
- Signs of overdose: Drowsiness, loss of consciousness, coma, depressed breathing
- Treatment of withdrawal: Phenobarbital is used to cross-taper, phenytoin to prevent seizures, treat the underlying psychiatric disorder
- Treatment of benzo overdose: flumazenil (Romazicon) *use only for benzo overdose

LSD/Mescaline/Mushrooms
- Signs/symptoms of "Bad Trips": Anxiety, paranoia, fear of impending death, loss of contact with reality, hallucinations
- Treatment: Change location/lighting, reassure, focus on breathing, don't leave user, surround user with friends they trust

PCP
- Signs of overdose: Characteristic nystagmus, psychosis (aggressive/violent behavior), coma, seizures, HTN, hyperthermia
- Treatment of overdose: Enhance urinary excretion by giving ammonium Cl or Vit C plus a diuretic, haloperidol for psychosis, benzo for seizures, nitroprusside for hypertensive crisis, iced IV fluids and cooling baths

Marijuana
- Signs of withdrawal: Irritability, anxiety, depression, mild muscular discomfort, craving, appetite/sleep disturbances
- Treatment: No real treatment, psychosocial interventions, education, counseling

Opioids
- Signs of withdrawal: (Similar to the flu) nausea/vomiting/diarrhea, anorexia, papillary dilation, rhinorrhea, piloerection, lacrimation, extreme anxiety

- Signs of acute intoxication: Abnormal mental status, decreased respiration, miotic pupils
- Morbidity/mortality due to: anaphylaxis, pulmonary edema, acute respiratory acidosis, aspiration pneumonitis
- Treatment for withdrawal: Substitution with long-acting opioids (methadone, buprenorphine), clonidine decreases catecholamine release, trazodone for sleep
- Treatment for overdose: **Naloxone 0.4-2mg IV q 3 minutes**, pure opioid antagonist, rapid onset of action, duration of action is 1-2h, well absorbed IV, IM, SC and via endotracheal tube, highly lipid soluble
- Methadone maintenance programs: Methadone has a longer half-life than heroin and prevents withdrawal and craving, also decreases high-risk behavior and diseases

Stimulants

- Signs of withdrawal
  - Abstinence syndrome = crash (drastic reduction in mood and energy), hypersomnolence, hyperphagia.
  - Protracted dysphoric syndrome = anhedonia, lethargy, depression, problems with concentration
- Signs of overdose: convulsions, cardiovascular collapse, aneurysms, stroke, MI, drug induced hyperthermia, amphetamine psychosis (hallucinations, paranoia, loss of contact with reality), "caine" reaction
- Treatment of withdrawal: Abrupt discontinuation does not cause physiologic sequelae, not tapered or cross-tapered with another drug, monitor for underlying mental disorders
- Treatment of overdose: Treatment is supportive, benzos for agitation/seizures, β-blockers for HTN, hypertonic saline/fluid restriction for symptomatic hyponatremia, iced IV fluids/cooling washes for hyperthermia

Drugs/Diseases that Can Cause False Positives	
Amphetamines	Ephedrine, pseudoephedrine, phentermine, Vicks Inhaler, Afrin
Barb/Benzos	Phenytoin
Cocaine	Amoxicillin, Fluoroquinolones, tonic water
LSD	Meds containing ergotamine, promethazine, amitriptyline, dicyclomine
Marijuana	NSAIDs, promethazine, riboflavin (vit B2)
Opiates	Rifampin, poppy seeds, DM, tonic water
PCP	Diazepam, DM

How Drugs Are Abused:	Onset of Drug Effect:
Inhalation	7 – 10 sec
IV ("Slamming")	15 – 30 sec
SC ("Skin Popping")	3 – 5 min
IM ("Muscling")	5 – 7 min
Mucosal Absorption: Snorting, Buccal, Vaginal/Rectal ("Bumping")	?
Oral	20 – 30 min
Contact Absorption: Intraocular, Lingual, Transdermal	?

How soon drugs are detected	
Amphetamines	4-6hrs
Cocaine/Crack	2-6hrs
Marijuana	1-3hrs
Opiates	2-6hrs
PCP	4-6hrs

How long drugs are detected	
Alcohol	½ - 1 day
Amphetamines	2 – 4 days
Barbiturates	2- 4 days
Benzodiazepine	Up to 30 days
Marijuana single use	1 – 3 days
Marijuana casual use (4/week)	5 – 7 days
Marijuana daily use	10 – 15 days
Marijuana heavy/chronic use	1 – 2 months
Cocaine	48 – 72 hrs
Ecstasy	24 – 72 hrs
Opioids – Codeine	2 days
Opioids – Heroin	2 – 4 days
Opioids – Methadone	2-3 days
Ketamine	Unknown
LSD	24 – 48 hrs
Mushrooms	Unknown
PCP casual use	2 – 7 days
PCP heavy/chronic use	Several months

FDA Pregnancy Risk Categories

A: controlled studies show no risk in 1st trimester; no evidence of 2nd or 3rd trimester risk; risk of fetal harm remote
B: animal studies show no risk or adverse fetal effects, but controlled human 1st trimester studies not available/do not confirm; no evidence of 2nd or 3rd trimester risk; fetal harm possible but not likely
C: animal studies show adverse fetal effects, but no controlled human studies OR no animal or human studies; weigh possible fetal risk vs. maternal benefit
D: positive evidence of human fetal risk; maternal benefit may outweigh fetal risk in serious or life-threatening situations
X: positive evidence of serious fetal abnormalities in animals, humans, or both; fetal risks clearly outweigh maternal benefit

GERIATRIC DRUG CONSIDERATIONS
Adapted from Steve Setter, PharmD, CGP, CDE, DVM

Goal of treatment is to keep independent as long as possible

Physiologic Changes Associated With Aging

- Absorption: Despite age related changes, no clinically significant decreases in drug absorption observed
- Distribution
  - Adipose tissue increases (barbiturates, benzodiazepines)
  - Total body water decreases (lithium, ethanol, diuretics) — "Triscuit Effect"
  - Lean body mass decreases (digoxin)
  - Serum albumin decreases (digoxin, theophylline, phenytoin, warfarin)
  - Acid glycoprotein increases (lidocaine, propranolol)
- Metabolism
  - Decreased hepatic blood flow
  - Decreased hepatic metabolism
    - Phase I: CYP450 function generally decreases with age
    - Phase II: Conjugation generally unaffected with age
  - Age-related decrease in liver function may necessitate dose reduction for some medications
- Elimination
  - Age-related decrease in kidney function is common
  - Accumulation and toxicity may occur frequently unless dose of renally eliminated drugs is reduced
  - Serum creatinine is not a good indicator of renal function in the elderly. Use Cockroft-Gault equation to estimate renal function:

$$CrCl = [(140 - age) \times (weight\ in\ kg)] / (72 \times SCr) \times (0.85\ if\ female)$$

Pharmacodynamic Changes Associated With Aging:

- Organ responsiveness to drugs: Changes in receptor binding, decreased number of receptors, and altered translation of receptor-initiated response.
- Decreased response: β-blockers (propranolol, atenolol, metoprolol)
- Increased response**:** Benzodiazepines, opiates, warfarin, anticholinergics (diphenhydramine, benztropine, hydroxyzine)

Cholinergic Effects (Turkey Dinner)	Anticholinergic Effects (Anti-Turkey Dinner)
1. Miosis	1. Mydriasis
2. Salivation	2. Xerostomia (dry mouth)
3. GI activity increased	3. GI activity decreased (constipation)
4. Urination	4. Urinary retention
5. Bradycardia	5. Tachycardia

Adverse Effect Profile Based on Receptor Blockade

- Alpha-1 Adrenergic: dizziness, postural hypotension, reflex tachycardia
- D2 Dopamine: extrapyramidal side effects (dystonia, pseudoparkinsonism, akathisia)
- H1 Histamine: sedation, weight gain
- M1 Muscarinic: blurred vision, cognitive impairment, constipation, dry mouth, sinus tachycardia, urinary retention
- Benzodiazepine: ataxia, depression, confusion

Drug Related Problems in Elderly (**Beers criteria = clinical practice guideline)

- Indication without drug (osteoporosis, Alzheimer's, pain, depression)
- Wrong drug (pain treated with benzo or hydroxyzine, insomnia with diphenhydramine or amitriptyline chronically)
- Too much/little drug (atypical antipsychotics, antidepressants, pain, Alzheimer's)
- Bad drug (amitriptyline, propoxyphene, meperidine, prednisone, metoclopramide)
- Iatrogenic (dental caries with amitriptyline, constipation with opioids, diabetes with prednisone)

Common Drugs with Anticholinergic Properties

- TCAs
- Scopolamine
- Amantadine
- Clozapine
- Cyclobenzaprine
- Sedating H1 blockers (diphenhydramine, hydroxyzine)
- Phenothiazines
- Meclizine
- Oxybutynin
- Tolterodine

Psychotropics and the Elderly: Use with caution

A. Antipsychotics: Used for agitation, aggressiveness, hallucinations, paranoia associated with dementia

Atypical antipsychotics: (generally use very small doses)			
Risperidone (Risperdal)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Aripiprazole (Abilify)
▪ Orthostatic hypotension ▪ Sedation	▪ Sedation ▪ Constipation	▪ Nasal congestion ▪ Xerostomia ▪ Dizziness	▪ Headache ▪ Somnolence

B. Benzodiazepines: Used for sleep and antianxiety

- Diazepam (Valium), Flurazepam (Dalmane): Highly lipid soluble, long half life, and they have active metabolites
- Lorazepam (Ativan), Temazepam (Restoril): No active metabolites, intermediate half-life
- Triazolam (Halcion), Oxazepam (Serax): No active metabolites, short half life

C. Nonbenzodiazepines for sleep:

- Diphenhydramine (Benadryl, Tylenol PM)
- Trazodone (Desyrel)
- Zolpidem (Ambien)
- Zaleplon (Sonata)

GLAUCOMA
Adapted from Terri Levien, PharmD

Open-angle bilateral, progressive changes in optic nerve head, visual field loss

- leads to loss of peripheral vision, depth perception, contrast sensitivity, and blindness
- Risk factors: ↑ intraocular pressure, age >50, black race, family history, diabetes, migraines, HTN, myopia
- Treatment
  - Goal: reduce IOP by 25-30% baseline (normal IOP range 10-21 mmHg)
  - 1st line = beta-blockers, prostaglandin analogues, brimonidine, topical carbonic anhydrase inhibitors
  - 2nd line = pilocarpine, epinephrine, dipivefrin, apraclonidine
  - 3rd line = carbachol, oral carbonic anhydrase inhibitors, topical cholinesterase inhibitors
  - When all else fails: surgery, marijuana (only 3 hr duration, but as effective as β-blockers and PG analogues)
- Monitoring: IOP and optic disk visualization q2-4 weeks until stable, then q1-6 months; visual field q3-12 months

Closed-angle physical blockage of trabecular meshwork by peripheral iris

- leads to complete blindness with in 1-5 days if not treated
- S/S: acute ↑ in IOP, moderately dilated pupil, poor pupil response to light, cloudy cornea, blurred vision, conjunctival redness, eye pain, HA, N/V, halos around light; may be proceeded by 1-2 hr attacks of symptoms
- Treatment: meds reduce IOP to preserve vision and facilitate surgery (usually high-dose pilocarpine, hyperosmotic agent, or beta-blocker)

Drug induced

- open-angle = ophthalmic/systemic/inhaled/nasal corticosteroids, fenoldopam, ophthalmic anticholinergics
- closed-angle = topical/systemic anticholinergics, topical sympathomimetics, antihistamines, heterocyclic antidepressants, phenothiazines, ipratropium

Color Coding for Topical Products

- Yellow or blue: β-blocker
- Green: cholinergic agonist
- Purple: adrenergic agonist
- Orange: carbonic anhydrase inhibitor
- Turquoise: prostaglandin analogue

Generic	Brand	Dosage Form	Strength	Dosing Interval	Primary MOA
Adrenergic Agonists					
Apraclonidine	Iopidine	Soln	0.5%, 1%	q8-12 hrs pre-op and post-op only	Decrease aqueous humor production
Brimonidine	Alphagan P Generics	Soln Soln	0.15% 0.2%	q8h	
Epinephrine	Epifrin, Glaucon, Epinal	Soln	0.25%-2%	q12h	Increase aqueous humor outflow
Dipivefrin	Propine, generics	Soln	0.1%	q12h	
β-blockers **β_1-selective**					
Betaxolol	Betoptic, generics Betoptic S	Soln Susp	0.5% 0.25%	q12h	Decrease aqueous humor production
Levobetaxolol	Betaxon	Susp	0.5%	q12h	
Nonselective					
Carteolol	Ocupress, generics	Soln	1%	q12h	Decrease aqueous humor production
Levobunolol	Betagan, generics	Soln	0.25%, 0.5%	q12-24h	
Metipranolol	OptiPranolol, gen.	Soln	0.3%	q12h	
Timolol hemihydrate	Betimol	Soln	0.25%, 0.5%	q12h	
Timolol maleate	Timoptic, generics Timoptic XE, gen.	Soln Gel	0.25%, 0.5% 0.25%, 0.5%	q12-24h q24h	
Cholinergic Agonists **Direct-acting Miotics**					
Pilocarpine	Pilocar, generics Pilopine HS Ocusert Pilo	Soln Gel Ocular Insert	0.25-10% 4% P-20, P-40	q4-12h q24h q week	Increase aqueous humor outflow
Carbachol	IsoptoCarbachol, Carboptic	Soln	0.75%, 1.5%, 2.25%, 3%	q8-12h	
Cholinesterase Inhibitor Miotics					
Demecarium	Humorsol	Soln	0.125%, 0.25%	q8-72h	Increase aqueous humor outflow
Echothiophate	Phospholine iodide	Powder	0.03-0.25%	q12-24h	
Carbonic Anhydrase Inhibitors					
Acetazolamide	Diamox, Dazamide	Tablets	~~125, 250 mg~~	~~q6-12h~~	Decrease aqueous

	Diamox	SR caps	500 mg	q12h	humor production
Dichlorphenamide	Daranide	Tablets	50 mg	q8-24h	
Methazolamide	Nepatzane, Glaucatabs, MZM	Tablets	25, 50 mg	q8-12h	
Brinzolamide	Azopt	Susp	1%	q8h	
Dorzolamide	Trusopt	Soln	2%	q8-12h	
Prostaglandin Analogues					
Latanoprost	Xalatan	Soln	0.005%	q hs	Increase uveoscleral and trabecular outflow
Unoprostone	Rescula	Soln	0.15%	q12h	
Bimatoprost	Lumigan	Soln	0.03%	q hs	
Travoprost	Travatan	Soln	0.004%	q hs	
Combination Products					
Dorzolamide/Timolol	Cosopt	Soln	2% / 0.5%	q12h	Additive
Latanoprost/Timolol	Xalcom	Soln	0.005% / 0.5%	q24h	
Pilocarpine/Epinephrine	E-Pilo-1, E-Pilo-2, P_1E_1, P_2E_2, etc	Soln	1, 2, 4, 6% / 1% epinephrine	q6-24h	

DRUG INDUCED LIVER DISEASE
Adapted from Jon Reynolds, PharmD

Liver function tests

- Measure damage not function
  - ALT (SGPT) *alanine transferase* – leaks into bloodstream from damaged hepatocytes
  - AST (SGOT) *aspartate transferase* – produced in liver and muscles, so elevations not always due to liver damage
  - Alk Phos *alkaline phosphatase* – elevated with bile duct diseases
  - GGT *gamma-glutamlytransferase* – elevated in bile duct diseases, liver disease, or in healthy people
  - LDH *lactate dehydrogenase*
- Measuring actual function
  - INR – raises in many liver diseases because of decreased clotting factor synthesis by damaged liver
  - Bilirubin – produced from erythrocyte destruction, removed from blood by liver, and secreted in the bile
    - Can be elevated with decreased liver function, bile duct obstruction, or shortened erythrocyte half-life
  - Albumin – liver synthesizes albumin, so albumin often decrease in liver disease

Alcohol-Induced Liver Disease (usually occurs with >6 drinks/day

- Progression from steatosis (fatty liver) to hepatitis (liver inflammation) to cirrhosis (fibrosis and nodules in liver)
- Steatosis and hepatitis are reversible with moderation of alcohol consumption; cirrhosis is permanent

Care of Patients with Alcohol-Induced Liver Disease

- Nutrition
  - Limit iron intake because patients' iron usually high
  - Supplement with thiamine (Vitamin B_1) because many are deficient plus it binds to iron
  - Balance protein intake to prevent hepatic encephalopathy
  - Supplement with zinc if deficient because it lowers ammonia levels
- Alcohol Withdrawal
  - Benzodiazepines (esp. lorazepam) to treat delirium tremens
  - Haloperidol and other antipsychotics to treat alcoholic hallucinosis
  - Large doses of Vitamin C and B complex
  - Hydrate with 1 liter 5% dextrose in normal saline, followed by 1 liter 10% dextrose in water
  - Phenytoin for seizures if albumin levels reasonable
- Ascites
  - Fluid restriction: 1-1.5 liters/day
  - Sodium restriction: <2 grams/day
  - Furosemide: maybe 40 mg/day
  - Spironolactone – treats secondary hyperaldosteronism, use high-dose maybe 100 mg/day
- Portal Hypertension
  - Propranolol ~20 mg BID
  - Vasopressin 20 units q3-4 hrs works temporarily; causes abdominal pain
- Esophageal and Gastric Varices
  - Vitamin K
  - Vasopressin 20 units q3-4 hrs to reduce blood flow to spleen
  - Octreotide (Sandostatin) 50-100 mcg q8 hrs SQ/IV bolus or 25-50 mcg/hr drip—not very effective
  - Propranolol, iron, folate, thiamine, H_2-blocker or PPI
- Hepatic Encephalopathy
  - Enemas
  - Limit dietary protein—especially animal protein
  - Wernicke-Korsakoff Syndrome: acute onset mental confusion caused by thiamine deficiency
    - Treat with thiamine 50-100 mg IM or IV
  - Hyperammonia
    - Lactulose 30-45 ml TID until producing 2-4 loose stools/day
    - Neomycin 4-6 grams/day divided QID to limit ammonia produced from gut flora
- Peritoneal Infections
  - Ascitic fluid is often infected with *E. coli*, *Klebsiella*, *Streptococcus*
  - Use broad-spectrum antibiotics because usually polymicrobial

Acetaminophen Overdose

- Acetylcysteine (Mucomyst)
  - Restores glutathione levels; prevents or limits liver injury
  - May aggravate nausea/vomiting – caution with esophageal varices
    - Always dilute in diet soft drinks unless going into gastric tube, then can dilute with water
    - Chill acetylcysteine to limit nausea

Other Drugs That May Cause Liver Damage

- Glyburide
- Ofloxacin (rarely)
- **TMP/SMX**
- -mycins
- -cillins
- Allopurinol
- **Acetaminophen**
- Valproate
- Aspirin
- Methyldopa
- Dantrolene
- **Isoniazid**
- Phenytoin
- Nitrofurantoin
- Trazodone

- **Methotrexate**
- Vit. A
- Vit E
- Sex hormones
- Halothane
- Diclofenac
- Tetracycline
- Amiodarone
- **Ketoconazole**
- Chlorpromazine
- Phenelzine
- **Niacin**
- Flutamide

SYSTEMIC LUPUS ERYTHEMATOSUS
Adapted from Tracy Skaer, BPharm, PharmD, FASCP, FASHP

Epidemiology (more information at www.lupus.org)
- Females with lupus:males with lupus 5:1
- Affects 1 in 2000 people
- More prevalent in African-Americans and Hispanics
- 10-year survival ~93%

Classification (need 4 out of 11 listed)
- Malar rash: fixed, flat or raised, erythema
- Discoid rash: erythema, raised patches with keratic scaling
- Photosensitivity: skin rash as a reaction to sunlight
- Oral Ulcers: oral or nasal, usually painless
- Arthritis: non-erosive involving 2 or more peripheral joints
- Serositis: Pleuritis or pericarditis
- Renal disorders: persistent proteinuria >0.5 gm/day cellular casts of any type
- Neurologic disorders: seizures or psychosis (w/o causes)
- Hematologic disorders: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia without causative meds
- Immunologic disorders: anti-double stranded DNA, anti-Smith, or positive for antiphospholipid antibodies
- Antinuclear antibodies (ANA): abnormal titer
- May also have cardiovascular, neurologic, pulmonary and various types of anemia as a result of SLE

Lab Findings
- Antinuclear antibodies
- Anti-dsDNA
- Anticardiolipin
- Anti-Smith
- Anti-Ro
- Anti-La
- Anti-ribonucleoprotein
- Lupus anticoagulant
- LE cell prep test
- Low Compliment (C3 or C4)

Concomitant Disease States
- Raynaud's
- Fibromyalgia
- Sjogren's syndrome
- Depression
- Anxiety
- Insomnia
- Chronic pain syndrome
- Migraines
- Hypertension
- Hyperlipidemia

Treatment Principles
- Target organ specific manifestations with lowest dose possible
- Aggressive treatment reserved for severe/life-threatening disease
- Adjunctive treatment for concomitant disease
- PPI for patients with GERD or over 65 on NSAIDs

Treatment of Specific Signs and Symptoms
- Skin: wear sunscreens >15 SPF
- Butterfly rash: topical corticosteroids (hydrocortisone 0.5%, triamcinolone 1%, or betamethasone 1%)
- Photosensitivity: hydroxychloroquine 200-400 mg/day (must get eye exams every 6 months)
- Cutaneous vasculitic lesions: chloroquine 250-500 mg/day
- Symmetric superficial lesions: prednisone 20-40 mg/day
- Seborrhea: tar with or without sulfur with or without aspirin shampoos

Treatment of Systemic Manifestations
- NSAIDs
- COX-2 inhibitors
- Hydroxychloroquine
- Methotrexate
- Cyclosporine

Drugs Causing Lupus-like Syndrome (just discontinue drug to resolve)
- Chlorpromazine
- Hydralazine
- Isoniazid
- Methyldopa
- Quinidine
- Penicillamine
- Procainamide

Herbals: avoid Echinacea, licorice, and excessive zinc supplements

Pregnancy
- Safe medications: prednisone, prednisolone, ASA, hydroxychloroquine, azathioprine
- Unsafe medications: methotrexate, cyclophosphamide, NSAIDS after 1st trimester
- Flares are uncommon but possible, more likely in 1st and 2nd trimester and 2 months after delivery
- High risk pregnancy because 20% have toxemia of pregnancy
- 3% will have a child with neonatal lupus: transient rash, blood count abnormalities and possible heart beat problems
- Do not breast feed unless approved by doctor

NAUSEA AND VOMITING
Adapted from Semra Stanley, PharmD

Causes

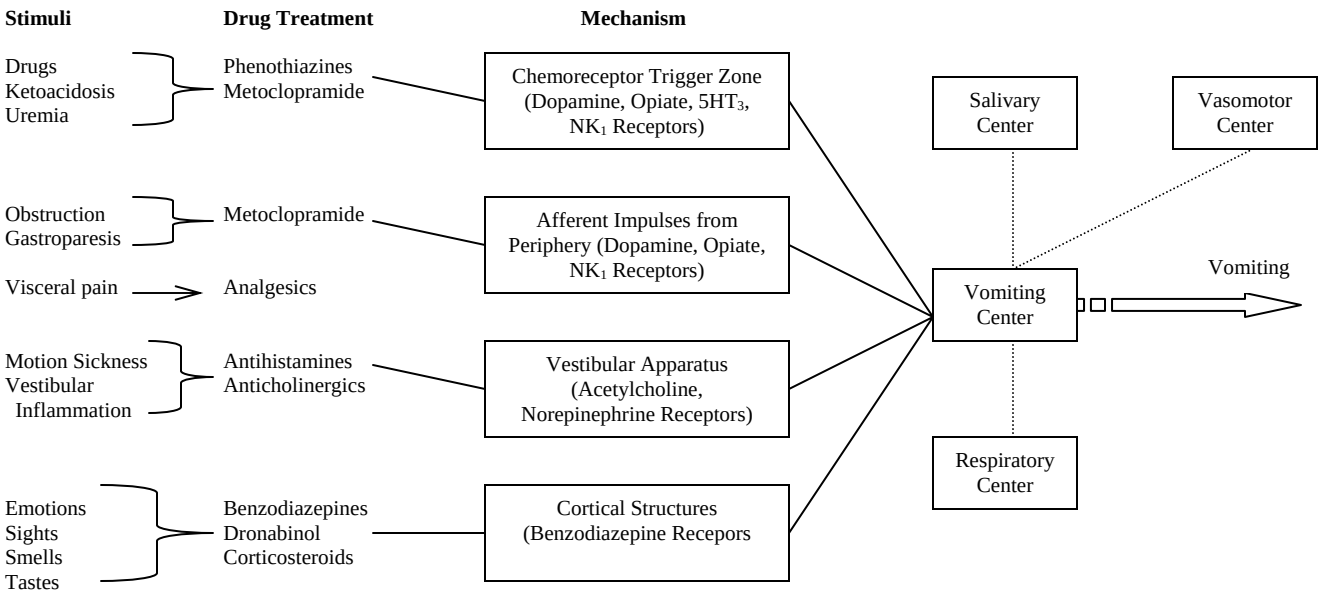
- Acute – gastroenteritis, chemotherapy, opiates, theophylline, antibiotics, anticholinergics, metabolic/endocrine disturbances, heart attack, heart failure, vestibular disorders, migraine headache
- Chronic – motility disorders, mechanical obstruction, psychogenic (bulimia), pregnancy

Treatment

- Non-pharmacologic
  - Prevent complications – dehydration, malnutrition, electrolyte disturbances
  - Address underlying pathophysiology
  - Dietary, physical, or psychological changes
- Drug therapy
  - H2 antagonists – simple N/V assoc. w/ heartburn
  - Antihistamines/Anticholinergics (meclizine, dramamine)
    - Disrupt visceral afferent pathways
    - Used for simple N/V, not complex
    - Caution in elderly
  - Phenothiazines (promethazine, compazine)
    - Block dopamine receptors in the chemoreceptor trigger zone (not as well as metoclopramide though)
    - Used for simple N/V or mildly emetogenic chemotherapy
    - Severe SE: EPS, excessive sedation
  - Butyrophenones (Haldol, Inapsine)
    - Block dopamine receptors in the chemoreceptor trigger zone
    - Used for complex N/V
    - SE: EPS, dystonia (can reverse with diphenhydramine or benztropine)
  - Corticosteroids – complex symptoms, delayed N/V with chemotherapy
  - Metoclopramide
    - Blocks dopamine receptors in chemoreceptor trigger zone
    - Increases lower esophageal sphincter tone, aids in gastric emptying, increases transit time through small bowel
    - SE: EPS, drowsiness, fatigue, diarrhea (give diphenhydramine 25-50 mg IV)
  - Serotonin Receptor Antagonists (ondansetron, granisetron, etc)
    - Block 5-HT3 receptors in the area postrema and vagal afferent fibers in the upper GI tract
    - Complex symptoms
    - Can be used in children > 2 y.o.; pregnancy category B
    - Very expensive
  - Aprepitant (Emend®)
    - Neurokinin 1 receptor antagonist
    - Decreases acute and delayed N/V in combination with 5-HT_3 antagonist and steroid

Chemotherapy Induced Nausea/Vomiting

- Acute N/V
  - Occurs within 24 hours of chemo
  - Emetogenicity of chemo regimen—cisplatin and cyclophosphamide are worst
  - Drug therapy must target CTZ
  - 5-HT3 antagonists lose effectiveness after 2-3 days
  - **give antiemetics around the clock with PRN antiemetics for break through N/V
- Delayed N/V
  - Occurs 2-4 days post chemo
  - Drug of choice: corticosteroids esp. dexamethasone
- Anticipatory N/V
  - Drug therapy should target cortical structure (benzodiazepines)
  - Patient perceptions, N/V from previous courses of chemo, general anxiety
  - **If N/V from first chemotherapy course treated appropriately, less anticipatory N/V later


Stimuli
Drug Treatment
Mechanism
Drugs
Ketoacidosis
Uremia
Phenothiazines
Metoclopramide
Chemoreceptor Trigger Zone (Dopamine, Opiate, 5HT3, NK1 Receptors)
Obstruction
Gastroparesis
Metoclopramide
Afferent Impulses from Periphery (Dopamine, Opiate, NK1 Receptors)
Visceral pain
Analgesics
Motion Sickness
Vestibular
Inflammation
Antihistamines
Anticholinergics
Vestibular Apparatus (Acetylcholine, Norepinephrine Receptors)
Emotions
Sights
Smells
Tastes
Benzodiazepines
Dronabinol
Corticosteroids
Cortical Structures (Benzodiazepine Recepors
Salivary Center
Vasomotor Center
Vomiting Center
Vomiting
Respiratory Center

OBESITY
Adapted from Louise Achey, PharmD

BMI = wt in kg / ht in m^2
- Overweight: BMI ≥ 27.8 (men) or ≥ 27.3 (women)
- Obese: BMI ≥ 31.1 (men) or ≥ 32.3 (women)

**Note: BMI doesn't take muscle mass into account, thus use waist circumference with BMI

Waist Circumference = narrowest point between lowest rib and top of iliac crest

Need to treat if:
- BMI > 30
- BMI of 25-29 **IF 2 risk factors present**
- Waist circumference > 35 inches (women) or > 40 inches **PLUS 2 risk factors present**

**Risk factors = hypertension, type II diabetes, dyslipidemia

Weight loss algorithm: Target weight loss is 5-10% of <u>starting</u> body weight

Option 1 (BMI ≥ 30 OR BMI 25-29.9 with 2 risk factors)
- 6 months duration
- Modify:
  - Diet
    - Decrease daily caloric intake by 500-1000 less per day
    - Fat intake not more than 30% of daily calories
  - Activity Level
    - Initial target: 30-45 minutes 3-5 times per week
    - Goal: 30 minutes moderate activity daily
  - Behavior
    - Eating patterns

Option 2 (BMI ≥ 30 OR BMI ≥ 27 with 2 risk factors)
- If patient has not lost at least 1 lb/week on Option 1 program
- Add drug therapy as adjunct
  - Appetite suppressants - amphetamines, phentermine, diethylpropion, sibutramine
    - Monitor for increase in BP
  - Nutrient absorption modifiers - orlistat (take daily multivitamin)
  - Thermogenic agents - ephedrine
  - Miscellaneous - bupropion, metformin, topiramate
- Maintain non-pharmacologic treatment

Option 3 (BMI ≥ 40 OR BMI ≥ 35 with 2 risk factors
- Surgical treatment- gastroplasty, gastric bypass

OSTEOARTHRITIS
Adapted from Steve Setter, PharmD, CGP, CDE, DVM

General Features of Osteoarthritis

Clinical	Laboratory	Radiographic
Age > 50	RF < 1:40	Osteophytes (bone spurs)
Morning stiffness < 30 minutes	Non-inflammatory synovial fluid	Asymmetric joint space narrowing
Crepitus (joint grinding)		Sclerosis
No inflammation		Misalignment
Bony enlargement		

Risk Factors of OA: congenital/development disorders, obesity, exercise, old age, high bone mineral density
NonPharmacologic Treatment: education, physical therapy, exercise, weight reduction, canes/walkers, massage, surgery
Pharmacologic Treatment

- APAP: 1st line, good for newly diagnosed cases (3-4g/day)
- NSAIDS: 2nd line, COX 1 and COX 2 inhibitors
    - Risk Factors for NSAID induced GI ulceration
        - Age >60
        - Increased NSAID dose, NSAID treatment >3 months, or more than one NSAID used
        - Concomitant corticosteroid use
        - History of peptic ulcer disease
        - Disability
    - GI Ulcerations:
        - 60% are asymptomatic
        - Symptoms are black, tarry stools, coffee-ground like vomit, and chronic fatigue
        - Consider concomitant misoprostol or proton-pump inhibitor for prevention
- Hyaluronan "Viscosupplementation"
    - Sodium hyaluronate: Hyalgan and Supartz (both weekly IA injection for 5 weeks)
    - Hylans: cross-linked derivatives of sodium hyaluronate: Synvisc (IA injections weekly for 3 weeks)
    - For pain relief
    - Restores viscosity/elasticity to joint fluid
- Capsaicin: must apply tid-qid for several weeks for maximal effect
- Corticosteroids (PO/IA)
    - IA steroids no more than once or twice a year (increased joint damage if used more frequently)
- Opioids
- Ca/Vit.D
- Tramadol
- Glucosamine/Chrondroitin
    - Recommended by rheumatologists
    - 1500 mg/day in 3 divided doses or 1500 mg daily. Try for at least 3 months.
    - Watch for shellfish allergy

All treatment for osteoarthritis is symptomatic. There is no disease modifying drug.

Miscellaneous Terms

- Bouchard's nodule: on proximal knuckles
- Herberden's nodes: on distal knuckles

OSTEOPOROSIS
Adapted from Steve Setter, PharmD, CGP, CDE, DVM

Osteoporosis Resources

- www.nof.org (National Osteoporosis Foundation)
- www.fore.org (Foundation for Osteoporosis Research and Education)
- www.osteofound.org (International Osteoporosis Foundation)
- www.osteo.org (NIH)
- www.rheumatology.org (American College of Rheumatology)

Consequences of 1st Fracture

- Increased risk of death
  - ~20% of women die within a year after hip fracture
  - Vertebral fractures increase all-cause mortality by 5%
- Increased risk of additional fractures
- Individual suffering—only ½ of vertebral fractures are diagnosed

Risk factors

- Postmenopausal
- Caucasian/Asian
- Female
- Small body frame (<127 lbs)
- Family history
- Cigarette smoking
- Alcohol abuse
- Sedentary lifestyle
- Inadequate intake of VitD/Ca^{2+}
- Excessive caffeine
- Low BMD
- History of eating disorder
- Live in the north (less Vit. D – less sun)
- Previous fracture
- Height loss (>4cm)

Drugs associated with osteoporosis:

- Corticosteroids
- GRH agonists/antagonists
- Anticonvulsants
- Heparin (long-term use)
- Excessive thyroxine (levothyroxine)
- Immunosuppressants (MTX, CsA)
- Cytotoxic drugs
- Lithium
- Tamoxifen (premenopausal use)

Recommendations for Prevention

- Adequate Vit D/Ca^{2+} intake
- Weight-bearing exercise
- Muscle strengthening/flexibility
- Smoking cessation
- Reduce alcohol/caffeine consumption
- Measure BMD
- Eliminate fall hazards in home

T-Score Evaluation of Osteoporosis

T-Score Evaluation	T-Score
Normal	> -1
Osteopenia	< -1 to > -2.5
Osteoporosis	< -2.5
Severe Osteoporosis	< -2.5 with fracture

*Fracture Risk doubles for every 1 standard deviation below the mean. 1 standard deviation = a 12% bone loss

Calcium and Vitamin D Supplementation

- Calcium supplements: 1000-1500 mg elemental calcium/day divided BID-TID
  - Better absorption with food (except calcium citrate)
  - SE : constipation, dyspepsia, N/V, flatulence
- Vitamin D: 400-800 IU/day **do not exceed 1,000 IU/day
  - Ensures adequate calcium and phosphorus absorption in small bowel

Dietary Sources of Calcium

Food	Serving Size	Calcium Content (mg)
Whole milk	1 cup	291
Ice cream	1 cup	302
Yogurt (low fat)	1 cup	200
American cheese	1 oz	345-415
Cheddar cheese	1 oz	150
Cottage cheese (low fat)	1 oz	115
Swiss cheese	1 oz	154
Cheese pizza	1 slice	250
Fortified OJ	1 cup	350
Sardines	3 oz	372
Salmon with bones	3 oz	167
Bokchoy	½ cup	126
Broccoli	1 cup	100-136

Collards, raw	½ cup	179
Figs, dried	5 medium	126
Soybeans	1 cup	131
Spinach	½ cup	113
Tofu	4 oz	106
Turnip	½ cup	126

Pharmacological Agents

DRUG	INDICATION	DOSE	ADVERSE EFFECTS	CONTRAINDICATION	COMMENTS
Raloxifene (Evista®)	Prevention and tx of PMO	60 mg QD	Hot flushes, leg cramps, peripheral edema, thromboembolic events	-Pregnancy/lactating -Thromboembolic disease -Immobility	For P & Tx May increase TG. Does not increase risk of breast CA.
Alednronate (Fosamax®) Risedronate (Actonel®) Ibandronate (Boniva)	-Prevention and tx of PMO -Tx of glucocorticoid induced osteoporosis -Tx of male osteoporosis (only Fosamax) -Prev and Tx of PMO	Prev: 5 mg qd or 35 mg weekly Tx: 10mg qd or 70 mg weekly Prev: 5 mg qd Tx: 35 mg weekly 150 mg monthly	Dyspepsia; abdominal pain; espophageal/GI irritation, perforation, ulceration, or bleed; Musculoskeletal pain, arthralgia, HA, rash	-Abnormalities of the esophagus which delay esophageal emptying, such as stricture or achalasia -Inability to stand or sit up right for at least 30 min. (60 min for boniva) -Hypersentitvity to any component of this product -Hypocalcemia -Fosamax is not recommended for Clcr<35ml/min. Boniva not for <30	**For P & Tx, best choice if pt w/severe osteoporosis.** -Take with 8 oz water before first food/drink/medicine of day; do not lie down for at least 30 min. (60 min for Boniva). -Ensure adequate Ca/Vit D -Report any dysphagia or worsening of heartburn
Calcitonin (Miacalcin®)	Tx of PMO and hypercalcemia	IN: 200 IU QD (1 activation) IM/SQ: 100 IU QOD	IN: rhinitis, epitaxis, nasal irritation, back pain SQ: GI symptoms, injection-site pain, flushing	-Fish hypersensitivity -Hypocalcemia -Pregnancy	-For Tx only -Alternate nostrils for each dose. -Agent is less effective if used in pt w/ fracture pain, or cannot use other medications.
Teriparide (Forteo®)	High risk of fracture (T-score<-3.0, Age>70),Prior fracture, Failure of antiresorptive: fracture, decreasing BMD, Intolerant of other therapies, Glucocorticoid osteoporosis	20mcg SC QD	HA, Nausea, Dizziness, Leg cramps, angina, GI problems	Children, adolescents, HX bone CA, Radiation therapy of the bones, Paget's dz, HX of hypercalcemia, Pregnant/nursing, Active gout	Can be used in men and women

Abbreviations: CA= cancer; IN= intranasal; Prev= prevention; TG=triglycerides; Tx= treatment; Hx=history, PMO=postmenopausal osteoporosis

PEDIATRICS
Adapted from Megan Undeberg, PharmD

Useful References

- Pediatric Dosing Handbook
- Drugs in Pregnancy and Lactation
- Guidelines for Administration of Intravenous Medications to Pediatric Patients
- The Harriet Lane Handbook

Classification of pediatric patients

- Preemie: variable
- Neonate: Day 0 to day 30
- Infant: Day 30 to 24 months
- Child: 2 years to puberty

APGAR Classification Scheme

- APGAR = appearance, pulse, grimace, activity, respiration
- Newborns evaluated at 1 min and 5 min after birth—again at 10 min if not doing well
- Score <4 at 1 minute = big problems, score 5-8 = monitor closely, score ≥8 = normal

APGAR Scores

	0	1	2
Color	Blue, Pale	Pink body, blue extremities	Pink
Heart Rate	Absent	<100	>100
Reflex Irritability	No response	Grimace	Sneeze/cough
Muscle Tone	Flaccid	Some flexion	Good flexion
Respiratory Effort	Absent	Weak, irregular	Good, crying

Estimating a Child's Weight

Age (years)	1	3	5	7	9
Weight (kg)	10	15	20	25	30

Pediatric Differences in Drug Absorption

- Topical
  - Immature stratum corneum; decreased skin thickness, and increased skin hydration
  - Increased ratio of skin surface area per kg body wt as compared to adult (3:1)
  - Common topical toxicities: iodine, boric acid, corticosteroid cream, chlorhexadine, and lindane
- Oral
  - Gastric pH is higher until 2-7 years old
    - Bioavailability increased for basic drugs and deceased for acidic drugs
  - Gastric emptying and GI transit time is slower in newborns and increased in children
    - Difficult to predict time to peak or rate of drug absorption
  - Decreased bile acid secretion and pancreatic secretions
- Intramuscular
  - Hard due to small muscle mass
  - Decreased muscle blood flow, decreased strength of muscle contractions, and increased % of water in muscle mass
  - Common IM injections in newborn: vitamin K, penicillin, aminoglycosides, phenobarbital
- Rectal: poor and erratic (although diazepam IV soln given PR)

Pediatric Differences in Drug Distribution

- Decreased protein binding: decreased albumin, increased free drug fraction = higher concentrations in body
- Increased total body water and extracellular water: result increased Vd

Pediatric Differences in Drug Metabolism

- Immature enzymes in neonates, decreased enzyme capacity
- Clearance decreased and drug half-life increased

Pediatric Differences in Excretion

- Decreased glomerular and tubular function in neonates
- May take weeks to months to fully develop: by 6 months GFR ~ adult GFR
- For 1-18 years of age:

$$CrCl = \frac{0.49 \times (\text{height in cm})}{SCr}$$

Contraindicated medications:

- Tetracyclines: dental staining and decreased bone growth
  - Avoid in kids <8 yo
- Fluoroquinolones: safety is unclear; not for use if <18 yo
- Sulfas: avoid use during first 2 months because displaces bilirubin from protein binding site causing kernicterus

- Chloramphenicol: accumulates in neonates causing "gray baby syndrome"
- Benzyl alcohol: causes metabolic acidosis and "gasping syndrome" (use preservative free solutions)
- Propylene glycol: at high doses→ hypo-osmolarity in Infants

Fever:

- Causes: infection and drug-induced
- Refer: children under 2 months of age or temp greater than 38.9 deg C in children 6-24 months
- Nonpharmacological treatment of fever: light clothing, remove blankets, tepid bath if > 40 deg C, encourage cool fluids— 30-50 ml/hr
- APAP: 1st line generally safest in peds
    - 10-15 mg/kg/dose PO Q 4-6 hr, NTE 65 mg/kg/day
- Ibuprofen: fever, inflammation
    - 5-10 mg/kg/dose PO Q 6-8 hr, NTE 40mg/kg/day
- ASA: not for use if <16 yo—risk of Reye's syndrome
    - Best use: juvenile rheum. arthritis, Kawasaki's disease, rheumatic heart disease
    - 10 mg/kg/dose PO Q 4-6 hr, NTE 60-80 mg/kg/day

Reye's Syndrome

- Acute illness characterized by encephalopathy and fatty degeneration of the liver
- Onset: profuse vomiting, neurological impairment
- Cause: unknown; usually preceded by a viral infection and correlated with use of aspirin

Cough and Cold

- Most common OTC products: decongestants, antihistamines, expectorants.
- Nasal (topical) decongestants in children:
    - Naphazoline NLT 12 years old
    - Ephedrine NLT 6 years old
    - Phenylephrine NLT 6 years old
    - Xylometazoline NLT 6 years old
    - Oxymetazoline NLT 6 years old
- Antihistamine
    - Most common side effects: sedation, dry eyes/nose/mouth, decreased urination, paradoxical excitation
- Expectorants: Water is the gold standard.
    - Pharmacotherapeutic alternative: guaifenesin (take with water)

Vomiting

- Watch for dehydration: sunken eyes, decrease urine output crying without tears.
- 5-10 ml oral rehydration solution every 10-15 minutes
- If emesis reoccurs wait 30-60 minutes and try again
- Rehydration solutions:
    - Na 90mEq/L, K 20mEq/L, 25 gm glucose/L 310 mOsm
    - Maintenance solution: ex Pedialyte
    - Na 45mEq/L, K 20mEq/L, 25 gm glucose, 250 mOsm

Gastroesophageal Reflux

- Common in infants
- S/S: vomiting, failure to thrive, anemia, dysphagia, pneumonia
- Treatment
    - Thicker formula with smaller feedings
    - Place child at 45 degree angle
    - Drug therapy for 3-4 months: metoclopramide, antacids, PPIs, H_2-antagonists
    - Surgery

Respiratory Distress Syndrome (RDS)

- Pulmonary surfactant deficiency that leads to respiratory failure
- Cortisol stimulates surfactant production at 30-32 weeks gestation, sufficient amounts present by 34-36 weeks
- Clinical Symptoms of RDS
    - Tachypnea
    - Cyanosis
    - Retracting respirations
    - Nasal flaring
    - Grunting
- Prevention:
    - Mimic natural production
        - Betamethasone 12 mg IM every 24 hours x 2 doses
        - Dexamethasone 6 mg IM every 12 hours x 4 doses
    - Tocolytics (terbutaline, Ritodrine, Mg sulfate): may delay/prolong pregnancy 2-7 days
- Treatment:
    - Empiric antibiotics

    - Oxygen therapy/ Mechanical ventilation: risk of blindness, deafness, damage to alveoli/bronchioles
    - Exogenous surfactant: natural, modified natural or synthetic
        - Administered intratracheally 10-20 minute via infusion pump
        - Usually 2-3 doses, 12 hours apart
        - Rapid improvement of oxygenation and lung compliance, 40% increase in survival rate
        - ADRs: bradycardia, oxygen desaturation, obstruction, and pulmonary hemorrhage

Bronchopulmonary Dysplasia (BPD)

- Complication from RDS
- Chronic pulmonary disease in infant, results from high levels of O_2 therapy also caused by mechanical ventilation in preemies
- Complications: pulmonary HTN, cor pulmonale, systemic HTN, LV hypertrophy, chronic respiratory difficulties, growth, nutritional and neuro-developmental problems
- Treatment: supplemental O_2, nutrition, diuretics for edema, albuterol, caffeine to stim. resp.

Respiratory Syncytial Virus (RSV)

- Characteristics: caused by enveloped, RNA virus, which is unstable in the environment and killed in soap and water
- Usual season: fall through early spring
- Treatment: Synagis (palivizumab); monoclonal antibody for passive immunity
    - 15 mg/kg/month IM for 12 months
    - Usually administered 1 month prior to start of RSV season and monthly throughout season

Colic

- Syndrome of sustained irritability, fussing or crying
- Usually between weeks 2-4; often spontaneously resolves by 3 months
- Causes: In breast-fed infants gassy foods like cabbage, onions, garlic, broccoli, and turnips; some may have true cow's milk allergy
- Therapeutic Options
    - Ask about mom's diet, and possibly change in formula
    - Simethicone for gas: <2 yrs- 0.3 ml QID PC and HS, can be mixed with 1 oz of formula or water
    - Wrap baby like a burrito

RHEUMATOID ARTHRITIS
Adapted from Steve Setter, PharmD, CGP, CDE, DVM

Definition: Autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and sometimes multisystem involvement. TNF and IL-1 are overproduced, and chronic fluctuation of the disease is common.

Epidemiology
- 1-2% of the population
- 3:1 females:males
- 50% stop working within 10 years after disease onset

most rheumatologists favor aggressive treatment early on in disease to slow progression and preserve functionality

Unique Labs
- Erythrocyte sedimentation rate (ESR)
- RF: 60-70% w/ RA are RF positive
- Antinuclear antibodies (ANA): 25% w/ RA are positive

Extraarticular Manifestations
- Rheumatoid nodules (~20% of patients)
- Sjogren's syndrome (dry, itchy eyes)
- Episcleritis and scleritis
- Interstitial lung disease (esp. with smokers)
- Pericardial disease (rarely symptomatic)
- Systemic vasculitis
- Felty's syndrome (splenomegaly and neutropenia)

Drug treatment
- Symptomatic Treatment
  - NSAIDs
    - May take 1-2 wks to see reductions in signs of inflammation
    - Doesn't alter the course of the disease or prevent joint destruction
    - Reduce joint pain, swelling, and improve function
    - No differences in efficacy between NSAIDs, only differences in side effects
    - Non-acetylated salicylates are safest for elderly patients
    - Consider misoprostol or PPI to prevent GI ulcerations
  - Glucocorticoids (GC)
    - Used for bridge therapy during flare-ups until slower acting disease modifying drugs begin to work (2-3 weeks)
    - May reduce the rate of progression
    - <10mg/d
    - Monitor: BP, chemistry panel, bone density
- Disease Modifying Anti-Rheumatic Drugs (DMARDs): use combinations for resistant RA
  - Hydroxychloroquine (HCQ): 400-800 mg/d
    - Response may take up to a year
    - No laboratory monitoring
    - Periodic ophthalmologic exams (rare retinal damage), >40 yo
    - Least toxicity, least costly to monitor
  - Sulfasalazine (SSZ): 0.5-3 grams/d
    - Sulfa allergy
    - Side effects: GI, HA, photosensitivity, yellow-orange urine, binds iron salts
    - Monitoring: CBC, LFTs, G6PD
    - Converts to sulfapyridine (active) and 5-aminosalicylic acid in colon
  - Methrotrexate (MTX): 5-20 mg/week
    - Inhibits dihydrofolate reductase (impairs DNA synthesis, which inhibits immune response)
    - Supplement with 1mg folic acid daily
    - Most predictable benefit of disease modifying agents
    - Pregancy category D/X
    - Side effects: hepatotoxicity, stomatitis, pulmonary fibrosis (rarely), and bone marrow suppression
    - Monitoring: CBC, LFTs, albumin, SCr
    - NSAIDS may increase MTX activity by inhibiting renal tubular secretion
  - Leflunomide (Arava®)
    - Tx of active RA to reduce S/S and slow the structural damage
    - Can be used with ASA, NSAIDS, and low dose steroids
    - Don't use with HCQ, MTX, or other disease modifying agents until further studies performed
    - Loading dose: 100mg QD for 3 days
    - Maintenance dose: 20mg QD
    - Contraindications: pregnancy, liver disease
    - Precaution: renal insufficiency and immunodeficiency
    - SE: diarrhea, alopecia, nausea, rash
    - Monitor: ALT/AST
    - Half life is 11 days due to biliary recycling
    - Those expecting to father a child should eliminate drug with cholestyramine 8 g for 11 days

- Less Common Therapies
  - IM Gold salts
  - Oral gold
  - D-penicillamine
  - Azathioprine
  - Cyclosphosphamide
  - Chlorambucil
  - Cyclosporine A

- Biologic Response Modifiers: up to 85% of patients respond to BRMs, but cost limits use
  - Enbrel
    - Recombinant human TNF-R fused with Fc fragment of IgG. Binds to TNF to prevent activation of receptors, hindering inflammation.
    - Adults with moderate to severe active RA refractory to DMARDs
    - Children with juvenile RA between the ages of 4-17
    - May be used in conjunction with DMARDs/NSAIDS
    - Dosage: 50 mg SQ (in two sites) once weekly or 25mg SQ twice weekly with 72-96 hours between doses
    - Effects seen within 2-12 weeks (15% people don't respond at all)
    - Refrigerated un-reconstituted vial (use reconstituted vial within 6 hours)
    - CI: immunosuppressive, sepsis, live vaccine administration, active infection
  - Remicade (infliximab)
    - Chimeric monoclonal antibody that binds to TNF
    - Indicated for Rheumatoid arthritis and Crohn's disease
    - Dosage: 3-10 mg/kg IV followed by additional doses given at 2 and 6 weeks after the first dose, and repeated every 4-8 weeks thereafter. **Take with methotrexate to prevent anti-Remicade antibody production.
    - Reconstitute with sterile water for injection. Do not shake. NO preservatives, so use vial right away
    - SE: Acute infusion rxns of fever, chills, pruritus, urticaria
    - CHF patients: NYHA class I/II: max 5mg/kg. Class III/IV don't use
  - Humira (adalimumab)
    - Recombinant human IgG1 MAB specific for human TNF
    - Dosage: 40mg SQ every other week or 40 mg every week if patient is not on MTX
    - Can be used with MTX, DMARDS, NSAIDS, steroids
    - Risk of tuberculosis = black box warning; must do Tb test before starting treatment
  - Kineret (Anakinra)
    - Recombinant human interleukin-1 reception antagonist (IL-1RA)
    - Monotherapy or in combination with DMARDS
    - Indicated for RA patients 18 years or older who have not responded to one or more DMARDS
    - Dosage: 100mg SC QD
    - SE: injection site rxn, HA, N/V, abdominal pain

Comparison of Osteoarthritis and Rheumatoid Arthritis

Clinical Feature	Osteoarthritis	Rheumatoid Arthritis
Age of onset	Generally >40	Any age
Disease distribution	Localized to joint	Systemic involvement
Erythrocyte Sedimentation Rate (ESR)	Generally normal	Elevated
Inflammation	Absent or mild	Present
Joint involvement	Anything goes (often 1 or 2 joints)	Bilateral, symmetric (often 3 or more joints)
Morning stiffness	Usually <60 minutes	> 1 hour
Osteophyte (bone spur)	Often present	Absent
Pannus (joint capsule overgrowth)	Absent	Often present
Rheumatoid factor	Negative	Frequently positive
Subcutaneous nodules	Absent	Frequently present
Swelling	Irregular/knobby	Diffuse/symmetric
Typical presentation	Deep aching pain in joint	Malaise, fatigue, musculoskeletal pain

WOMEN'S HEALTH TOPICS
Adapted from Brandi Kimball, PharmD

Dysmenorrhea (painful menstruation)

- Symptoms: mild to severe cramping in the lower abdomen, back, or thighs; headache, diarrhea or constipation, nausea, dizziness or fainting.
- Primary dysmenorrhea is a term used to describe painful menstrual cramping with no recognized physical cause
- Most commonly seen in women of 20-24 years old
- Treatment Options
  - NSAIDS (OTC and RX): diclofenac, ibuprofen, ketoprofen, naproxen
  - COX-2s: celecoxib
  - Oral contraceptives – not FDA approved for dysmenorrhea

Endometriosis

- Endometrial tissue presents outside the uterus, most commonly the peritoneal cavity. Leads to pelvic pain, infertility, and hysterectomy
- Laparoscopy/laparotomy needed for definitive diagnosis; classified by stages I-IV (minimal to severe)
- Treatment Options
  - Dietary therapy to control prostaglandin synthesis
  - Empiric NSAIDS and Oral Contraceptives
  - Danazol 200-800mg per day in 2 divided doses. Dosing should be employed for at least 3-6 months, but should not exceed 9 months. Antiestrogenic and weakly androgenic
  - Leuprolide 3.75mg IM once monthly, or 11.25mg IM once every 3 months, max of 6 months
  - Nafarelin 1 spray (200 mcg) into one nostril in the morning and 1 spray into the other nostril in the evening, started between days 2 and 4 of cycle. Duration of treatment = 6 months
  - Depo-medroxyprogesterone 150mg IM every 13 weeks
  - Total hysterectomy and bilateral salpingo-oophorectomy

Premenstrual Syndrome (PMS) & Premenstrual Dysphoric Disorder (PMDD)

- **PMS**: Anxiety, irritability, fatigue, moodiness, back ache, breast tenderness, headache and bloating
- **PMDD**: Symptoms are more severe than PMS and interfere with activities of daily living (DSM-IV diagnosis)
  - Includes at least one of the following: depressed mood or hopelessness, tension or anxiety, affective lability (sudden mood swings) or irritability
  - OR any combination of the following: decreased energy or interest in activities, difficulty concentrating, change in appetite and/or sleep, easily overwhelmed, physical symptoms (pain, bloating, etc)

Treatment Options for PMS/PMDD

LIFESTYLE MODIFICATIONS	VITAMIN/MINERAL SUPPLEMENTS	OTC PAIN RELIEVERS	HERBALS (effectiveness not proven)	PRECSRIPTION MEDICATIONS
- Reduce fat, sugar caffeine and salt in diet - Abstain from alcohol, nicotine and illicit drugs - Exercise at least three times per week - Get at least 8 hours of sleep - Manage stress	- Vitamin E 400 IU - B Vitamins - Calcium 1200mg to 1600mg (divided doses) - Magnesium 200mg to 360mg	- Acetaminophen (not to exceed 4000mg per day) - Ibuprofen (not to exceed 2400mg per day) - Naproxen sodium 220mg q 8-12 hours - Combo products: Midol or Pamprin	**For PMS**: - Dong quai, Angelica sinesis - Gamma-linoleic acid (GLA) - Valerian **For PMDD**: - St. John's Wort *Hypericum perforatum*	**For Pain:** - NSAIDS (diclofenac, ibuprofen, naproxen) - Opiods, if severe (hydrocodone/acetaminophen) **For Mood**: - Fluoxetine 20mg QD - Paroxetine 5-30mg QD - Sertraline 50-150mg QD - Off label: citalopram, fluvoxamine, nefazodone, nortriptyline, venlafaxine

Infertility Treatment

- Clomiphene
  - Use: infertility due to anovulation, irregular ovulation, or luteal phase defects incl. polycystic ovarian syndrome
  - Dose: 50 mg PO once daily for 5 days
  - Initiated on 5th day of cycle following first day of withdrawal of menstrual bleeding
- Progesterone
  - Use: infertility in women with progesterone deficiency, supplement/replace progesterone as part of an Assisted Reproductive Technology (ART)
  - Dose: 90 mg (8% gel) PV once daily (BID if partial or complete ovarian failure)
  - If pregnancy occurs, continue using for 10-12 weeks until placental autonomy achieved
- Ovulation Stimulants
  - Use: infertility due to anovulation without primary ovarian failure including those who have received an GnRH agonist or antagonist, or in those women with hypogonadism
    - Menotropins: 75 IU of FSH/LH activity given IM once daily for 5-12 days

        - HCG: 5000-10,000 USP units IM as a single dose
        - Follitropins, lutropin: specialized dosing for infertility based on weight, LFTs

Menopause

- Causes: natural consequence of aging, premature ovarian failure, or premature ovarian removal
- Symptoms: hot flushes/flashes, dyspareunia, stress incontinence, urethral syndrome, mood alterations, changes in sleep cycle
- Women's Health Initiative Findings with HRT
    - Estrogen plus progestin versus placebo
        - Increased risk of heart attack, stroke, blood clots, breast cancer, dementia
        - Decreased risk of colorectal cancer, fractures
    - Estrogen alone versus placebo
        - Increased risk of stroke, blood clots
        - Reduced fracture risk
        - No difference in risk of heart attack, colorectal cancer, dementia
- FDA Recommendations for HRT: use lowest doses for shortest duration to relieve symptoms of menopause, or to prevent osteoporosis in women who cannot tolerate alternative therapies (e.g. bisphosphonates)

HRT Products

Oral	Transdermal	Miscellaneous
- Enjuvia (synthetic conjugated estrogens; B) - Femhrt (norethindrone acetate/ethinyl estradiol) - Prefest (estradiol/norgestimate) - Premarin (conjugated estrogens) - Prempro & Premphase (conjugated estrogens/medroxyprogesterone acetate)	- Alora (estradiol) - Climara (estradiol) - Climara Pro (estradiol/levonorgestrel) - Combipatch (estradiol/norethindrone acetate) - Estraderm (estradiol) - Vivelle & Vivelle-Dot (estradiol)	- Premarin vaginal cream (conjugated estrogens) - Estrasorb (estradiol topical emulsion) - Delestrogen (estradiol valerate injection) - Premarin Intravenous (conjugated estrogens) - Calcium and Vitamin D supplementation - Bisphosphonates or SERMs to prevent osteoporosis

- HRT Contraindications
    - Breast, cervical, endometrial, hepatocellular, ovarian, uterine, or vaginal cancer
    - Endometrial hyperplasia
    - Hepatic disease
    - Hypercalcemia
    - Jaundice
    - Pregnancy
    - Stroke
    - Thromboembolic Disease
    - Thrombophlebitis
    - Vaginal Bleeding
- Alternative treatment options for hot flashes:
    - Venlafaxine 75 mg daily (quicker onset than HRT)
    - Fluoxetine 20 mg daily
    - Paroxetine 20 mg daily
    - Black Cohosh (not shown to be effective)
    - Phytoestrogens (from food sources-apples, soy, carrots, garlic, beans, peas—or as a supplement—Promensil® 40-160 mg daily)
- Alternative treatment options for genitourinary symptoms: topical estrogens, vaginal lubricant (for dryness and discomfort)

ACETAMINOPHEN
Adapted from Wil Edwards, PharmD and Gregory Holmquist, PharmD

Mechanism
MOA: Largely unknown. Inhibits prostaglandin synthesis in CNS, and blocks peripheral pain transmission (very mild), Does **NOT** inhibit cyclooxygenase to any extent.

Benefits of APAP
- Fewer GI side effects than NSAIDs
- Cheap and effective for many patients

Dosing
- 4 gram/day in healthy adult
- 3 gram/day in elderly
- 2 gram/day in alcoholic
- 10-15 mg/kg q4-6h pediatric

Disadvantages to APAP
- Nephrotoxicity: National Kidney Foundation discourages chronic use
- GI bleed—esp. at >2 gms/d or with NSAID
- No anti-inflammatory effect
- Ceiling effect to analgesia
- Hepatotoxicity

Treating Overdose
- N-acetylcysteine (Mucomyst®)
  - 140mg/kg PO for first dose, then 70mg/kg q4h for 17 doses
- N-acetylcysteine (Acetadote®)
  - 150mg/kg in 200mL of D5W over 15min for 1st dose
  - Maintenance: 50 mg/kg in 500 ml D5W over 4 hr, then 100 mg/kg in 1L D5W over 16 hr

ACID/BASE HOMEOSTASIS
Adapted from Brent Albertonson, PharmD

Disorder	Causes	Compensation	Treatment*
Respiratory Alkalosis	Hyperventilation	Renal HCO_3 Excretion	▪ Rebreathing Device (paper bag) ▪ Sedation
Respiratory Acidosis	▪ Decreased CO_2 removal ▪ Hypoventilation (pulmonary edema, COPD, pneumonia) ▪ CNS disturbance (trauma, stroke, CNS depressants) ▪ Mechanical ▪ Neuromuscular (MS)	Renal H^+ Excretion—leads to HCO_3 reabsorption and ammonia loss in urine	▪ Acute: supplemental oxygen, treat underlying cause (naloxone, flumazenil, bronchodilation) ▪ Chronic: bronchodilation, antibiotics, **careful with oxygen and only if $pO_2 < 50$ mmHg
Metabolic Alkalosis	▪ Loss of H^+ ion (vomiting) ▪ Addition of bicarb or bicarb precursors (citrate, acetate, carbonate) ▪ Loss of Cl^- rich, bicarb poor fluids (diuretics)	Hypoventilation	▪ NaCl responsive (GI, diuretics, CF): o NaCl solns with K^+ o Carbonic Anhydrase Inhibitor o PPI/H_2RA when NG suction unavoidable ▪ NaCl unresponsive (Cushing's, hyperaldosteronism, profound K^+ loss): ▪ Remove excess mineralocorticoid (e.g. fludricortisone)
Metabolic Acidosis	▪ Increased anion gap – ketoacidosis, uremia, salicylate, methanol, antifreeze, lactic acidosis ▪ Normal AG – acid ingestion, carb anhydrase inhibitors, GI disorders, dilutional acidosis, renal tubular acidosis	Hyperventilation	▪ Fluids and electrolytes ▪ Insulin if DKA ▪ Manage poisonings ▪ Dialysis with renal failure ▪ Sodium bicarb as last resort

**always treat underlying cause first if identifiable

Determining acid/base disturbances

1. Assess pH: < 7.35 = acidosis, > 7.45 = alkalosis
2. Assess pCO_2/Bicarb:
    - acidosis and pCO_2 > 45 mmHg = respiratory acidosis
    - acidosis and HCO_3 < 22 mEq/L = metabolic acidosis
    - alkalosis and pCO_2 < 35 mmHg = respiratory alkalosis
    - alkalosis and HCO_3 > 26 mEq/L = metabolic alkalosis
3. Assess compensation
    - Uncomp: pH abnormal and $PaCO_2$ OR HCO_3 abnormal
    - Partially comp: pH abnormal and $PaCO_2$ AND HCO_3 abnormal
    - Fully comp: pH normal, but $PaCO_2$ AND HCO_3 abnormal
4. Calculate anion gap if metabolic acidosis:

$$AG = (Na^+) - (Cl^- + HCO_3^-)$$; normal = 3-11 mEq/L

Expected Compensation

Disorder	Expected Compensation
Metabolic Acidosis	$PaCO_2$ should decrease by 1-1.5 x the drop in HCO_3
Metabolic Alkalosis	PaCO2 should increase by 0.25-1 x the increase in HCO3
Acute Respiratory Acidosis	HCO_3 should increase by 0.1 x the increase in $PaCO_2$ ± 3 mEq/L
Chronic Respiratory Acidosis	HCO_3 should increase by 0.4 x the increase in $PaCO_2$ ±4 mEq/L
Acute Respiratory Alkalosis	HCO_3 should decrease by 0.1-0.3 x the drop in $PaCO_2$ but not less than 18 mEq/L
Chronic Respiratory Alkalosis	HCO_3 should decrease by 0.2-0.5 x the drop in $PaCO_2$ but not less than 14 mEq/L

**If $PaCO_2$ or HCO_3 change more or less than expected, consider mixed acid-base disorder

AIDS-RELATED OPPORTUNISTIC INFECTIONS
Adapted from Colleen Terriff, PharmD

Primary Prophylaxis:

- Prevention of the first episode of disease
- HAART = cornerstone of prophylactic therapy

Secondary Prophylaxis:

- Patient previously developed OI
- Prevention from developing "full-blown" again

When to Start Prophylaxis

- Oropharyngeal candidiasis: Frequent recurrences
- PCP: CD_4 < 200, fever >100, or thrush
- Toxoplasmosis: CD_4 < 100
- MAC: CD_4 < 50-75

NIH Recommendations for AIDS-Associated Opportunistic Infection Treatment

Opportunistic Infection	Preferred Therapy and Duration	Alternative Therapy	Other Options
Pneumocystis jiroveci (PCP) **Acute Therapy**	Trimethoprim – Sulfamethoxazole (TMX/SMX) TMP 15-20mg and SMX 75-100 mg/kg/day IV administered every 6-8 hrs **-OR-** The same daily dose administered in 3 divided doses orally **-OR-** TMP/SMX DS two tabs 3 times daily Total duration of 21 days	<u>For Severe PCP:</u> Pentamidine 4mg/kg IV QD infused over at least 60 minutes. <u>For Mild-Moderate PCP:</u> Dapsone 100 mg PO daily and TMP 15 mg/kg/day PO (in three divided doses) **-OR-** Primaquine 15-30 mg (base) PO daily and Clindamycin 600-900 mg IV every 6-8 hours or Clindamycin 300-450 mg PO every 6-8 hours.	<u>Indications for Corticosteroids:</u> PaO2< 70 mm/Hg at room air or alveolar arterial O2 gradient > 35 mm/Hg Prednisone should begin within 72 hours of initiating PCP Therapy: 40 mg BID days 1-5, 40 mg days 6-10, and 20 mg daily days 11-21 IV methylprednisolone can be administered as 75% of prednisone dose
PCP Chronic Maintenance Therapy	TMX/SMX DS one tablet PO daily **-OR-** TMP/SMX single strength one tablet daily PO daily	Dapsone 50 mg PO BID or 100 mg PO daily **-OR-** Dapsone 50 mg PO daily plus Pyrimethiamine 50 mg PO weekly plus Leucovorin 25 mg PO weekly **-OR-** Aerosolized Pentamidine 300 mg every month via a Respirgard nebulizer **-OR-** Atovaquone 1500 mg PO daily	Prophylaxis should be discontinued if CD4+ count increases in response to ART from < 200 to > 200 cells/mm^3 for ≥ 3 months
Mycobacterium avium complex disease (MAC)	<u>Initial Therapy (at least 2 meds):</u> Clarithromycin 500 mg PO BID And Ethambutol 15 mg/kg PO daily	<u>Alternative to Clarithromycin</u> Azithromycin 500-600 mg PO daily	If symptoms persist, short term (4-8 weeks) of systemic corticosteroid (20-40 mg of prednisone daily) can be used

	Consider adding third drug for patients with advanced immunosuppression (CD4+ <50), high mycobacterial loads, or in the absence of effective ART. Rifabutin 300 mg PO daily (dosage may need to be adjusted based on drug-drug interactions)	Alternative third or fourth drug for patients with more severe symptoms or disseminated disease Ciprofloxacin 500-750 mg PO BID **-OR-** Levofloxacin 500 mg PO daily **-OR-** Amikacin 10-15 mg/kg IV daily	
MAC chronic Maintenance Therapy	Clarithromycin 500 mg PO BID plus Ethambutol 15 mg/kg PO daily with or without Rifabutin 300 mg daily	Azithromycin 500 mg PO daily plus Ethambutol 15 mg/kg PO daily with or without Rifabutin 300 mg PO daily	Maintenance therapy can be discontinued in patients who completed ≥ 12 months therapy and remain asymptomatic, and have sustained (≥ 6 months) CD4+ count > 100 cells/mm^3
Toxoplasmosis gondii	Acute Treatment pyrimethamine + leucovorin + sulfadiazine x 3-6 weeks Prophylaxis TMP-SMX DS 1 tab QD	Acute Treatment Azithromycin, clarithromycin, trimetrexate, doxycycline Prophylaxis Dapsone or atovaquone + pyrimethamine +leucovorin	Begin prophylaxis in patients with CD_4 < 100 cells/mm^3
Bacterial Pneumonia	Empiric Therapy (targeting Streptococcus pneumoniae and Hemophilus influenzae): Extended spectrum cephalosporins (e.g. cefotaxime or ceftriaxone)	For High-Level Penicillin Resistant Isolates (MIC ≥ 4 mcg/mL) Consider adding: Vancomycin of Fluoroquinolone	Patients with a CD4+ T-cell count of ≥ 200 cells/mm^3 should receive a Pneumovax vaccine (if not already received in the preceding 5 years.)

	-OR- Fluoroquinolones with enhanced activity against pneumococcus (e.g. gatifloxacin, levofloxacin or moxifloxacin) <u>Empiric Therapy in Patients with Severe Illness:</u> Extended spectrum cephalosporin and a macrolid or quinolone.		Yearly influenza vaccine might be useful in preventing pneumoccocal superinfection after influenza respiratory infection. Antibiotic prophylaxis may be considered among patients with frequent recurrences.
Oropharyngeal Candidiasis **most common infection	<u>Initial Episodes:</u> (7-14 day treatment) Fluconazole 100 mg PO daily **-OR-** Itraconazole oral solution 200 mg PO daily **-OR-** Nystatin suspension 4-6 ml QID or 1-2 flavored pastilles 4-5 times daily	<u>Fluconazole-Refractory Oropharyngeal Candidiasis:</u> Itraconazole oral solution ≥ 200 mg PO daily **-OR-** Amphotericin B 0.3 mg/kg IV daily	Clotrimazole troches 5x/d x 14d Chronic or prolonged use of azoles may promote development of resistance—benefit outeweighs risk, however
Esophageal Candidiasis	Fluconazole 100 mg (up to 400 mg) PO or IV daily **-OR-** Voriconazole 200 mg PO BID **-OR-** Caspofungin 50 mg IV daily	<u>Fluconazole-Refractory Esophageal Candidiasis</u> Caspofungin 50 mg IV daily **-OR-** Amphotericin liposomal or lipid complex 3-5 mg/kg IV daily	
Cytomegalovirus (CMV) Retinitis	<u>For Immediate Sight-Threatening Lesions:</u> Ganciclovir intraocular implant and	Ganciclovir 5 mg/kg IV every 12 hours for 14-21 days, then 5 mg/kg IV daily	Choice of initial therapy for CMV retinitis should be individualized on the basis of

	valganciclovir 900 mg PO daily <u>For Peripheral Lesions:</u> Valganciclovir 900 mg PO BID for 14-21 days, then 900 mg PO daily <u>Chronic Maintenance:</u> Valganciclovir 900 mg PO daily **-OR-** Foscarnet 90-120 mg/kg IV daily	**-OR-** Ganciclovir 5 mg/kg IV every 12 hours for 14-21 days then valganciclovir 900 mg PO daily <u>Chronic Maintenance</u> Cidofovir 5 mg/kg IV every other week with probenecid 2 gm PO 3 hours before the dose followed by 1 gm PO 8 hours after the dose (total of 4 gm)	location and severity of lesions, level of immunosuppression, and other factors such as concomitant medications and ability to adhere to treatment Initial therapy among patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include optimization of ART. May discontinue when CD_4 > 100-150 for 3-6 mo, good vision, and durable HIV suppression
CMV Esophagitis or Colitis	Ganciclovir IV or Foscarnet IV for 21-28 days or until signs and symptoms have resolved; oral valganciclovir may be used if symptoms not severe enough to interfere with absorption	Maintenance therapy generally not necessary, but consider after relapse	Initial therapy among patients with CMV retinitis, esophagitis colitis, and pneumonitis should include optimization of ART.
CMV Pneumonitis	Treatment should be considered in patients with histological evidence of CMV pneumonitis and who do not respond to treatment of other pathogens	Role of maintenance therapy is not yet established	Initial therapy among patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include optimization of ART.
Herpes Simplex Virus (HSV)	<u>Orolabial Lesions and Initial or Recurrent Genital HSV:</u> Famciclovir 500 mg PO BID **-OR-**	<u>Acyclovir-Resistant HSV:</u> Foscarnet 120-200 mg/kg/day IV in 2-3 divided doses until clinical response. **-OR-**	Chronic suppressive therapy with oral acyclovir, famciclovir, or valacyclovir might be indicated among patients with frequent or severe recurrences

	Valacyclovir 1 gm PO BID **-OR-** Acyclovir 400 mg PO TID (Duration = 7-14 days) Moderate-to-Severe Mucocutaneous HSV Infections: Initial therapy acyclovir 5 mg/kg IV every 8 hours After lesions begin to regress: Change to famciclovir 500 mg PO BID or valacyclovir 1 gm PO BID or acyclovir 400 mg PO TID, continue therapy until lesions have completely healed	Cidofovir 5 mg/kg IV weekly until clinical response	
Oral Hairy Leukoplakia (Epstein-Barr Virus)	HAART Topical podophyllin Surgical excision or cryotherapy High-dose acyclovir (4 g) x 2-3 weeks then 1.2-2 g daily		

ANESTHETICS
Adapted from Julie McCoy, PharmD

Inhaled Anesthetics

Agent	MAC (%) Potency	B:G Solubility	Onset (min)	Emergence Time (min)	Notes
Nitrous Oxide (gas)	104%	0.5	2-5	Rapid	➢ Used with O_2 and other agents. ➢ Used @ 40-70% ➢ Non-irritating ➢ 20% = 15mg morphine sulfate ➢ Least potent ➢ Associated bone marrow suppression
Volatile liquids					
Desflurane (Suprane®)	6%	0.42	1-2	~5min	**Primary SE** = hypotension, arrhythmias, possible increase in intracranial pressure.
Sevoflurane (Ultane®)	2%	0.59	1-2	~4-14min	➢ Smells good ➢ Mask-able for pediatrics ➢ 3% is metabolized causing increased risk of side effects
Isoflurane (Forane®)	1.2%	1.4	2	~10-15min	➢ Wide margin of cardiovascular safety ➢ Used as maintenance therapy

1. The lower the MAC the greater the potency

2. MAC values are additive
3. MAC decreases with age, opioid use; increases with fever
4. Lower solubility = faster induction and faster recovery
5. Ventilation rate dictates speed of onset and wash-out
6. Use **DANTROLENE** to reverse malignant hyperthermia

Neuromuscular Blocking agents

Drug	Onset	T_{Dur}	Dose (mg/kg)	Elimination	Notes
Ultrashort acting					
Succinylcholine (depolarizing)	30-60s	2-3min	IV induction 1-1.5 mg/kg NTE 200mg Infusion: 0.5-10 mg/kg/min	Hydrolysis by plasma pseudocholinesterases	➢ Antagonism w/ non-depolarizing agents ➢ Flaccid paralysis after fasciculations ➢ Caution in pre-existing hyperkalemia ➢ SE: malign. hyperthermia, $\uparrow K^+$
Short acting					
Mivacurium (competitive)	2-4min	12-18min	IV bolus: 0.15-0.25mg/kg Maint: 0.1mg/kg q 15min	Hydrolysis by plasma pseudocholinesterases	➢ Use ideal body weight ➢ Give 10% of initial dose for priming
Intermediate					
Cisatracurium	2-3min	20-35min	Intubating dose: 0.15-0.2mg/kg Maint: 0.5-10mcg/kg/min	Hoffman elimination Ester hydrolysis	➢ Caution in renal and hepatic insufficiency
Vecuronium	2-4min	60-90min	Initial: 0.08-0.1mg/kg Maint: 0.01-0.015mg/kg 25-40min after initial dose	Liver metabolism and clearance; renal elimination	➢ Caution in pre-existing electrolyte imbalance ➢ Dose reduction in liver disease

					➢ Final Conc is 1mg/ml
Rocuronium	1-2min	30-60min	Intubation: 0.6-1.2mg/kg Maint: 4-16mcg/kg/min	Liver metabolism and renal elimination	➢ Caution in valvular heart disease, pulmonary disease and hepatic impairment
Atricurium	2-4min	30-60min	Initial: 2-5mg/kg Maint: 5-10mcg/kg/min	Hoffman degradation	➢ Rates for peds may be higher ➢ Avoid or administer corticosteroids at lowest possible dose
Long-acting					
Pancuronium	4-6min	2-3hrs	Initial: 0.06-0.1mg/kg Maint: 0.01mg/kg 60-100 min after initial dose then q 25-60min or 0.8-1.7mcg/kg/min	Renal elimination	➢ Caution in renal and hepatic insufficiency

All agents except succinylcholine are reversible with edrophonium, neostigmine, and physostigmine
Use atropine or glycopyrrolate to limit side effects
Use ideal body weight for obese pts
Caution in pre-existing electrolyte imbalance

Dosing is very specific to the setting. Be sure to clarify the precise procedure.

GENERAL PRINCIPLES OF ANTIMICROBIAL THERAPY
Adapted from Mark Garrison, PharmD

Heuristics

1) 25-40% of *Haemophilus influenzae* are resistant to ampicillin
2) Virtually 100% *Staphylococcus aureus* are resistant to penicillin
3) 25-35% of *S. aureus* are resistant to methicillin (MRSA)—varies with institution
4) 50-70% of coagulase-negative *Staphylococcus* are resistant to methicillin
5) There have been 3 reported cases of vancomycin-resistant *Staph aureus* in the United States to date
6) Vancomycin is the drug of choice for infections involving MRSA & coag-negative *Staphylococci*
7) Vancomycin should be reserved for MRSA, *S. pneumoniae* with high-level β-lactam resistance, & patients with significant (life-threatening) penicillin allergies
8) No current 3rd generation cephalosporins should be used to treat MRSA infections
9) No current 3rd generation cephalosporins should be used to treat enterococcal infections
10) *Enterococcus* should preferably be treated with a combination of a β-lactam and aminoglycoside—usually ampicillin (or vancomycin) and gentamicin
11) 1st & 2nd generation cephalosporins do not provide adequate coverage for *Pseudomonas aeruginosa*
12) Cefazolin is the preferred parenteral 1st generation cephalosporin due to its longer half-life
13) The cephalosporin with the longest half-life & once daily indication is ceftriaxone; however, it tends to be overused to a significant extent
14) Of the 3rd generation cephalosporins, only ceftazidime, cefoperazone & cefepime provide coverage for *Pseudomonas aeruginosa*; non-cephalosporin antibiotics may be preferred (anti-*Pseudomonal* penicillins—use both with aminoglycoside)
15) Cefotaxime & ceftriaxone should be the only cephalosporins considered for treating meningeal (CNS) infections—if susceptible, penicillin G is the drug of choice
16) Cefamandol, cefoperazone, moxalactam, cefmetazole & cefotetan are the only cephalosporins with a 3-methiotetrazole substitution which is likely responsible for both the coagulation problems observed with cephalosporins & the disulfiram reaction that can occur
17) Ceftriaxone & cefoperazone undergo biliary excretion & therefore can cause "biliary sludge"
18) Of the 3rd generation cephalosporins, only cefotaxime has an active metabolite
19) Of the cephalosporins, only cefoxitin, moxalactam, cefmetazole & cefotetan have adequate coverage for *Bacteroides fragilis* infections
20) Clindamycin, metronidazole, imipenem/cilastatin, piperacillin/tazobactam, ampicillin/sulbactam, & ticarcillin/clavulanic acid provide adequate coverage for *Bacteroides fragilis* infections
21) Of the cephalosporins, ceftriaxone should be used to treat infections involving penicillinase producing *Neisseria gonorrhoeae* (PPNG)
22) Ampicillin is the drug of choice for *Listeria* infections. Avoid cephalosporins
23) *H. influenzae, S. pneumoniae, & M. catarrhalis* are the most common bugs encountered in community acquired infections—especially upper respiratory
24) *H. influenzae* & *M. catarrhalis* are common β-lactamase producers
25) Macrolide agents are effective against the "atypical" respiratory pathogens*: Chlamydia pneumoniae, Mycoplasma pneumoniae, & Legionella pneumophilia*
26) Imipenem/cilastatin has the broadest spectrum of activity relative to all other antibiotics
27) Type I β-lactamase production is most frequently seen in *Enterobacter cloacae, Pseudomonas aeruginosa, Citrobacter, Serratia, Proteus* & *Acinetobacter*

28) Levofloxacin & newer quinolones (moxi, gati, gemi) have greater gram-positive activity compared to ciprofloxacin, but have poorer activity against *Pseudomonas*
29) Trovafloxacin is potentially hepatotoxic & should be limited to severe, life-threatening infections
30) IV formulations of fluoroquinolones should be reserved for patients unable to take meds orally or patients with compromised absorption from the GI tract.
31) Gatifloxacin is associated with hypo- and hyperglycemia, particularly in diabetic patients
32) New antibiotics targeted at resistant gram-positive infections like MRSA, VRE, & resistant pneumococci include: linezolid, daptomycin, & tigecycline
33) Telithromycin is a ketolide antimicrobial, similar to macrolides but with greater activity and lower potential for developing resistance

Minimizing Resistance in the Hospital Setting

- Limit unnecessary use of antimicrobials (tight formulary, automatic stop orders, antibiotic review teams)
- Fine-tune empiric therapies after culture results are known
- Drug use evaluations and education to promote appropriate selection and use of antimicrobials
- Educate health care providers about proper infection control measures—HAND WASHING
- Isolation of patients with resistant organisms
- Familiarization with hospital-specific antibiograms of resistance patterns

Classification of Common Bacteria

- Gram Positives
  - Staphylococci: *S. Aureus,* Coag-Negative *Staph*
  - Streptococci: Group A, B, D (incl. *Enterocci*)
  - Non-Lancefields: *S. pneumoniae*
  - Bacilli: *Bacillus anthracis*, *Listeria monocytogenes*, *Corynebacterium diphtheriae*, *Mycobacterium*, *Nocardia*
- Gram Negatives
  - Cocci: *Neisseria gonorrhoeae*, *Neisseria meningiditis*, *Moraxella catarrhalis*
  - Bacilli: Enterobacteriacae Family (*E. coli, Enterbacter, Proteus*, *Klebsiella, salmonella*, etc), *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Acinetobacter*, *Campylobacter*, *Eiknella/Pasturella*
- Anaerobes
  - Gram (+) cocci: *Peptostreptococcus*
  - Gram (-) Cocci: *Veillonella*
  - Gram (+) Bacilli: *Clostridium difficile*, *Clostridium perfringes*, *Clostridium tetani*, *Clostridium botulinum*, *Propionibacterium*
  - Gram (-) Bacilli: *Bacteroides fragilis*

REVIEW OF ANTIBIOTIC CLASSES
Adapted from Mark Garrison, PharmD

Aminoglycosides

- MOA: inhibit protein synthesis = bactericidal
- Activity: mostly gram (-), but some gram (+)
- Good *Pseudomonas* coverage (tobra>gent)
- Gent is frequently used for synergistic activity vs *Enterococcus*
- Monitor serum levels for efficacy/toxicity
  - Gent or tobra (trough < 2mg/L; peak 5-10mg/L)
  - Amikacin (trough < 4mg/L; & peak 20-35mg/L) reserved for resistant/refractory infections
- Indications: serious or hospital-acquired stubborn gram (-) rods; neomycin (oral) is used for bowel prep for surgical procedures
- SE: nephrotoxicity (reversible) & ototoxicity (irreversible); Check pts for other nephro/oto-toxic agents
- Once daily dosing (5-7 mg/kg/day)- short treatment course; still need to monitor

Cephalosporins

- MOA: β-lactams, inhibit cell wall synthesis (bactericidal)
- Activity: as you progress from 1st generation to 3rd generation, you gain gram (-) and lose gram (+)coverage (except 4th generation)
- SE: generally well tolerated, about 10% of PCN allergic pts are cross-reactive to cephalosporins
- Most are renally eliminated—may need to adjust in renal dysfunction

1st Gen Cephalosporins

- Activity: primarily gram (+) including *Staph* (its penicillinase does not work on cephalosporins), but not *Enterococci*. Some wimpy gram (-) bugs (*E. coli*, *Klebsiella*, *Proteus*)
- Indications: widely used for surgical prophylaxis, cellulitis and other skin infections; *Strep* infections (otitis media, pharyngitis, meningitis and skin infections)
- **Cefazolin is the only parenteral 1st generation cephalosporin

2ND Gen Cephalosporins

- Activity: increased gram (-) activity (*Haemophilus*, *Enterobacter*, *Neisseria*) and anaerobes
- Two types of agents: those with anaerobic coverage (most) and those without anaerobic coverage (cefuroxime)
- Cefuroxime available in PO form and has good activity for respiratory infections
- Not commonly used outside of surgical prophylaxis

3rd Gen Cephalosporins

- Activity: stubborn gram (-) bugs (*Pseudomonas*, *Serratia*, *Providencia*, *Citrobacter*, *Acinetobacter*)
- Indications: hospital-acquired infections, serious gram (-) infections, empiric therapy until culture results are known, ceftriaxone IM as a single dose for STDs

**Ceftriaxone has longest half-life—once daily dosing
**Cefotaxime crosses the blood-brain barrier well
**Ceftazidime is preferred for *Pseudomonas* infections

4th Gen Cephalosporins (cefepime)

- Same activity as 3rd gen ceph (including *Pseudomonas*) but without losing the gram (+) activity (*Staph* and *Strep*)

Cephalosporins By Generation

1st generation	2nd generation	3rd generation	4th generation
Cefadroxil (Duricef ®)*	Cefaclor (Ceclor ®)*	Cefdinir (Omnicef ®)	Cefepime (Maxipime ®)†
Cefazolin (Ancef ®)	Cefamandole (Mandol ®)	Cefixime (Suprax ®)*	
Cephalexin	Cefmetazole	Cefoperazone	

(Keflex ®)* Cephalothin (Keflin ®) Cephapirin (Cefadryl ®) Cephradine (Anspor ®)* Cephaloridine (Loridine ®)	(Zefazone ®) Cefonicid (Monocid ®) Ceforanide (Precef ®) Cefotetan (Cefotan ®) Cefoxitin (Mefoxin ®) Cefprozil (Cefzil ®)* Cefuroxime (Zinced ®)* Cefuroxime axetil (Ceftin ®) Loracarbef (Lorabid ®)	(Cefobid ®)† Cefotaxime (Claforan ®) Cefpodoxime (Vantin ®)* Ceftizoxime (Cefizox ®) Ceftriaxone (Rocephin ®) Ceftazidime (Fortaz ®)† Moxalactam (Moxam ®)	

* Oral dosage form available
† Anti-pseudomonal activity notable

Carbapenems

- MOA: β-lactams, inhibit cell wall synthesis (bactericidal)
- Agents: Imipenem/Cilastatin (Primaxin®), Meropenem (Merrem®), and Ertapenem (Invanz®) all are IV.
- Activity: **Broadest Spectrum** antibiotics currently available
- Indications: empiric treatment pending culture results, polymicrobial infections, and severe infections resistant to other agents
- **Monitor duration of therapy—should switch therapies if possible to avoid resistance development
- SE: pseudomembranous colitis and seizures (meropenem has less seizure risk)
- Cilastin inhibits renal dipeptidases and prolongs imipenem half-life

Lincosamides (clindamycin)

- Activity: ANAEROBES, staph & strep; used in acne
- Alternative for penicillin allergy
- #1 cause of antibiotic-associated pseudomembranous colitis

Fluoroquinolones:

- MOA: inhibit DNA gyrase = bactericidal
- Activity
  - Older agents (cipro, levo): good gram (-) and decent gram (+) coverage (Cipro has no *Strep. pneumo* coverage)
  - Newer agents (gati, moxi, gemi): better gram (+), but reduced gram (-) coverage
  - **Newer quinolones targeted towards *Strep. pneumoniae* = respiratory quinolones
- Indications: pneumonia, bone and joint infections, prostatits, cellulits, UTIs, infectious diarrhea, empiric therapy
- SE: well tolerated mild: CNS problems, glucose control, GI complaints, agitation, phototoxicity, anxiety (rare)
- Some agents have been withdrawn due to side effects (hepatotoxicity, cardiovascular side effects)
- Divalent cation interaction: Ca, Fe
- NOT FOR USE IN PEDIATRICS!!!

Macrolides

- MOA: inhibit protein synthesis
- Agents: Erythromycin (oral & IV), Clarithomycin (oral), Azithromycin (oral & IV)
- Activity: Mostly gram (+); particularly community-acquired infections that may involve atypical bacteria, little activity against hospital-acquired gram (-)
- Indications:
  - Frequently used as an alternative to β-lactams in penicillin-allergic pts
  - Community-acquired pneumonia from atypical pathogens

    - Azithromycin: 1000 mg dose x 1 dose for STD's
    - Clarithromycin for MAC infections in HIV
- SE: Erythro—GI upset with PO, IV can cause severe pain; Clarithro-metallic taste at large doses
- **Azithromycin is the only macrolide that does not inhibit CYP3A4

Metronidazole
- Activity: anaerobes; also amebicidal and trichomonicidal
- Use: antibiotic-associated diarrhea, protozoal infections, *H. pylori* infections, once daily dosing for bacterial vaginosis
- Disulfiram reaction with alcohol—avoid mouthwash, cough syrups, etc.

Penicillins:
- MOA: β-lactams, inhibit cell wall synthesis (bactericidal)
- **Natural:** Pen VK (oral), Pen G (IV), Pen G procaine or benzathine (IV/IM)
    - Activity: Gram (+) except *Staph*, non-*Bacteroides* anaerobes, little gram (-) activity
    - Indications: strep infections (OM, pharyngitis, meningitis, cellulites), STDs (syphilis, gonorrhea)
    - **Increasing incidence of penicillin-resistant *S. pneumoniae* and penicillinase-producing *N. gonorrhea*
    - SE: wide range of hypersensitivity reactions, high dose PCN—seizures
- **Anti-staphylococcal:** cloxacillin & dicloxacillin (PO), methicillin & nafcillin (IV)
    - Activity: similar to 1st gen cephs; covers *Staph*
    - Indications: primarily for *Staph* infections, empiric therapy for bacterial endocarditis
- **Extended-Spectrum:** Amoxicillin (PO) and ampicillin (PO/IV); inactivated by penicillinases (No good against *Staph*)
    - Activity: like natural penicillins, but increased gram (-) coverage (*H. influenzae*, *E. coli*, *Klebsiella*)
    - Indications: upper respiratory tract infections like otitis media, sinusitis; amoxicillin commonly used in peds
    - β-lactamase inhibitor combos: Augmentin & Unasyn
    - High dose amoxicillin can overcome some penicillin-resistant *S. pneumoniae*
- **Anti-pseudomonal:** piperacillin, ticarcillin
    - Activity: broadest spectrum of all penicillins—extends to cover anaerobes and stubborn gram (-) bugs
    - Indications: serious gram (-) infections and hospital-acquired infections, esp *Pseudomonas*

Tetracyclines
- Activity: gram (-) and gram (+); only routinely used for gram (-) infections
- Indications: *Chlamydia, Mycoplasma pneumoniae*, and rickettsial infection;
- SE: photosensitivity, avoid in peds because bone deformation
- Mineral interaction: magnesium, calcium, iron

Vancomycin:
- Activity: Gram (+) only
- Indications: drug of choice for MRSA, infections in patients with life threatening PCN allergy, high-level PCN resistant *Strep pneumo* 2nd line for *C. difficile*-associated pseudomembranous colitis after trying metronidazole
- SE: phlebitis, Red Man Syndrome (purity and rate-related), ototoxicity and nephrotoxicity (esp. when used with AGs)
- Peak 10-15 mg/kg; Trough 5-10mg/L (usually only trough measured)
- Restrict use to minimize resistance (VRE, VISA, VRSA, etc.)

SYSTEMIC FUNGAL INFECTIONS
Adapted from James Lewis, PharmD

Candidiasis

- Risk Factors
  - o >3 days in ICU
  - o Central lines
  - o Broad-spectrum antibiotics
  - o Diabetes
  - o Severe illness
  - o Dialysis
  - o TPN
  - o GI perforation/surgery
  - o Immunosuppression

  **Candida* colonizes plastic well
- Treatment **must know species before treatment**
  - o Can you afford to be wrong for 24 hrs?
    - Use echinocandin if no, otherwise fluconazole for empiric therapy
  - o Check renal function with ampho, liver function with vori

General Antifungal Susceptibility of *Candida*

Species	Fluc	Itra	Vori	Candins	Ampho
albicans	S	S	S	S	S
tropicalis	S	S	S	S	S
parapsilosis	S	S	S	S to I	S
glabrata	S-DD to R	S-DD to R	S to I	S	S to I
krusei	R	S-DD to R	S to I	S	S to I
lusitaniae	S	S	S	S	S to R

**oftentimes select for different species with treatment rather than resistant strains

Antifungal Medications

- Amphotericin B
  - o MOA: disrupts polyenes in cell membrane
  - o Dosing varies with formulation
    - Regular ampho: 1 mg/kg
    - Lipid ampho: 5 mg/kg (regardless of lipid type)
  - o Regular ampho is cheaper, and useful for short-course (10-14 days) in neonates, HIV pts with CNS symptoms
  - o Lipid formulations buy more time before nephrotoxicity, but don't eliminate it and are expensive
    - Toxicity: liposomal < lipid complex < colloidal
    - Price: liposomal > lipid complex > colloidal
  - o Broadest-spectrum, but use other drugs first for *Candida* or *Aspergillus*
- Echinocandins
  - o MOA: inhibits 1,3-β-D glucan synthesis in cell wall
  - o Agents: caspofungin, micafungin, anidulafungin
  - o Fungicidal against most *Candida*
  - o Strengths: well tolerated (red-man if IV push), QD dosing, few drug interactions (rifampin), no cross-resistance with azoles
  - o Weaknesses: limited spectrum (*Candida*, *Aspergillus*, PCP), not effective against *Crypt. neoformans*, Zygomycetes), no oral dosage form, expensive

- Azole Antifungals
  - Inhibit lanosterol 14-α demethylase to disrupt cell membrane function
  - **interact with CYP450 enzyme metabolism esp. itraconazole and voriconazole
  - Fluconazole
    - Most common, little toxicity, oral bioavailability excellent, extremely active against most *Candida*
    - Often underdosed: 400-800 mg/day should be used for systemic infections

    **No mold activity
  - Itraconazole
    - Very poor absorption esp. with PPI
    - Cyclodextrin in IV formulation accumulates in renal failure
    - Black-box warning for heart failure
  - Voriconazole
    - Drug of choice for *Aspergillus* sp.
    - Also useful for *Fusarium* sp., *Scedosporium apiospermum* which are usually ampho resistant
    - May use for *Candida* if no prior azole—*C. glabrata* usually azole cross-resistant
    - No *Zygomycetes* coverage
    - Oral bioavailability ~96%
    - Must monitor LFTs every week
    - Cyclodextrin in IV formulation, lots of drug interactions
  - Posaconazole
    - Spectrum: voriconazole + *Zygomycetes*
    - Oral dosage form only
    - Very well tolerated and fewer drug interactions

VIRAL INFECTIONS
Adapted from Colleen Terriff, PharmD

Definitions
- Incubation period- offending virus is introduced into the body (serologic evidence +, s/s -)
- Prodrome- vague flu-like symptoms (myalgias, arthralgias, fatigue, loss of appetite), fever can occur, mild tenderness over liver may be appreciated, marked elevation of AST and ALT, (serologic evidence +, s/s +)
- Icteric phase- jaundice and scleral icterus (bilirubin >2.5-3.0 mg/dl), yet symptoms are beginning to resolve and transaminases are declining, mild hepatic tenderness
- Resolution phase- symptoms are diminished, transaminases return to normal, serologic testing confirms the appearance of protective antibodies
- Anicteric hepatitis- most common form of viral hepatitis, lacking icteric symptoms
- Fulminant hepatitis- most dreaded complication of viral hepatitis, acute liver failure
- Prolonged hepatitis- elevated transaminases >6 months, many progress to chronic hepatitis

Hepatitis A
- RNA virus; A = acute
- Transmitted via oral-fecal route
- Virus incubation 2-6 weeks (large quantities of virus shed in feces = still infectious)
- People at risk: travelers to endemic areas, day-care centers (children and workers – due to hygiene risks), homosexuals (MSM), close contact with infected individual, illegal drug users (injection and non-injection), and patients with chronic liver disease
- Serology- tests, monitoring
  - Virus present in blood only for short time
  - IgM detected early in infection and remains for 2-3 mo
  - IgG (protective antibody) positive later and remains positive for life (immunity)
- Clinical course and sequela:
  - Patient may become jaundiced
  - Complete recovery is rule (fulminant hepatitis rare)
  - Chronic hepatitis from acute infection or chronic carriers – not documented
- Prevention:
  - Hand washing!!!
  - Vaccination – inactivated lysed whole viruses

Vaccine	Age	Schedule
Havrix	2-18 >18	0, 6-12 mos. 0, 6-12 mos.
Vaqta	2-17 >17	0, 6-18 mos. 0, 6-12 mos.
Twinrix	≥ 18	0, 1, 6 mos.

  - Prophylaxis:
    - IgG IM – short-term passive immunity (within 2-4 weeks of exposure)

        - Administration – IM, preferably in gluteal region (divide doses >10ml and inject into several sites)
        - Efficacy - 80-95% for prevention (depending on time of administration and exposure)
    - For immediate and long-term protection- HepA vaccine + IgG IM (separate syringes, different sites). However, lower antibody titers might result in protection of less duration from vaccine

Hepatitis B

- 300,000 persons infected with HBV/year in U.S.; 1,000,000 U.S. people are infectious carriers
- Transmission (more infectious than Hep. C or HIV)
    - Blood – transfusion, needles
    - Body fluids – semen, saliva?
    - Perinatally (time of delivery?)
- Viral incubation period is 2-6 months
- Serology- tests, monitoring
    - HBcAg- core antigen; resides in viral core, not detected in serum, yet antibodies to HBcAg are most sensitive marker of infection
    - HBsAg- surface antigen; identifies acute vs. chronic hepatitis. HBsAg antibodies associated with immunity
    - HBeAg- fragment of core antigen; cleaved during HBV replication and excreted into serum (can demonstrate high infectivity); used to select patients for interferon therapy. Antibodies to HBe indicate low infectivity
    - HBV DNA- measurement of hepatitis B viral load
    - Transaminases- i.e. ALT, AST- higher levels may indicate better response to interferon
- Clinical course and sequela:
    - Onset of acute disease is generally insidious
    - S/S- anorexia, malaise, n/v, abdominal pain, jaundice
    - Skin rashes, arthralgias, arthritis, vasculitis can also
    - 90-95% completely recover, with 5-10% unable to eradicate the virus
- Prevention and prophylaxis:
    - Education
    - Vaccination – everyone, but esp. if high risk of infection
    - Hep B immune globulin if source HBsAg positive or unknown, and person exposed is not vaccinated
    - Interferon – predictors of good response: short duration of infection, low pretreatment viral levels, high pretreatment liver enzyme values, active histologic changes, female gender, wild type HBV, and absence of complicating illness
- Treatment – Interferon, lamivudine, or others?
    - In patients with ALT levels less than 2 times normal, with severe liver disease or cirrhosis, lamivudine is the treatment of choice
    - Many patients will choose lamivudine over IFNα , due to convenience of therapy and increased tolerability.
    - Combination therapy possible but needs further study.
    - Many newer options that may be considered first line (adefovir and entecavir)

Hepatitis C

- 150,000 persons infected with HCV/year in U.S.
- Transmission

    - Blood products or blood – transfusion, needles
    - Sexual transmission – less common
    - Other – hemodialysis, household contact, percutaneous exposures, high-risk drug use (intranasal cocaine). Up to 40% unknown.
- Viral incubation period 2-20 weeks
- Serology- tests, monitoring
    - Anti-HCV- usually appear 2-6 months after exposure, yet can take up to 1 yr; indicates past or present infection; may persist in chronic hep C; does not indicate immunity; does not determine infectivity (yet, infectious until proven otherwise). ELISA test is limited. RIBA (recombinant immunoblot assay) is a useful confirmatory test. 2nd generation ELISA tests are more sensitive and specific.
    - HCV RNA- measurement of hepatitis C viral load and can confirm active
    - Transaminases- chronic Hep C- sometimes normal, some have prolonged elevation in ALT that may transiently revert to normal, only to rise again
    - Liver biopsy needed to confirm chronic hepatitis.
- Clinical course and sequela:
    - Acute- varies from mild to severe (fatigue, fever, body aches, nausea, jaundice, and elevated ALT)
    - Many can be asymptomatic!
    - >60% patients will develop chronic Hep C
    - 20-50% of chronic Hep C patients will develop cirrhosis
    - 20% of cirrhosis patients will develop hepatic failure- leading cause of liver transplantation in U.S.
    - 20% of cirrhosis pts develop hepatocellular carcinoma
    - Chronic hepatic failure- portal hypertension, ascites, esophageal and gastric varices, hepatic encephalopathy
- Prevention- no vaccine to date
- Treatment: interferon alfa, ribavirin
- Predictors of good HCV responses to IFN: short duration of infection, low pretreatment viral levels, absence of cirrhosis or minimal amounts of hepatic fibrosis, mild inflammation, genotype other than 1, young age, low hepatic iron stores, negative for HIV
- Contraindications to Treatment with Interferon
    - Absolute: pregnancy or absence of reliable form of contraception, end-stage renal failure, anemia, hemoglobinopathies, severe heart disease
    - Relative: uncontrolled hypertension, old age
- Contraindications to Treatment with Interferon Alfa
    - Absolute: Current or history of psychosis, severe depression, neutro- or thrombocytopenia, symptomatic heart disease, decompensated cirrhosis, uncontrolled seizures, organ transplantation (other than liver)
    - Relative: autoimmune disorders, uncontrolled diabetes

Hepatits B Treatment Options

Medication	Brand	MOA	Dose	SE	Comments
Interferon alfa-2b	Intron A	Inhibits viral replication, immuno-modulation	5 MU/day SC OR 10 MU TIW for 16 weeks	Flu-like symptoms, fatigue, depression, myelosuppression, HA Caution with decompensated liver dz., psychiatric disorders, cardiovascular dz.	▪ Decrease dose if WBC, granulocytes, or platelets decrease ▪ Multi-dose pen, vial
Interferon alfa-2a pegylated	Pegasys	Similar to above	180 mcg SC once weekly	Similar as short-acting IFN	▪ Half-life ~50-80 hrs ▪ Prefilled syringes ▪ Not FDA-approved for Hep B
lamivudine (3TC)	Epivir-HBV	Inhibits reverse transcriptase	100 mg PO QD	Fatigue, HA, abd. pain, mild nausea	Decrease dose for renal impairment
emtricitabine (FTC)	Coviracil	Inhibits reverse transcriptase	200 mg PO QD	Similar to 3TC, discolored palms/feet	Decrease dose for renal impairment
entecavir	Baraclude	Inhibits reverse transcriptase	0.5 mg QD for NRTI naïve pts, 1 mg QD in refractory pts	HA, fatigue, dizziness, mild nausea	▪ Give on empty stomach ▪ Decrease dose for renal impairment
adefovir	Hepsera	Nucleotide analog, inhibits DNA synthesis	10 mg PO QD	well tolerated, but watch nephrotoxicity	Increase dosing interval in renal impairment

Hepatitis C Treatment Options

Medication	Brand	MOA	Dose	SE	Comments
interferon alfa-2b	Intron A	Similar to other interferons	3 MU SC or IM TIW	Similar to other interferons	▪ See Hep B chart
interferon alfa-2a	Roferon-A	Similar to other interferons	3 MU SC or IM TIW	Similar to other interferons	▪ Pre-filled syringes
interferon alfacon-1 (consensus)	Infergen	Similar to other interferons	9 mcg SC TIW 15 mcg SC TIW x 48 wks for relapse	Similar to other interferons	▪ Decrease dose from 9 mcg to 7.5 mcg if intolerable SE ▪ Solution for injection
interferon alfa-2b pegylated	PegIntron	Similar to other interferons	1 mcg/kg SC weekly 1.5 mcg/kg SC weekly with ribavirin	Similar to short-acting interferons	▪ Powder for injection (vial or Redipen®) ▪ 30-50 hr half-life
interferon alfa-2a pegylated	Pegasys	Similar to other interferons	180 mcg SC weekly	Similar to short-acting interferons	▪ Pre-filled syringes ▪ 50-80 hr half-life
Ribavirin	Rebetol, Copegus	Decrease cellular purine metabolism, increase RNA virus mutation, increase antiviral cytokines	Genotype 1: ≤ 75 kg: 400 mg PO AM, 600 mg PO PM > 75 kg: 600 mg PO AM, 600 mg PO PM Genotype 2 or 3: 800 mg/day	Anemia—can be severe	▪ Decrease dose for patients experiencing anemia
interferon alfa-2b + ribavirin	Rebetron	Combo enhances HCV clearance	Ribavirin dose + IFN dose	Same as each individually	▪ Previously packaged together, but no unbundled

Cytomegalovirus (CMV)

- Most common, life-threatening viral infection in HIV/AIDS (retinitis → blindness)
- Common infection in post-transplant patients
- Transmission: intimate exposure by mucosal contact with infectious tissues, secretions and excretions (urine, saliva, breast milk, cervical secretions, semen)
- At risk: fetuses, organ-transplant recipients, AIDS patients
- Serology/monitoring:
  - Anti-CMV (general population 60-80%, homosexual men with AIDS 100%)- not useful
  - CMV viral load- new test, not utilized clinically yet
- Clinical course and sequela:
  - virus is ubiquitous, very contagious
  - Incubation: 3-12 weeks (yet, virus can be excreted for years)
  - Manifestations: retinitis, esophagitis, hepatitis, GI infection, radiculopathy, encephalitis, pneumonitis

CMV Treatment

Medication	Induction / Maintenance	SE	Comments
ganciclovir IV (Cytovene)	I- 5 mg/kg q12h x 14-21d M- 5 mg/kg QD	neutropenia, thrombo-cytopenia, infusion-related	can ↑ the dose for refractory disease
ganciclovir PO	M- 3 - 6 g/D	bone marrow, diarrhea, nausea	3 divided doses with food
valganciclovir PO (Valcyte)	M- 900 mg QD	same as ganciclovir	same bioavailability as ganciclovir IV
foscarnet IV	I- 90 mg/kg q12h x 14-21d M- 90-120 mg/kg QD	nephrotoxicity, electrolyte abnormalities, catheter sepsis	renally adjust dose, hydration
cidofovir IV (Vistide)	I- 5 mg/kg qweek x 2 wks M- 5 mg/kg q2 weeks	nephrotoxicity, neutropenia, uveitis, hypotonia	renally adjust dose, hydration, probenecid
Others			
intraocular implants- ganciclovir intravitreous- ganciclovir, foscarnet, cidofovir		combo: IV ganciclovir and foscarnet or IV foscarnet + (implants or PO ganciclovir)	

Herpes Varicella-Zoster

- Varicella: chickenpox (children)- peaks 5 to 9 years of age
- Zoster: shingles (adults, esp. elderly and immunocompromised)
- Transmission/susceptibility:
  - Person to person by direct contact, airborne, scabs not infectious
- Incubation 14 days, yet may be prolonged after passive immunization or immunodeficiency
- Contagious! 1-2 days before onset of rash and ends when all lesions have crusted over.

- Episode of chickenpox generally confers lifelong protections against subsequent attacks.
- Clinical course and sequela:
    - **Chickenpox** (varicella):
        - Maculopapular or vesicular lesions first on face, scalp or trunk
        - Fever in up to 70% of cases
        - Malaise, loss of appetite or headache
        - Usually self-limiting and benign
        - Bacterial superinfections, pneumonia, encephalitis, or death can occur
        - Adult chickenpox cases are rare, yet can be more serious
    - **Zoster or shingles**:
        - varicella-zoster can remain dormant in sensory nerve roots for life
        - Reactivation of the virus usually occurs after age 50 and incidence ↑ with age
        - Neurologic pain (numbness/itching to severe pain)
        - Clusters of blister-like lesions follow within 3 to 4 days (disappear in 2-3 weeks) and generally form on only one side of body
        - Up to 15% of pts experience persistent, stabbing neurologic pain for months- years

Treatment of Herpes Varicella-Zoster

Condition	Drug and Dose	Dosage Forms	When	Side Effects
varicella (pediatrics)	acyclovir 200 mg/kg (max 800 mg) PO 4 x/day for 5 days	200 mg capsules 200 mg/5ml banana-flavored susp	within 24 hrs of rash	generally well tolerated, diarrhea, rash, vertigo, arthralgia
varicella (adoles-adults)	acyclovir 800 mg PO 4x/day for 5 days	400mg tabs 800mg tabs	within 24 hrs of rash	watch nephrotoxicity, same
varicella (pneumonia or pregnancy)	acyclovir 800 mg PO 4x/day or 10 mg/kg IV q8h x 5days	400 mg, 800 mg tabs 500 mg IV	3rd trimester	same phlebitis, some CNS
varicella (immunocomp.)	acyclovir 10-12 mg/kg IV q8h x7days	500 mg IV	aggressive!	same phlebitis, some CNS
zoster (normal host)	acyclovir 800 mg PO 5x/day x7-10days (± prednisone)	400 mg, 800 mg tabs	-	-
	famciclovir 500 mg PO q8h x7days	500 mg tabs	-	-
	valcyclovir 1000 mg PO TID x7days	500 mg tabs	-	-
zoster (immunocomp - not severe)	acyclovir 800 mg PO 5x/day x7days	400 mg, 800 mg tabs	-	-
zoster (immunocomp severe)	acyclovir 10-12 mg/kg IV q8h x7-14 days (7.5 mg/kg older pts)	500 mg IV	aggressive! use foscarnet for resistance	-

Post-herpetic neuralgia treatment: Mild analgesic drugs: aspirin, NSAID- limited efficacy

- Topical:
  - Lidocaine- useful
  - Capsaicin – delayed onset, burning may be intolerable in up to 1/3 of patients
- Nerve blocks- invasive, effective in immediate, short-term relief
- Neuroactive drugs:
  - TCA's- amitriptyline, desipramine, nortriptyline
  - Anticonvulsants: carbamazepine, phenytoin, valproate sodium
  - Gabapentin –titrate up as needed to 1,800 mg/day. SE: dizziness, somnolence and peripheral edema.
- Amantadine – placebo-controlled trial and case reports of benefit
- Corticosteroids – controversial, benefit unclear
- Aggressive and early treatment of zoster with antivirals!

Herpes Labialis/Genitalis

- Labialis (lips and mouth)
  - Topical treatment shown to shorten the time to healing and decrease the duration of pain by 1 day:
    - Acyclovir (Zovirax) ointment to affected area 5 times a day
    - Penciclovir (Denavir) cream to affected area 5 times a day
  - Systemic options (initial)
    - Acyclovir 400 mg PO TID or 200 mg 5 x day or 800 mg q8h for 7 to 10 days
  - Recurrent outbreaks
    - Acyclovir for 5 days
    - Valacyclovir 2 g PO Q 12 hours for 2 doses
- Genitalis (genital area)
- Pregnancy:
  - Risk for herpes is high in infants of women who acquire genital HSV in late pregnancy
  - Managed in consultaiton with HSV specialist
  - Acyclivir therapy vs. cesarean section vs. both
- Neonatal herpes:
  - Consultation with a specialist
  - IV acyclovir promptly after evaluation
- HIV patients:
  - May have prolonged or severe episodes of genital, perianal, or oral herpes
  - Episodic or suppressive therapy with oral antiviral agents is often beneficial
  - If lesions persist or recur in patient receiving therapy, HSV resistance should be suspected
  - Foscarnet 40 mg/kg IV q8h until clinical resolution

2002 CDC STD Guidelines to Herpes Genitalis

Episode	Oral Treatment	Length of Therapy
First	**acyclovir** 400 mg TID or 200 mg 5 x day or **famciclovir** 250 mg TID	7-10 days

	or **valacyclovir** 1gm BID	
Recurrent	**acyclovir** 800 mg BID or 400 mg TID or 200 mg 5 x day or **famciclivir** 125 mg BID or **valacyclovir** 500 mg BID or 1g QD	5 days
Suppressive	**acyclovir** 400 mg BID or **famciclovir** 250 mg BID or **valacyclovir** 500-1000 mg QD	daily

Influenza

- Influenza Virus Strains:
  - Type A (90%): Moderate to severe illness, all age groups, humans and other animals
  - Type B (10%): Milder epidemics, humans only, primarily affects children
  - Type C: Rarely reported in humans. No epidemics
- Influenza Antigenic Changes
  - Antigenic Shift: Major Change, new subtype. Caused by exchange of gene segments. May result in pandemic.
  - Antigenic Drift: Minor change, same subtype. Caused by point mutations in gene. May result in epidemic.
- Influenza Epidemiology:
  - Reservoir: Human animals only (type A only)
  - Transmission: Respiratory (aerosolized). Probably airborne.
  - Temporal pattern: Peak December – March in temperate area. May occur earlier or later.
  - Communicability: Maximum 1-2 days before to 4-5 days after onset.
- Influenza Pathogenesis:
  - Respiratory transmission of virus. Replication in respiratory epithelium with subsequent destruction of cells
  - Viral shedding in respiratory secretions for 5-10 days.
- Influenza Complications:
  - Pneumonia (Primarily influenza. Secondary bacterial), Reye's syndrome, myocarditis.
  - Death 0.5 – 1 per 1,000 cases—most are elderly
- Influenza Clinical Features:
  - Incubation period 2 days (range 1-4 days).
  - Severity of illness depends on prior experience with related variants.
  - Abrupt onset: fever, myalgia, headache, malaise, cough, sore throat, and rhinitis.
- Influenza Diagnosis:
  - Clinical and epidemiological characteristics.
  - Isolation of influenza virus from clinical specimen (e.g. nasopharynx, throat, sputum).
  - Tests: Viral culture (5-10 d), IF Ab Staining (2-4 hrs), RT-PCR (1-2 d), serology (>2 wks), EIA (2 hrs), rapid test (<30 min.)
- Fluzone
  - Inactivated trivalent IM vaccine.

- 2 type A strains and 1 type B strain. Two weeks for Ab to develop. May contain egg protein.
- Vaccinate high risk groups first.
- Efficacy of inactivated IM vaccine: 30-70%

- Flumist
  - Live (cold) attenuated trivalent intranasal vaccine.
- Antiviral Agents:
  - 1st generation: Influenza A activity: amantadine (Symmetrel®) and rimantadine (Flumadine®).
  - 2nd generation: Neuraminidase inhibitors – A & B activity: zanamivir (Relenza®) and oseltamivir (Tamiflu®).
- Impacts of Antiviral Drug Therapy:
  - Prophylaxis – 70-90% effective in preventing illness when started before exposure.
  - Therapy – neuraminidase inhibitors (oseltamivir)
    - Reduce duration of illness (1- > 3 days based on time from symptom onset therapy).
    - ↓ hospitalization by 59%, ↓lower resp. tract illness by 55%, ↓ antibiotic use by 27%
- Outbreak / Treatment Issues:
  - Prevention: Respiratory hygiene / cough etiquette programs and standard/droplet precautions
  - Treatment: Need to diagnose and start early! 5-7 days.
  - Prophylaxis: Dosing is usually less frequent - Nursing home (e.g.): all residents for a minimum of 2 weeks.

BIOTERRORISM
Adapted from Colleen Terriff, PharmD

Useful Resource Centers for Disease Control and Prevention website: www.bt.cdc.gov

Disease	Transmission	Incubation	Signs/Symptoms	Post-Exposure Prophylaxis	Treatment	Vaccine
Smallpox	Highly contagious *Variola* virus—person may be infectious but have no signs/symptoms	7-17 days (average 12)	▪ Prodrome (fever, headache, high temp, malaise, myalgia) ▪ Rash→ lesions (most dense on face and distal extremities)	Vaccination	▪ Supportive care ▪ Investigational: IV cidofovir, ribavirin, *Vaccinia* immune globulin, adefovir	Live, unattenuated *Vaccinia* virus
Botulism	Toxin produced by *C. botulinum*—could be spread by aerosol or contamination of food or water	12-36 hours or longer	▪ Acute, afebrile, symmetric, descending flaccid paralysis ▪ Diplopia ▪ Dysarthria ▪ Dysphonia ▪ Dysphagia	Close monitoring for resp. failure	▪ Supportive care ▪ Passive immunization with antitoxin	Pentavalent toxoid vaccine for military and lab workers
Tularemia	Very infectious, yet no person to person transmission		▪ Fever ▪ Chills ▪ Headache ▪ Malaise ▪ Primary pleuro-pneumonia ▪ Conjunctivitis ▪ Pharyngitis ▪ Oral ulcers ▪ Exanthemas	Doxycycline or quinolone x 14d	▪ Quinolone, streptomycin, or gentamicin x 10d OR ▪ Doxycycline x 14-21d	Not available to general public

Plague	Highly contagious—respiratory droplet precautions	1-6 days	▪ High fever ▪ Chills ▪ Headache ▪ Malaise ▪ GI ▪ Cough ▪ Severe pneumonia with sepsis and hemoptysis	Cipro or doxycycline PO x 7d	▪ Streptomycin, gentamicin, quinolone, or doxycycline for at least 10 days	Not available to general public
Anthrax	Inhalational anthrax: ▪ Inhale spores Cutaneous anthrax: (eschar) ▪ Touch spores Gastrointestinal anthrax: ▪ Eat spores		Inhalational anthrax: ▪ Initial phase (1 wk- 1 mo) o Fever o Malaise o Myalgia o Non-productive cough ▪ Severe phase (fatal in 5-7d) o Respiratory distress o Meningitis o Shock	Cipro or doxycycline BID x 60d with monitoring OR x 100d OR x 100d with anthrax vaccine	▪ Cipro or doxycycline PLUS ▪ Rifampin, vancomycin, imipenem, chloramphenicol, penicillin, ampicillin, clindamycin, clarithromycin, or amoxicillin depending on susceptibility	Biothrax ▪ SQ injections at 0, 2, 4 weeks then 6, 12, 18 mo then annually ToxBlox ▪ Investigational

SUPPORTIVE CARE IN CANCER PATIENTS
Adapted from Semra Stanley, PharmD

Mucositis/Stomatitis

- Onset 7-10 days after treatment—extends throughout GI tract
- Common culprits: 5-FU, doxorubicin, methotrexate
- Presentation: Sore mouth/throat, dry mouth, difficulty swallowing, mouth ulceration, bleeding
- Complications: infection, dehydration, malnutrition, diarrhea, blood loss
- Prevention: Oral hygiene, brush after meals, soft toothbrush, rinse frequently with isotonic bicarb solution, oral cryotherapy (w/ 5-FU tx), eat softer foods
- Treatment:
  - Supportive care: fluids, nutrition, sugar-free candy
  - Oral hygiene
  - Topical analgesics: viscous lidocaine, Magic Mouth wash (Maalox+ lidocaine + Benadryl), sulcralfate slurry, artificial saliva
  - Systemic analgesics
  - Treat any infection: most commonly *Candida*
  - Treat diarrhea

Chemotherapy Induced Nausea and Vomiting (CINV)

- Goal: prevent dehydration, malnutrition, delay of chemotherapy
- Route: PO preferred, IV only if PO not tolerated
- Administer oral meds 30-45 minutes prior to chemotherapy
- Risk factors: younger age, female, nausea during pregnancy, no alcohol use, prior chemotherapy, motion sickness hx, chemo regimen
- Acute N/V: within 0-24 hours or less
  - Drug of choice: 5HT-3 antagonists
  - Add other agents depending on emetogenicity: corticosteroids, prochlorperazine, metaclopramide
  - *Level 1*: (lowest) Usually no treatment required.
    - Optional: Prochlorperazine 5-10 mg x 1 dose ± Lorazepam 0.5-2 mg x 1 dose
  - *Level 2*: Prochlorperazine 10 mg x 1 dose ± Dexamethasone 10 mg x 1 dose ± Lorazepam 0.5 – 2 mg x 1 dose
  - *Level 3-5*: (highest) Dexamethasone 20 mg AND ondansetron 24 mg po or 8 mg IV x 1 dose ± Lorazepam 0.5 – 2 mg x 1 dose ± Prochlorperazine 10 mg x 1 dose
- Delayed N/V: can occur 24 hours to 5 days post treatment
  - Drug of choice: corticosteroids (dexamethasone)
  - Biggest culprits: cisplatin and cyclophosphamide
  - *Level 1*: (lowest) Usually no treatment required.
    - Optional: Prochlorperazine 5-10 mg po q 6 hours prn
  - *Level 2*: Prochlorperazine 10 mg po q 6 hours prn OR dexamethasone 2 – 4 mg po BID x 2 days ± Lorazepam 0.5 – 2 mg po q 4-6 hours prn
  - *Level 3*: Dexamethasone 4 mg po BID x 2-3 days AND prochlorperazine 10 mg po q 6 hrs prn ± Lorazepam 0.5 – 2 mg po q 4-6 hours prn
  - *Levels 4-5*: (highest) Dexamethasone 8 mg po BID x 3-4 days AND ondansetron 8 mg po BID x 2 days ± Prochlorperazine 10 mg po q 6 hrs prn ± Lorazepam 0.5 – 2 mg po q 4-6 hours prn
- Anticipatory N/V: hard to control even with benzodiazepines
  - Drug of choice: benzodiazepines
  - Relaxation techniques: deep breathing, biofeedback, positive images

Emetogenic Potential of Chemotherapy Agents

Level 1 <10%	Level 2 10-30%	Level 3 30-60%	Level 4 60-90%	Level 5 >90%
Bleomycin	Cytarabine (<1000mg/ m2)	Capecit-abine*	Amifostin	Carmustine (>250mg/m2)
Busulfan*	Docetaxel	Cyclophos-phamide*	Carboplatin	Cisplatin (>50mg/m2)

Chlor-ambucil*	Doxo-rubicin liposomal <20mg	Cyclophos-phamide ≤750mg/m2	Carmustine ≤250mg/m2	Cyclophos-phamide >1500mg/m 2
Fludarabine	Etoposide	Dauno-rubicin	Cisplatin (<50mg/m2)	Dacarbazine
Hydroxy-urea	Fluoro-uracil <1 g/m2	Doxo-rubicin 20-60 mg/m2	Cyclophos-phamide 751-1499 mg/m2	Lomustine >60 mg/m2
Interferon (3-9 MU)	Gemcit-abine	Doxo-rubicin liposomal ≥20mg	Cytarabine >1000mg/m2	Mechlor-ethamine
Melphalan	Metho-trexate 52-249 mg/m2	Epi-rubicin ≤90 mg/m2	Doxorubicin >60mg/m2	Streptozocin
Metho-trexate <50mg/m2	Mitomycin	Gemtuz-amab	Imatinib*	
Vinblastine	Paclitaxel	Idarubicin	Irinotecan	
Vincristine	Rituximab	Ifos-famide	Methotrexate >1000mg/m2	
Vinorelbine	Trastuz-umab	Interferon α-2b 20 MU/m2	Mitoxantrone ≥15mg/m2	
	Topotecan	Metho-trexate 250-1000mg/m2	Procarb-azine*	
		Mito-xantrone <15mg/m2		
		Temozol-amide*		

* Oral route

Neutropenia = ANC < 1500

- Nadir: 7 – 10 days
- ANC<500 → increased risk of infection
- Complications: Risk increases with severity/duration; source of infection
- Management:
  - Wash hands, avoid public places and infectious people, monitor temperature
  - Reduce dose or delay next cycle of chemotherapy
  - Colony Stimulating Factors (CSF)

Drug Name	CSF	Lineage stimulated	Side Effects	Dose
Filgrastim (Neupogen)	G-CSF	Neutrophil	Bone pain	5 mcg/kg/d SC/IV
Pegfilgrastim (Neulasta)				6 mg Q 21-28 days
Sargramostim (Leukine)	GM-CSF	Neutrophil Macrophage Eosinophil	Bone pain, HA, fever, myalgia, arthralgia	250 mcg/m^2/d SC/IV

Start at least 24 hours post-chemo
Stop when ANC >2000 x 2 days OR ANC >5000 x 1 day

- CSFs for Primary Prophylaxis
  - Use only in patients at high risk for febrile neutropenia.
  - High risk according to NCCN is ≥ 20% and ASCO is ≥ >40%
  - Risk assessment based on chemotherapy regimen, patient risk factors, and treatment intent (curative vs. palliative)
- CSFs for Secondary Prophylaxis (goal: prevent recurrent neutropenia)

- Not recommended EXCEPT in pts with a potentially curable cancer and no existent organ toxicity
- CSFs for Treatment of Established Neutropenia
  - Not recommended but may be warranted in high risk pts: ANC <100, pneumonia or active fungal infections, hypotension

Thrombocytopenia
- Nadir: ~10 days
- Culprits: mitomycin, carboplatin, carmustine and gemcitabine
- Management:
  - Standard: platelet transfusion
  - Reduce or delay next cycle of chemotherapy
  - PATIENT COUNSELING!
  - Oprelvekin (Neumega)
    - Growth factor IL-11 to stimulate platelet production
    - Dose: 50 mcg/kg/day SC for 10-21 days or until platelet count is >50,000
    - SE: fluid retention, anemia, atrial arrhythmias, HA, nausea, SOB
    - Possible role in secondary prevention
- ASCO guidelines: prophylactic platelet transfusion when platelets <10,000 OR <20,000 in pts with necrotic tumors or decreased performance status

Anemia
- Nadir measured in weeks
- Complications: fatigue, decreased quality of life/effectiveness of radiation/performance status, transfusion related risks
- Classification of anemia:
  - Mild = Hgb 10 to normal
  - Moderate = Hgb 8-9.9
  - Severe = Hgb 6.5 -7.9
  - Life threatening = < 6.5
- Management:
  - Stress management, sleep, nutritional support
  - Blood transfusion when Hgb falls below 7 or patients are symptomatic
  - Colony stimulating factors:

Drug Name	CSF	Lineage stimulated	Side Effects	Dose
Epoetin (Procrit, Epogen)	EPO	Erythrocyte	Bone pain, HTN	150 u/kg **TIW** or 40,000 units q week
Darbepoetin (Aranesp)				1.5 mcg/kg **Q week** or 3 mcg/kg **QOW**

- ASCO guidelines for use of Epoetin
  - Hgb 10 to 12: defer till levels fall closer to 10 depending on circumstances
  - Hgb ≤ 10: Epoetin recommended as treatment option. RBC transfusion also an option depending on circumstances
  - Escalate dose for patients who do not respond to Epoetin but discontinue if no response after 6-8 weeks

Extravasation
- Infiltration of vesicant into soft tissue causing inflammation, irritation, necrosis and ulceration
- Common vesicants: anthracyclines, vinca alkaloids, mitomycin C
- Prevention is KEY
  - Use vein in distal portion of arm
  - Slow IV push through side arm of running IV solution
  - Verify needle stability
  - Verify adequate blood return
  - Avoid administration at crucial structures (joints, tendon)
- Management:
  - STOP injection immediately and do not remove the needle

    - Aspirate drug from needle and infiltrated area
    - If antidote is not used remove catheter; if antidote used apply through catheter before removing
    - Apply COLD pack to site *unless* vinca alkaloid then apply HOT pack. ELEVATE.
- Antidotes:
    - Sodium thiosulfate (cisplatin, dacarbazine and mechlorethamine)
        - 2-4% solution (5-10ml) through IV line and/or SC in affected area

Alopecia

- Onset: 1-2 weeks
- Prevention: NOT RECOMMENDED
- Management: psychosocial support and cosmetic measures

SKIN INFECTIONS (CELLULITIS)
Adapted from Mark Garrison, PharmD

Cellulitis
**Usually there is a source of trauma/break in the skin (2/3 of cases)

Typical Signs & Symptoms	Likely causative bacteria	Therapy
▪ +/- Fever ▪ Increased WBC ▪ Mild lymphadenopathy ▪ Local tenderness ▪ Warmth & erythema ▪ Pain and tightness ▪ Swelling	▪ Group A *Strep* (most common) ▪ *Staphylococccus aureus* (injection drug users) ▪ *Clostridium perfringes* (anaerobe-causes gas gangrene/foul odor present) ▪ *Haemophilus influenzae* (big decrease since Hib vaccine) ▪ Sometimes gram (-) like *E. coli* ▪ Diabetic foot infections are typically polymicrobial: anaerobes, gram (+) & gram (-)	▪ Mild infections: dicloxacillin or cephalexin ▪ More serious infections: IV nafcillin/oxacillin or cefazolin +/- gentamicin ▪ Penicillin allergic patients: clindamycin, macrolides, amoxicillin/clavulanate, +/-TMP/SMZ ▪ *Clostridium perfringes*: IV clindamycin plus IV penicillin G and debridement

- Usually treat for common organisms and if therapy fails, obtain "leading edge" wound culture. Wound cultures are often contaminated with normal skin flora, so interpret with caution
- Possible complications if infection progresses
  - Bacteremia can occur in up to 30% of the cases
  - Osteomyelitis: typically requires prolonged therapy with IV agents (4-6 weeks)
  - Spread to lymph system: lymphangitis
  - Abscess: Stubborn to manage; consider when draining sinus tract present; may involve anaerobes (foul odor); requires surgical drainage and IV ABX

Impetigo

- Definition: honey-crusted, superficial skin lesions (usually no scaring), particularly on face, nose, lips
- Group A *Strep* cause 80-90% of cases, but *Staph. aureus* can also cause
- Common in kids, usually follows recent head cold
- Contagious – no daycare
- Treat with oral antibiotics to cover *Strep* (cephalexin, amoxicillin, dicloxacillin or cloxacillin)
- Topical ABX improve lesion healing time (mupirocin)

Erysipelas

- Definition: facial cellulitis; bright red, tender, hard, painful; extensive lymph node involvement, usually elderly patients
- Almost always caused by Group A *Strep*—1/3 of patients have recent *Strep* infection
- Newborns with erysipelas often caused by Group B *Strep*
- Treatment: 7-10 day treatment course, but must change drug if no improvement in 24-48 hrs
    - Mild to moderate symptoms: cephalexin or dicloxacillin
    - More severe symptoms: IV oxacillin/ nafcillin or cefazolin

CHEMOTHERAPEUTIC AGENTS
Adapted from Semra Stanley, PharmD

Drugs	Class	MOA	Dose limiting toxicity	Dose modification
Alkylating Agents – Cell cycle non-specific				
Mechlorethamine Cyclophosphamide Ifosfamide	Nitrogen mustards	Cross-linking of DNA	- Myelosuppression - Hemorrhagic cystitis caused by build up of acreolin (ifosfamide > cyclophosphamide) • Manage/prevent: ALWAYS hydrate • Administer **Mesna** – binds acreolin (always give Mesna w/ ifosfamide) - N/V - CNS toxicity (ifosfamide): confusion, somnolence, death	Adjust dose for renal dysfunction
Cisplatin Carboplatin Oxaliplatin	Platinum analogues (act like alkylating agents)		- Nephrotoxicity (more w/ cisplatin)! • Management/Prevention: aggressive hydration with chloride containing solution, careful diuresis (mannitol) and magnesium replacement - Neuropathy: • Peripheral neuropathy (cisplatin & oxalipatin >> carboplatin): numbness and tingling in extremities • Pharyngo-laryngeal dysesthesia : cold sensitive (oxaliplatin) • Ototoxicity (cisplatin) - N/V - delayed	• Adjust dose for renal dysfunction • Carbo…Calvert Formula: **Dose (mg) =** Target AUC X (CrCl ml/min + 25)

			- Myelosuppression (carboplatin)	
Topoisomerase II inhibitors				
Doxorubicin Daunorubicin Epirubicin	Anthracyclines ("red" drugs)	Cell cycle non-specific - Topoisomerase II inhibition → prevent religation of DNA - Intercalation between base pairs → DNA breaks - Free radical formation	- Cardiotoxicity: • Life time cumulative dose 450-550 mg/m2 • Monitor ejection fraction: Pt should have a baseline MUGA or ECHO and periodic evaluation • **Dexrazoxane**: an iron chelator approved for use with doxorubicin to prevent cardiomyopathy. Give IV immediately before doxorubicin - Myelosuppression - Extravasation can occur. They are vesicants. * Drug interaction with antioxidants	Adjust dose for hepatic dysfunction
Mitoxantrone	Miscellaneous ("blue" drug)	Cell cycle non-specific - Topoisomerase II inhibition - Intercalation between base pairs - NO Free radical formation	- Myelosuppression - Discoloration of skin, sclera and urine - Conjunctivitis	Adjust dose for hepatic dysfunction
Etoposide Tenoposide	Epipodophyllotoxins	Cell cycle specific: S / G2 - Forms a cleavable complex with topoisomerase II & DNA leading to overwhelming double & single strand DNA breaks	- Myelosuppression - Hypersensitivity rxn due to solvents in products - (Irritant)	Adjust dose for renal & hepatic dysfunction

Drugs	Class	MOA	Dose limiting toxicity	Dose modification
Topoisomerase I inhibitors – Cell cycle specific				
Irinotecan (produg of SN-38) Topotecan	Camptothecins	- S phase - Forms cleavable complex with DNA + Topo I & leads to replication arrest and cell death	- Myelosuppression - Diarrhea (Irinotecan only): • Acute diarrhea (within 24 hrs of administration) – tx: atropine • Delayed diarrhea (after 24 hrs) – tx: loperamide	Adjust dose for hepatic dysfunction Adjust dose for renal dysfunction
Antimicrotubules – Cell cycle specific				
Vincristine Vinblastine Vinorelbine	Vinca alkaloids	- M phase - Prevent microtubule formation	- Neurotoxicity (Vincristine >>> vinorelbine >> vinblastine) • Numbness and tingling in extremeties • Jaw pain • Constipation - Myelosuppression – vinorelbine & vinblastine, NOT vincristine - Potential for extravasation. ALL are vesicants	Dose reduced for hepatic dysfunction
Paclitaxel Docetaxel	Taxanes	- M phase - Prevent microtubule disassembly	- Myelosuppression (neutropenia) - Neurotoxicity - Infusion related hypersensitivity, pre-medicate before giving Paclitaxel with: • H2 antagonist AND • H1 antagonist AND • Steroid - Fluid retention (peripheral edema) (Docetaxel) - Total alopecia	Dose reduced for hepatic dysfunction

Antimetabolites – Cell cycle specific				
Fludarabine Cladribine	Purine analogues	- S phase - Incorporated directly into DNA/RNA - Inhibit DNA synthesis enzymes	- Myelosuppression (thrombocytopenia) - Neurotoxicity (fludarabine) - (Fever, chills)	Dose reduced for renal dysfunction
Mercaptopurine				Major drug interaction with mercaptopurine & allopurinol. Reduce mercaptopurine dose by at least 50% or omit allopurinol
Cytarabine Gemcitabine	Pyrimidine analogues	- S phase - Incorporated directly into DNA/RNA and inhibit DNA polymerase	- Myelosuppression: • Predominate w/bolus - Mucosal damage (fluorouracil & capecitabine): • Predominate w/continuous infusion • Mucositis, diarrhea - Palmar-plantar erythrodysesthesia (fluorouracil & capecitabine): hand & foot syndromes (drying, red, crack, painful) - CNS toxicity (cytarabine only): nystagmus, ataxia, encephalopathy, seizures	• Fluorouracil & gemcitabine: NO dose adjustments needed for renal or hepatic dysfunction • Capecitabine & cytarabine: may adjust for renal dysfuction
Fluorouracil (5-FU) Capecitabine (prodrug of 5-FU)		- S phase Multiple mechanisms: - Prodrug converted to 5-FdUMP which binds to thymidylate synthase (TS) & prevents the synthesis of thymidine. **Leucovorin,** a reduced folate can be administered with 5-FU to enhance cytotoxicity (synergistic effect) - The metabolite 5-FUTP may be incorporated into RNA as a false base		

		- 5-FU can also be incorporated directly into DNA		
Drugs	**Class**	**MOA**	**Dose limiting toxicity**	**Dose modification**
Methotrexate	Folate antagonist	- S phase - Inhibits the enzyme (DHFR) which converts dietary folates to their active form (FH4), which is necessary for DNA synthesis **Leucovorin** can be used to "rescue" pts from toxicity. Usually given with any methotrexate dose > 100mg/m^2	- Myelosuppression - Mucositis - Nephrotoxicity * Drug interaction w/NSAIDs	Dose reduced for renal dysfunction. Do not give if CrCl < 50ml/min
Antitumor antibiotics				
Bleomycin		- G2 phase - Generation of free radicals - Drug interaction w/ antioxidants	- Pulmonary infiltrates - Hypersensitivity: TEST DOSE (1-2 units SQ or IV) - Palmar-plantar eythrodysthesia (PPE)	
Monoclonal antibodies				
Rituximab (Rituxan)	NHL	Recognizes cell surface antigen (CD20) on B-cells &	- Infusion-related rxns: chills, dyspnea, nausea, anaphylaxis	

		induces antibody dependent and/or complement-mediated cellular toxicity	- Premedicate: diphenhydramine & APAP	
Trastuzumab (Herceptin)	Breast cancer	Binds human epidermal growth factor receptor 2 protein (HER2) and induces antibody-dependent cell mediated toxicity	- Infusion-related rxns: chills, dyspnea, nausea, anaphylaxis	
Bevacizumab (Avastin)	Colon/lung/renal cancer	Binds to vascular endothelial growth factor (VEGF) and inhibits growth of new blood vessels to the tumor	- Infusion-related rxns: chills, dyspnea, nausea, anaphylaxis - Impaired wound healing, gastric perforations, hemorrhage	
Cetuximab (Erbitux)	Colon cancer	Binds epidermal growth factor receptor 1 (EGFR) and inhibits cell growth and induces apoptosis	- Infusion-related rxns: chills, dyspnea, nausea, anaphylaxis - Severe acneform skin rash & dry skin	

CNS INFECTIONS
Adapted from Mark Garrison, PharmD

Signs and Symptoms

- Headache
- Fever
- Stiff neck/back
- Brudzinski's sign
- Kernig's reflex
- Nuchal rigidity
- Light sensitivity
- Lethargy
- Elevated WBC
- Purpura common with *N. meningitides* infections

Risk Factors

- Respiratory tract infection
- Otitis media
- Mastoiditis
- Head trauma
- Alcoholism
- High-dose steroids
- Splenectomy
- Sickle cell disease
- Immunoglobulin deficiency
- Immunosuppression

Normal vs. Infected CSF

Parameter	Normal	Bacterial Infection	Viral or Fungal Infection
WBC (mm^3)	<5	400-100,000	V: 5-500 F: 40-400
Differential	> 90% monocytes	> 90% PMNs	V: 50% lymphs 50% PMNs F: >50% lymphs
Protein (mg/dL)	< 50	80-500	30-150
Glucose (mg/dL)	2/3 serum	< 1/2 serum	< 30-70

Recommended Empiric Treatment by Age

Age	Organisms	Empiric Tx*
0 – 1 mo	▪ Gram-neg. enterics ▪ Group B strep ▪ *Listeria*	Ampicillin + cefotaxime or aminoglycoside
1 mo – 4 yo	▪ *H. influenzae* ▪ *N. meningitides* ▪ *S. pneumoniae*	3rd generation cephalosporin + vancomycin + dexamethasone
5 – 29 yo	▪ *N. meningitides* ▪ *S. pneumoniae* ▪ *H. influenzae*	3rd generation cephalosporin + vancomycin + dexamethasone
30 – 60 yo	▪ *S. pneumoniae* ▪ *N. meningitides*	3rd generation cephalosporin + vancomycin + dexamethasone
> 60 yo	▪ *S. pneumoniae* ▪ Gram-neg. enterics ▪ *Listeria monocytogenes*	Ampicillin + 3rd generation cephalosporin or aminoglycoside AND vancomycin AND dexamethasone

Sanford's Specific Recommendations for Meningitis

Bacteria	Preferred*	Alternative*

H. influenzae	Ceftriaxone	If pen. allergic: chloramphenicol
Listeria	Ampicillin ± gentamicin	▪ Meropenem ▪ If pen. allergic: TMP/SMZ
N. meningitidis	Ceftriaxone	▪ Meropenem or gati/moxifloxacin ▪ If pen. allergic: chloramphenicol
S. pneumoniae	▪ Pen G or Ampicillin if Pen G MIC < 0.1 mcg/ml, otherwise ceftriaxone or cefotaxime ▪ Add vanco if Pen G MIC > 2.0 mcg/ml	▪ Gati/moxifloxacin ▪ Meropenem ▪ Cefepime ▪ Chloramphenicol
Coliforms or *Pseudomonas*	Ceftazidime or cefepime ± gentamicin	▪ Ciprofloxacin ▪ Meropenem

***Dosing**

- Dexamethasone 0.15 mg/kg IV q6h x 2-4 days 15-20 min prior to or with 1st antibiotic dose useful for *H. influenzae*, *S. pneumoniae*, and *N. meningitides*
- Cefotaxime 2 gm q4-6h IV; Peds 200 mg/kg/d divided q6-8h
- Ceftriaxone 2 gm q12h IV; Peds 100 mg/kg/d divided q12h
- Vancomycin 500-750 mg q6h IV; Peds 15 mg/kg q6h IV
- Ampicillin 2 gm q4h
- Gentamicin 2 mg/kg loading dose, then 1.7 mg/kg q8h
- Penicillin G 4 million units IV q4h
- Ceftazidime 2 gm IV q8h
- Cefepime 2 gm IV q8h

CRITICAL CARE ISSUES
Adapted from Clayton Littell, RPh, BCPS

Sepsis

Signs and Symptoms	Risk Factors	Likely Causative Organisms	Treatments
▪ Fever ▪ Rigors/Chills ▪ Tachycardia ▪ Tachypnea ▪ Altered mental status ▪ Leukocytosis w/ left shift or neutropenia ▪ Hyperglycemia	▪ Immunosuppression (cancer, steroid use, diabetes, HIV) ▪ Invasive Devices ▪ Elderly ▪ Surgery/Trauma ▪ Malnutrition ▪ Chronic antibiotic use	▪ *E. coli* ▪ *Pseudomonas* ▪ *Staph. aureus* ▪ *Strep. pneumo.* ▪ *Staph. epidermidis* ▪ Anaerobes ▪ Fungus ▪ *Enterococcus*	▪ Antibiotics ▪ Pull lines, caths, etc. ▪ Fluids (crystalloids) ▪ Vasopressors first then inotropes ▪ Insulin ▪ Hydrocortisone ▪ Vasopressin ▪ Activated Protein C (Xigris®)

Definitions Related to Sepsis
- Systemic Inflammatory Response Syndrome (SIRS): at least 2 of the following: temperature > 38˚C or < 36˚C, HR > 90 bpm, RR > 20 or $PaCO_2$ <32 torr, WBC > 12000, <4000, or > 10% bands
- Sepsis: SIRS secondary to infection
- Severe Sepsis: sepsis associated with MODS
- Multiple Organ Dysfunction Syndrome (MODS): organs failing and need intervention to maintain homeostasis
- Compensatory Anti-inflammatory Response Syndrome (CARS): cytokine-mediated physiologic response to SIRS

Cytokines Involved in SIRS, Sepsis, MODS
- Pro-inflammatory: IL-1 and TNF-α primarily, also IL-2, IL-6, IL-8, IFN-γ
- Anti-inflammatory: IL-4, IL-10, IL-1 receptor antagonist

**Inflammation leads to activation of clotting cascade—activated protein C blocks clotting cascade

Complications from SIRS, Sepsis, MODS
- DIC, ARDS, Stress ulcers and bowel ischemia, acute renal failure, myocardial infarction, shock liver

Shock

- Hypovolemic – loss of preload (volume) e.g. hemorrhage, dehydration
  - Labs: ↓ urine output, BUN:SCr > 20
  - Treatment
    - Volume - lactated ringers, NS, albumin, packed RBC (in bleeding)
    - Do not be afraid of large volumes
- Cardiogenic – loss of contractility e.g. AMI, CHF
  - Labs: cardiac enzymes and BNP to rule out MI and HF
  - Treatment
    - Inotropes- medium-dose dopamine, dobutamine, epinephrine, milrinone
    - Afterload reduction- nitroprusside, nicardipine, enalaprilat
- Distributive – loss of afterload (SVR) e.g. anaphylaxis, sepsis, head trauma
  - BP remains low despite massive fluid administration
  - Treatment
    - α-1 agonists – phenylephrine, norepinephrine, high-dose dopamine, epinephrine

ELECTROLYTE ABNORMALITIES
Adapted from Brent Albertson, PharmD and Carol Vanevenhoven, PharmD

Hyponatremia <125mEq/L
- Causes
  - Dilutional/Fluid Overload
    - Cirrhosis, CHF, Renal Failure, SIADH
  - Sodium Depletion
    - Mineralocorticoid deficiency, Na wasting, Renal dz, fluid replacement with non-saline fluids
- Clinical Presentation
  - Fluid Overload (JVD, SOB, pitting edema)
  - Muscle Cramps
  - Disorientation
  - Headache
  - Seizure/coma

**Most are asymptomatic

Hyponatremia (hypotonic) Correction
Isovolemic- Treat underlying disease(s): SIADH, hypothyroidism, adrenal/renal insufficiency, polydipsia (compulsive water consumption>20L/day, phenothiazines-dry mouth) fluid restriction, low solute and protein diets

Hypovolemic
- Replace volume with normal saline
- Empiric saline: 500 ml NS bolus, then 200-300 ml/hr
  - Change to 100-150 ml/hr once volume restored
  - Recheck sodium q 2-4 hrs
- Correct underlying cause (diuretics, Addison's, diarrhea)

Rate of Correction:
- Asymptomatic: 0.3-0.5 mEq/L/hr rate of rise
- Symptomatic: 1-2 mEq/L/hr initially until symptoms resolve
- Max 12 mEq/L in first 24 hrs to prevent Central Pontine Demyelination (paralysis, mutism, death 5-7 days after Tx)

Hypervolemic- Water restriction, salt restriction, diuretics, ACE-Inhibitors, or increase oncotic pressure with albumin infusion followed by diuretics.

Hyponatremia (hypertonic) Correction
- Excess effective osmoles e.g. glucose, mannitol
- Add 1.7 mEq/L Na for every 100 mg/dL glucose above 100 mg/dL

Hypernatremia >150 mEq/L
- Causes
  - Loss of water/dehydration
    - N/V/D, drugs (diuretics)
  - Excessive sodium intake
    - Diet, IV fluids, Drugs (Antibiotics, kayexalate)
- Clinical Presentation
  - Thirst
  - Seizure
  - Restlessness
  - Hyperreflexia
  - Irritability
  - Coma
  - Lethargy
  - Death (>160 mEq/L = 75% mortality)
  - Muscle twitching

Hypernatremia Correction

Isovolemic- replace fluid with D5W or 1/2NS

- Diabetes insipidus: correct with desmopressin 10 mcg/d
- Nephrogenic: (could be caused by Li, demeclocyline)
  - Na restriction and HCTZ 25 mg QD
  - Indomethacin 50 mgTID as adjunct (potentiates ADH)
  - Amiloride 5-10 mg/d if lithium-induced

Hypovolemic- replace fluid with NS 200-300 ml/hr until stable
Water Deficit= TBW x [(SNa/140) -1] TBW~0.6 x BW

Hypervolemic (sodium overload)

- Use D5W to fill water deficit
- Furosemide to enhance sodium loss

Hypokalemia <3.5 mEq/L

- Causes:
  - Decreased Intake
    - Alcohol, Eating disorders, K^+ free IV fluids, hypomagnesemia
  - Increased Loss
    - Drugs (corticosteroids, loop diuretics, ampho B), Cushing's or Hyperaldosteronism, Diarrhea/laxative abuse, vomiting
  - Intracellular Shift
    - Alkalosis, Insulin, β2 adrenergic stimulation
- Clinical Presentation
  - Cardiovascular (EKG changes, Hypotension)
  - Neuromuscular (Cramps, weakness, areflexia)
  - Renal (Inability to concentrate urine)

Hypokalemia Correction

- Oral replacement in divided doses preferred
- Must correct hypomagnesemia
- K^+ sparing diuretics (Spironolactone, Triamterene, Amiloride)
- IV replacement (KCL, KAcetate, KPhos)
  - Use Saline base instead of dextrose
  - Concentration not to exceed: 40mEq/100ml **central,** 10mEq/100ml **peripheral**
  - Rate NTE 10 mEq/hour unless on a EKG monitor, then NTE 20 mEq/hour

Sacred Heart Protocol for Hypokalemia

**Use ½ dose if SCr ≥ 2.5 mg/dL

	IV	PO (preferred)
< 3 mEq/L	1) 40 mEq 2) Check K^+ after 1 hour 3) Repeat table	**Use IV**
3 – 3.4 mEq/L	1) 20 – 40 mEq 2) Check K^+ after 1 hour 3) Repeat table	1) 20 mEq q 2hr x 2 doses (40 mEq total) 2) Check K^+ after 2 hours 3) Repeat table
3.5 – 3.9 mEq/L	1) 20 mEq 2) Check K^+ in morning	1) 20 mEq 2) Check K^+ in morning

Hyperkalemia >5.5 mEq/L

- Causes
  - Inability to excrete
    - Renal Dysfunction, drugs (ACE-I, Spirinolactone)
  - Cell Breakdown
    - Burns, Tumor Lysis Syndrome, Crush injuries
  - Excessive Intake
    - Salt Substitute, TPN or IV fluids
  - Extracellular Shift
    - Metabolic acidosis—add 0.6 mEq/L for each 0.1 unit pH drop from 7.4
- Clinical Presentation
  - EKG (enlarged T waves, Hypotension, Bradycardia)

Hyperkalemia Correction

1. Abnormal EKG – yes -> Calcium Gluconate/Chloride
   - 1 g IV over 5-10 min
2. Hyperglycemia – yes -> Insulin/Glucose depending
   - BG> 250mg/dL 10 units
   - BG< 250mg/dL 10-20 units with 25-50g glucose
3. Consider Albuterol to shift K+ into cells
4. Consider Bicarbonate if acidotic
5. Consider Kayayexylate, diuresis, or hemodialysis
   - Kayexelate 15-60g in 70% sorbitol
   - Furosemide 20-40mg IV

Hypomagnesemia <1.6 mEq/L

- Causes
  - Diarrhea
  - Diuretics
  - Chronic Alcoholics
- Clinical Presentation
  - Muscle Weakness
  - Tremor
  - Dysrhythmias
  - Trousseau's Sign (hand spasm)
  - Chvostek's Sign (face spasm)
  - Refractory hypokalemia/calcemia

Hypomagnesemia Correction

- Replace over 3-5 days because Mg is 50% renally excreted
- Renal threshold – avoid bolus
- Use lower dose if CrCl <30mL/min
- IV – 50% MgSO4-dilute to 20% (phlebitis) Slow infusion to avoid flushing and sweating
- IM – painful
- Oral – Diarrhea
  - Mg Oxide (Mag-Ox) 50 mEq/gm
  - Mg Hydroxide (MOM) 34 mEq/gm
  - Mg Carbonate (Gaviscon) 21 mEq/gm
  - Mg Chloride (Slow-Mag) 5.2 mEq/gm

Sacred Heart Protocol for Hypomagnesemia

**Use ½ dose if SCr ≥ 2.5 mg/dL

	IV	PO
< 1 mEq/L OR Symptomatic OR	1) Mag sulfate 2 g IV push 2) Mag infusion 4 g over 4 hrs	**Use IV**

Emergent	3) Check Mg^{2+} 2 hrs after infusion 4) Repeat table	
1-1.4 mEq/L	1) Magnesium sulfate 2 g over 2 hrs 2) Check Mg^{2+} ≥ 2 hrs after dose 3) Repeat table	1) Magnesium oxide 400 mg TID 2) Check Mg^{2+} 8 hrs after dose or in morning 3) Repeat table
1.5-1.8 mEq/L	1) Magnesium sulfate 1-2 g over 1-2 hrs 2) Check Mg^{2+} ≥ 2 hrs after dose	1) Magnesium oxide 400 mg QD-BID 2) Check Mg^{2+} in morning

Hypermagnesemia > 2.4 mEq/L

- Causes
  - Renal Failure
  - Increased Intake – Mg containing Antacids
- Clinical Presentation
  - 2 – 5 mEq/L: bradycardia, flushing, sweating, N/V, often asymptomatic
  - 6 mEq/L: drowsiness, decrease deep tendon reflexes
  - 10 – 15 mEq/L: flaccid paralysis, increased PR and QRS intervals
  - 15 mEq/L: respiratory distress & asystole

Hypermagnesemia Correction

Treatment – (Magnesium is a "Physiologic CCB")

- Calcium Chloride 1g IV short duration-multiple doses.
- Renal Excretion: IV fluids / Furosemide
- Dialysis

Hypocalcemia < 8.5 mg/dL

Corrected Ca=((4- Albumin) (0.8)) + SerumCa

- Causes:
  - Vitamin D Defiency
  - Hypoparathyroidism
  - Hyperphosphatemia (Phosphate binds to Ca^{+2})
  - Loop Diuretics
  - Renal Failure
  - Hypoalbuminemia (asymptomatic, correct calcium level)
- Clinical Presentation:
  - **Tetany**
  - Fatigue
  - Memory Loss
  - Depression
  - Severe Cardiac Arrhythmias
  - Trousseau's Sign
  - Chvostek's Sign

Hypocalcemia Correction

- Treat underlying cause (diseases)
- Oral Replacement (asymptomatic) 1-3g/day
  - Assess q 1-2 days initially then weekly
  - Calcium carbonate 1g=400 mg=20 mEq
- IV Replacement (symptomatic)-bolus and infusion
  - Assess Q 4-6 H
  - Change to oral once >8.5mg/dL

Sacred Heart Protocol for Hypocalcemia

**Use ½ dose if SCr ≥ 2.5 mg/dL

	IV	PO

Symptomatic OR Severe	1) Ca. gluc. 3 g over 10 min 2) Ca Gluc. inf. 6 g over 6 hrs 3) Check Ca^{2+} q4h after infusion 4) May need to titrate for symptoms and maintain Ca^{2+} 8-9 mg/dL	**Use IV**
Asymptomatic OR Moderate	1) 1-2 g Ca gluc over 30-60 min 2) Check Ca^{2+} in 4-6 hrs 3) Repeat table	1) Ca carb 1500 mg tab: 2-3 tab TID ± 50,000 units Vit D qd OR Calcitriol 0.25-0.5 mcg qd 2) Check Ca^{2+} in morning
Osteoporosis	**Use PO**	1) Ca carb with Vit D 500 mg TID

Hypercalcemia >10.5 mg/dL
- Causes
  - Malignancy
  - Hyperparathyroidism
- Clinical Presentation:
  - Nausea/Vomiting
  - Abdominal Pain/Anorexia
  - Severe Symptoms (Lethargy, Cardiac Arrhythmias, Coma, Death)

Hypercalcemia Correction
1. Normal saline +/- furosemide
2. Zolendronate 4-8mg IV or pamidronate 60-90mg one dose: 2 day onset
3. Calcitonin 4 units/kg BID IM/SQ or 10-12 units/hr IV
   - Onset 1-2 hr
4. Glucocorticoids

Hypophosphatemia < 2.4 mg/dL
- Causes:
  - Aluminum antacids (binds to PO_4)
  - Malnourishment
  - Chronic Alcoholics
- Clinical Presentation:
  - Nervous System Dysfunction
  - Muscle Weakness
  - Cardiac Irregularities
  - Dysfunction of Leukocytes and Erythrocytes
  - Resp. failure in patients with decreased lung function

Hypophosphatemia Correction

**do not correct if hypercalcemic—precipitates

- Phosphate 1.0-2.5mg/dLw/o symptoms.
  - Replace with up to 2g/day divided BID to QID
- Phosphate <1.0mg/dLor symptomatic
  - 15-30mmol PO4 in 250mL D5W or NS over 3 hours
  - Phosphorous Products
    - Sodium (4mEq/L) Phosphate (3mmol/mL)
    - Potassium (4.4 mEq/L) Phosphate (3mmol/mL)
  - Phosphorous level Q 4-6hrs. Repeat until normal

Hypophoshpatemia

**Use ½ dose if SCr ≥ 2.5 mg/dL

	IV	PO
< 1 mg/dL OR Symptomatic	1) 24-30 mmol NaPhos OR KPhos over 6 hrs 2) Check Phos 2-4 hrs after dose 3) Repeat table	**Use IV**
1-2.1 mg/dL	1) 15-21 mmol NaPhos OR KPhos over 6 hrs 2) Check Phos 2-4 hrs after dose 3) Repeat table	1) NeutraPhos OR Neutra PhosK: 1-2 pkts BID-TID OR KPhos Neutral: 1-2 tabs BID-TID OR KPhos Original: 2 tabs BID-TID OR Dietary supplement 2) Check Phos in morning
2.1-2.4 mg/dL	**PO if available** 1) 15 mmol KPhos OR NaPhos over 4-6 hrs 2) Check Phos in morning	

Hyperphosphatemia > 4.5 mg/dL

- Causes:
  - Renal Dysfunction
  - Hypervitamininosis D
  - Hyperparathyroidism
- Clinical Presentation:
  - Short term (minimal)
  - Long-term (Renal Failure)

***Caution Administering Calcium replacement → can lead to precipitation*

Hyperphosphatemia Correction

Phosphate Binders: take prior to a meal

- Calcium Carbonate (40% calcium)
- Calcium Acetate (25% calcium)
- Calcium Citrate (21% calcium)
- Sevelamer-(Renagel)-A polymeric compound

GENERAL PRINCIPLES OF CANCER
Adapted from Barbara Arnold, PharmD

Resources
American Cancer Society: www.cancer.org
National Cancer Institute www.cancer.gov
Cancer statistics by the National Cancer Institute: http://seer.cancer.gov/

Cancer Terminology
- -oma – tumor
- carcinoma = malignance from epithelial tissue
- sarcoma = malign. from connective tissue (bone, musc., blood, etc)
- muscle= myo-, smooth musc = leiomyo-, striated musc = rhabdomyo-, bone= osteo-, glands= adeno-, blood= -emia
- Cancer is classified by tissue of orgin, not site of tumor

Factors that contribute to the development of cancer
- Internal (5-10% of cancer from inherited mutations)
- External (carcinogens, radiation (UV), viruses, drugs)

Tumor Progression
- Hyperplasia = cells divide excessively
- Dysplasia = abnormal change in size, shape, organization of cells
- Carcinoma in situ = Pre-invasive stage
- Cancer = cells invade surrounding tissue

Tumor Growth
- Growth fraction: proportion of tumor cells actively dividing
- Early phase growth exponential (large growth fraction)
- Late phase growth is slower because nutrients can't reach cells in tumor's core
- Can't feel or see tumor on X-ray until ~1 billion cells

7 Early Warning Signs of Cancer
Change in bowel or bladder habits
A sore that does not heal
Unusual bleeding or discharge
Thickening or lump in breast or elsewhere
Indigestion or difficulty swallowing
Obvious change in mole or wart
Nagging cough or hoarseness

Cancer Staging
- Primary Tumor (T): Tumor Size
  - T_X Primary tumor cannot be assessed
  - T_O No Evidence of primary tumor
  - T_{is} Carcinoma in situ
  - T_1 Tumor invades submucosa
  - T_2 Tumor invades muscularis propria
  - T_3 Tumor invades into subserosa
  - T_4 Tumor perforates the visceral peritoneum
- Regional Lymph Node (N): Nodal Extent
  - N_X Regional lymph node cannot be assessed
  - N_O No regional lymph node metastasis
  - N_1 Metastasis in 1 to 3 pericolic/perirectal lymph nodes
  - N_2 Metastasis in 4 or more pericolic/perirectal lymph nodes
  - N_3 Metastasis in any lymph node
- Distant Metastasis (M):
  - M_X Presence of distant metastasis cannot be assessed
  - M_O No distant metastasis
  - M_1 Distant Metastasis

Staging and Dukes Classification

Stage 0	Tis	NO	MO	
Stage I	T1 or T2	NO	MO	Dukes A
Stage II	T3 or T4	NO	MO	Dukes B

Stage III	Any T	N1, N2, N3	MO	Dukes C
Stage IV	Any T	Any N	MI	

Tumor Characteristics

Benign	Malignant
Encapsulated/localized	Invasive
Indolent	Unstable
Resemble surrounding cells	Atypical
Rarely metastasize or reoccur	Metastasis and reoccurrence is common

Response Terminology

- Complete response/remission: complete disappearance of all evidence of tumor
- Partial response: 50% reduction in tumor size >1 month and no new tumors
- Stable disease/no response: <50% reduction of <25% increase
- Progressive disease: 25% increase in tumor size or new evidence of lesions
- Cure: complete response or disease free survival out to a point in time where risk of recurrence = general population's risk

HIV/AIDS
Adapted from Colleen Terriff, PharmD

Useful Guidelines
- AIDS Info: A Service of the U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. October 6, 2005. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
- CDC website: http://www.cdc.gov/hiv

Definition of AIDS
- CD_4 count<200 or <14% of total lymphocytes **and/or** AIDS defining illness (person may have CD_4>200 and still have AIDS).
- Caused by HIV: HIV-1 most common in US, while HIV-2 more common in Africa (most drugs work best on HIV-1)
- AIDS Defining Illnesses: bacterial, fungal, protozoal, viral infections; sarcomas, lymphomas

CD_4 Cells
- Levels tell us: immune function, opportunistic infection susceptibility, when to start/change therapy
- Normal count: 800-1200—also reported as percent or CD_3/CD_4 ratio
- **HIV patients typically lose 75-100 CD_4 cells per year

Viral Load
- Levels tell us: virus activity, drug efficacy/resistance
- Many ways to measure (PCR vs. bDNA), but use same test each time
- **Want greater than 1 log drop in viral load 2-8 weeks after starting HAART, then <50 at 4-6 months
- Blips = short-term elevations in viral load—recheck levels in ~1 month to make sure just a blip

Indications for Viral Load Testing

Clinical Indication	Information	Use
Signs and symptoms of acute HIV infection	Establishes diagnosis when HIV antibody test is negative or inconclusive	Diagnosis
Evaluation of newly diagnosed HIV infection	Baseline viral setpoint	Use with CD_4 count for decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	Use with CD_4 count to determine when to start therapy
2-8 weeks after starting or changing antiretroviral therapy	Initial assessment of drug efficacy	Decide whether to continue or change therapy
Every 3-4 months after starting therapy	Assess drug efficacy	Decide whether to continue or change therapy
Clinical event or significant decline in CD_4 count	Discerns whether associated with changing or stable viral load	Decide whether to continue or change therapy

**acute illness and vaccinations can cause an increase in plasma HIV RNA for 2-4 weeks—avoid testing during this time
**typically verify changes in viral load with second test before making changes in therapy

HIV Replication Cycle
1. Virus attaches to and binds CD_4 receptors
2. Virus enters T-cell via co-receptors: R5, X4
3. Virus enters T-cell (fusion) and sheds coat
4. Reverse transcription of viral genome from RNA to DNA
5. Viral DNA integrates into host DNA
6. Viral proteins manufactured

7. Release/budding of new virus from T-cell (1 T-cell can produce ~1000 new virus/day)
8. Viral safe havens = CSF, resting CD_4 cells, lymph tissue

Acute HIV Infection
- Symptoms 2-6 weeks after infection
- Rapid, extensive viral replication
- Flu-like symptoms (fever, fatigue, myalgia, arthralgia, adenopathy, diarrhea, headache, pharyngitis, rash, weight loss)
- "Set point" of viral replication established

HIV Testing
- Who to test: high-risk populations, individual request, symptoms of HIV infection, pregnancy, infections associated with HIV (Tb, Hep B/C, STD)
- Earliest detection at 3 weeks, but most reliable detection 3 months after exposure
- Standard HIV test: ELISA + Western Blot to confirm; commercial products: Home Access, OraSure
- Rapid HIV tests: OraQuick Advance, Reveal G2, Uni-Gold Recombigen

Post-Exposure Prophylaxis
- Risk of transmission is very low, but must treat promptly
- Usually AZT + 3TC BID for 28 days
- Alternative regimen: AZT + 3TC + NFV 1250 mg BID for 28 days
- **Do HIV testing at baseline, 6 weeks, 12 weeks, and 6 months; drug toxicity monitoring 2 weeks post-exposure

HAART (Highly Active Antiretroviral Therapy)
- 2 NRTIs (never AZT+d4T) *plus* a PI (1 or 2) *or* NNRTI *or* 3rd NRTI
- Preferred Therapies
  - Efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir)
  - Lopinavir/ritonavir + (lamivudine or emtricitabine) + zidovudine
- Monotherapy is never recommended
- Watch overlapping toxicities with ddI and d4T—especially in pregnancy because increased risk of lactic acidosis
- Change therapy when: CD_4 counts are declining, clinical disease progression, suboptimal therapy, toxicity
  - **Must change at least 2 drugs in regimen
  - **Must take at least 95% of scheduled doses to be effective—adherence is crucial

When to start HAART

Symptoms	CD_4 Count	Plasma HIV RNA	Recommendation
AIDS-defining illness or severe symptoms	Any value	Any value	Treat
Asymptomatic	$CD_4 < 200/mm^3$	Any value	Treat
Asymptomatic	$CD_4 > 200/mm^3$, but $\leq 350/mm^3$	Any value	Treatment should be offered
Asymptomatic	$CD_4 > 350/mm^3$	≥100,000	Can offer treatment, but most clinicians defer therapy
Asymptomatic	$CD_4 > 350/mm^3$	<100,000	Defer

**severe symptoms include unexplained fever or diarrhea >2-4 weeks, oral candidiasis, or >10% unexplained weight loss

When to Change Therapy
- Virologic failure
  - Incomplete response: viral load > 400 copies/mL after 24 weeks or > 50 after 48 weeks

    - Virologic rebound: repeated detection of HIV RNA after viral suppression
- Immunologic failure: CD_4 increase <25-50 cells in first year of therapy or decrease below baseline
- Clinical failure: occurrence of HIV related events after 3 months of therapy

Resistance
- Usually due to noncompliance, but drug interactions, poor bioavailability, non-optimal dosing contribute
- Resistance to one drug, often offers cross-resistance to other drugs in the same class

When to Order Drug-Resistance Assays

Situation	Rationale
Drug-resistance assay recommended	
Failure or suboptimal viral suppression after starting HAART	Determine resistance to current drug regimen, and to optimize number of active drugs in new regimen
Acute HIV infection, if starting HAART	Determine if drug-resistant virus was transmitted, and optimize drug regimen
Drug-resistance assay should be considered	
Chronic HIV infection prior to starting HAART	Assays may not detect minor drug-resistant species, but should be considered if patient infected by someone likely to have resistant strain e.g. someone on HAART
Drug-resistance assay usually not recommended	
After discontinuation of therapy	Assays may not detect minor drug-resistant species, and drug-resistant species may become less dominant without selective drug pressure.
Plasma viral load <1,000 copies/mL	Too little virus for evaluation with current assays

Vertical Transmission Prophylaxis
- Give mother AZT 2 mg/kg IV bolus then 1 mg/kg/hr until delivery—restart oral meds ASAP
- Give baby AZT 2 mg/kg PO q6h x 6 weeks beginning 8-12 hrs after birth

Generic	Code	Brand	Type	Dosing-Adults	Administration	Dosage Form	Side Effects
zidovudine	AZT, ZDV	Retrovir	NRTI	200 mg TID or 300 mg BID	±food	cap, tab, IV, syrup	anemia, leukopenia, GI, HA, malaise
didanosine	ddI	Videx	NRTI	≥60 kg: 400 mg QD; <60 kg: 250 mg QD (caps) or ≥60 kg: 250 mg BID; <60 kg: 167 mg BID (powder)	empty stomach	capsule, powder	pancreatitis, GI, peripheral neuropathy
zalcitabine	ddC	Hivid	NRTI	0.75 mg q8h	empty stomach	tablet	GI, rash, neuropathy, stomatitis, pancreatitis
lamivudine	3TC	Epivir	NRTI	150 mg BID or 300 mg QD; <50 kg: 2 mg/kg BID	±food	tab, soln	GI, pancreatitis (esp w/ peds), peripheral neuropathy (rare)
stavudine	d4T	Zerit	NRTI	≥60 kg: 40 mg BID <60 kg: 30 mg BID	±food	cap, powder	peripheral neuropathy, lactic acidosis, pancreatits
abacavir	ABC	Ziagen	NRTI	300 mg BID (tab or soln) or 600 mg QD (tab)	±food	tab, soln	HA, rash, hypersensitivity, GI, cough (rare)
emtricitabine	FTC	Emtriva	NRTI	200 mg QD (cap) or 240 mg QD (soln)	±food	cap, soln	GI, skin discoloration
zidovudine + lamivudine	AZT + 3TC	Combivir	NRTI	300 mg AZT/150 mg 3TC BID	±food	tab	same as zidovudine and lamivudine
zidovudine + lamivudine + abacavir	AZT + 3TC + ABC	Trizivir	NRTI	300 mg AZT + 300 mg ABC + 150 mg 3TC BID	±food	tab	same as AZT, 3TC, and ABC
lamivudine + abacavir	3TC + ABC	Epzicom	NRTI	300 mg 3TC/600 mg ABC QD	±food	tab	same as 3TC, ABC
emtricitabine + tenofovir	FTC + TFV	Truvada	NRTI + NTRTI	200 mg FTC/300 mg TFV QD	±food	tab	same as FTC, TFV
tenofovir	TFV	Viread	NTRTI	300 mg QD	±food	tab	GI, nephrotoxicity
saquinavir	SQV	Invirase	PI	1000 mg BID boosted with 100 mg RTV BID	w/ food	cap, tab	GI, HA, ↑LFTs, lipids, and BG, ↑CPK
ritonavir	RTV	Norvir	PI	600 mg BID or 100-200 mg QD-BID as booster	caps: w/ food syrup: w/	cap, syrup	GI, taste, ↑LFTs, lipids, and BG, circumoral paresthesias

					Ensure		
indinavir	IDV	Crixivan	PI	800 mg q8h	light meal w/ lots of water	cap	GI, ↑LFTs, lipids, and BG, ↑Bili, kidney stones
nelfinavir	NFV	Viracept	PI	750 mg TID or 1250 mg BID	w/ food	tab, powder	GI , HA, ↑LFTs, lipids, and BG, diarrhea, fatigue, rash
amprenavir	APV	Agenerase	PI	1200 mg BID (cap) or 1400 mg BID (soln)	±food (light meal)	cap, soln	GI, ↑LFTs, lipids, and BG, perioral paresthesias, rash
lopinavir + ritonavir	LPV + RTV	Kaletra	PI	400 mg LPV/100 mg RTV BID or 800 mg LPV/200 mg RTV QD (only if naïve)	±food	tab, soln	GI, ↑LFTs, lipids, and BG, HA, Pancreatitis
atazanavir	ATV	Reyataz	PI	400 mg QD or 300 mg ATV/100 mg RTV QD	light meal	cap	GI, HA, ↑Bili, ↑LFTs, rash, PR prolongation (mild)
fosamprenavir	f-APV, LXV	Lexiva	PI	Naïve: 1400 mg BID or 1400 mg/200 mg RTV QD or 700 mg/100 mg RTV BID (naïve or exp'd)	±food	tab	GI, rash, ↑LFTs, lipids, and BG
tipranavir	TPV	Aptivus	PI	500 mg TPV/200 mg RTV BID	with food (fatty meals)	cap	GI, rash, ↑LFTs (watch!), lipids, and BG
nevirapine	NVP	Viramune	NNRTI	200 mg QD x 14d then 200 mg BID	±food	tab, syrup	severe rash, nausea, fever, HA, ↑LFTs
delavirdine	DLV	Rescriptor	NNRTI	400 mg TID	±food	tab	severe rash, HA, fatigue, GI, LFTs
efavirenz	EFV	Sustiva	NNRTI	600 mg qHS	avoid high fat meal	cap,tab	dizziness, insomnia, anxiety, hallucinations, rash
enfuvirtide	T-20	Fuzeon	fusion inhibitor	90 mg SQ BID	N/A	kit (reconstitute)	injection site rxns, pneumonia

HYPOVOLEMIA
Adapted from Brent Albertson, PharmD

Causes
- Dehydration
- Volume Depletion
  - Intravascular Volume Depletion
    - Water and salt losses from vomiting, diarrhea, diuretics
  - Third Spacing (edema)
    - Loss of plasma proteins
    - Increased hydrostatic pressure
  - Trauma/Shock
    - Decreased sympathetic tone

Physiologic Compensation
- Increased sympathetic output
  - Increased HR and SVR
- RAAS activation – sodium and water retention
- ADH release – water reabsorption

**RAAS and ADH active despite hypo-osmolality if blood pressure is low
- Increased Thirst

Presentation
- Increased HR and stroke volume
- Cold, clammy skin
- Decreased urine output
- Increased LFTs
- BUN:SCr > 20:1
- Light-headed/altered mental status
- Hypotension/orthostasis

Treatment
- Dextrose
  - Equal distribution throughout body
  - Rehydrate with dextrose
- Crystalloids (contain sodium)
  - Stay in extracellular fluid
  - Use isotonic crystalloids (NS, LR) for resuscitation
  - Use ½ NS for maintenance
- Colloids
  - Oncotic fluid pulls fluid intravascularly
  - Agents
    - Hetastarch 6% = iso-oncotic
    - Dextran = hyperoncotic
    - Albumin: 5% = iso-oncotic, 25% = hyperoncotic
  - Use for third-spacing, resuscitation
  - SE = bleeding, anaphylaxis (with Dextran)
- Blood
  - Packed red-blood cells (PRBCs): red cells only
  - Fresh frozen plasma (FFP): plasma only
  - Platelets

Infections in the Neutropenic Patient
Adapted from Mark Garrison

** Infection is the number one cause of death in a neutropenic patient**

Definitions

- *granulocytopenia* – Decrease in neutrophils, basophils, & eosinophils—esp neutrophils (↓90%).
- *agranulocytosis* – insufficient neutrophil or granulocyte number. Caused by bone marrow failure to make neutrophils, or white cells are destroyed faster than produced. Affected people are susceptible to infections.
- *neutropenia* – Decreased neutrophils; ANC < 1000 = neutropenia; < 500 = breakpoint (start antibiotics)
- *profound neutropenia* – ANC < 100; extreme risk of infection
- *ANC* – absolute neutrophil count; ANC = PMNs + bands
- *fever* – body temperature > 38 °C / 100.5°F - 101°F
- *nadir* – lowest point.

Risk Factors

- Other impairments of host defenses
  - Splenectomy, steroids
- Break in mucosal barrier
  - Mucositis → gaping ulcers in the mouth → lots of gram + bacteria
  - Indwelling catheters / IVs
  - Radiation
- Co-morbid diseases
  - Malignancy / steroids
  - Hypogammaglobulinemia (decreased immune gamma globulins)
- Hospital environment
  - Stubborn bugs (gram negative bacteria) (nosocomial)
  - Intubation
  - Spread from health care workers
  - Broad spectrum antibiotics

Clinical Manifestations

- Fever, fever, fever – assume it's an infection from the start
  - Non infectious causes of fever
    - Endocrine, prescription induced, chemo agents, tumor lysis syndrome, citrated blood products
- Over ½ cases are culture negative – blood x 2, chest x-ray, catheter tip, others (GI – stool culture)
- Other localized signs / symptoms of infection (lungs, skin, GI tract)

Etiology

- 70% die in 48 hours without treatment (associated with Gram neg. especially).
- Recent shift: Decreasing prevalence of gram (-) and increasing prevalence of gram (+)
  - Why?: mucosistis, loss of gram (-) coverage, catheters
- Gram (-): *Pseudomonas aeruginosa, E. coli*, *Klebsiella*, *Enterobacter*
- Gram (+): *Staph aureus*, Coag (-) *Staph*, *Streptococci viridans* grp, *Enterococci*
- Morbidity & mortality gram (-) >>> gram (+)
- Anaerobes are rarely encountered (unless there is an abscess)
- Longer out – see invasive fungal disease (Candida, Aspergillosis), viral (HSV), possible PCP
  - 7 days continued temp spikes: add antifungal
  - Except: History of broad spectrum antibiotics can lead to super infection

Management

- DO NOT wait for culture results – initiate empiric therapy ASAP
- Not consensus on which agent(s) to use – combo therapy vs. monotherapy – lots of opinions
- Primary EMPIRIC approaches include:
  - Monotherapy

    - Standard therapy of aminoglycoside PLUS anti-pseudomonal beta-lactam
    - Addition of vancomycin to above regimens
    - Double beta-lactam therapy
    - Quinolone agents to the above regimens
- After 2-3 days, critical to re-assess the patient and modify / add agents as needed. Check for temperature spikes and ANC
- Fungal coverage if patient is still febrile 4-7 days out, despite being on broad-spectrum agents
    - i.e. fluconazole, amphoteracin
- Duration of therapy: use ANC as gauge for therapy.
    - *Optimal to continue antibiotics until
        - ANC > 500 for 2-3 days
        - Patient is clinically stable – afebrile for 2- 3 days
        - Cultures become negative
        - Need a minimum of 7 days of antibiotics
        - If ANC is < 100 treat regardless
    - If patient is afebrile – usually continue until ANC > 500

Exception: OK to d/c agents if patient has an ANC < 500, but is clinically stable and has been afebrile for a week – but need to **monitor closely.**

Empiric Therapy for Neutropenia

Regimen	Potential Advantages	Potential Disadvantages
B-lactam monotherapy • Ceftazidime 1-2 g q8h or cefepime 1-2 g q12h • Pipercillin/tazobactam 4.5 g q6h • Imipenem/cilastatin 0.5 g q6h or meropenem 1 g q8h	Efficacy apparently comparable to combo regimens; decreased drug toxicities; ease of administration; possibly less expensive	Possibly less efficacy in profound/prolonged neutropenia; limited gram (+) activity; no additive/synergistic potential; increased resistance selection; increased colonization/superinfection
Antipseudomonal B-lactam plus aminoglycoside • Pip/tazo 4 g q6h OR… • Ceftazidime 1-2 g q8h + gentamicin or…tobramycin	Traditional regimen best studied; broad spectrum; optimal *Pseudomonas* therapy; rapidly bactericidal; synergistic; decreased resistance; reduced superinfections	Limited gram (+) activity; nephrotoxicity potential; monitoring aminoglycoside concentrations **avoid once daily aminoglycoside dosing
Empiric regimens containing vancomycin • Ceftazidime 1-2 gm q8h + vancomycin 0.5-1 g q6-12h ** When should you add vanco?? → you can usually hold off w/ vanco until culture results are back (24-48 hours). Exceptions include line sepsis, mucosistis, and increased MRSA rate	Early effective therapy of gram (+) infections	No decrease in morbidity/mortality due to gram (+) infection; increased vancomycin-resistant enterococci selection risk; toxicities; cost; therapeutic monitoring of vanco concs
Fluoroquinolones • Ciprofloxacin 0.4 g q8-12h + Ceftazidime 1-2 g q8h • Aminoglycoside or vancomycin 0.5-1 g q6-12h ** Used for follow up PO in those with significant PEN allergy	Efficacy similar to other regimens in combo; no cross-resistance with β-Lactams; safe; possibile oral admin; useful with renal impairment when AGs undesirable.	Marginal gram (+) activity; less efficacious as monotherapy; resistance may develop rapidly.

Adjunctive Therapy

- GM-CSF (sargramostim): granulocyte-macrophage colony stimulating factor
- G-CSF (filgrastim): granulocyte colony stimulating factor (used daily)
  - Neulastin – pegfilgrastim – used every 3 weeks (compared to daily)
- Touted to enhance neutrophils – result in a less severe and shorter duration of neutropenia (decreasing the time below the critical threshold).
- Dose-dependent efficacy and toxicity (Toxicity = bone pain)
- Large studies demonstrate no clear cut role, except in high-risk patients
  - Patients with ≥7-10 days of neutropenia and/or a > 40% chance of infection
  - Disadvantages: expensive, ± utility, SQ administration, ADR
- Not used in all patients → only in high risk patients
  - Start: < 24 hours post chemotherapy
  - D/C: ANC > 2000 for 2 days --or—an ANC >5000 for one day
  - Used even if ANC is persistently < 100, even if no fever is present.

Prophylaxis

- 85% of infections stem from patients own flora (GI tract and skin)
- Selective decontamination (quinolones / TMP-SMX – no real benefit and possibly aid resistance)
- Better to reserve agents for documented infections than waste on possible infections
- Bottom line…use prophylaxis in patients you expect to have > 1 week duration of neutropenia, or when other supportive evidence exists that place the patient at risk. Agents should be d/c'd when **ANC > 500**.

Influenza Antiviral Agents

	Relenza (zanamivir)	Tamiflu (oseltamivir)	Flumadine (rimantadine)	Symmetrel (amantadine)
Manufacturer	GlaxoSmithKline	Roche	Forest, generic	BMS, Endo, generic
Dosage form	5 cartridges with 4 x 5 mg blisters each	75 mg hard gel capsule, 12 mg/ml tutti-fruiti susp.	100 mg tablets, 50 mg/5 ml raspberry syrup	100 mg tablets, capsules, 50 mg/ 5 ml raspberry syrup
Packaged	diskhaler (5 cartridges with 4 doses/cartridge)	capsules- blisterpack of 10, susp- 25 ml bottle	tablets- bulk syrup- bulk 8 oz bottle	tablets, capsules- bulk syrup- bulk 16 oz bottle
Storage	room temp	cap- room temp susp- room temp or frig (reconst.)	tablets- room temp syrup- room temp	tabs, capsules- room temp syrup- room temp
Strain	Influenza A and B	Influenza A and B	Influenza A	Influenza A
Adult Prophylaxis	2 oral inhalations QD*	75 mg QD (within 2 days; to at least 7 days)	100 mg BID; ≥65 yrs: 100 mg QD	200 mg QD/100 mg BID; ≥65yrs: ≤ 100 mg QD
Adult Treatment[1]	2 oral inhalations BID x 5 days	75 mg BID x 5 days	100 mg BID x 5-7 days ≥65 yrs: 100 mg QD	200 mg QD/100 mg BID x 5-7 days; ≥65 yrs: ≤100 mg QD
Pediatric Prophylaxis	7 years and older 2 oral inhalations QD*	13 years and older 75 mg QD	<10 yrs: 5 mg/kg (max. 150 mg /day) QD; >10 yrs- adult dose	same dose as txment, prior to exposure- 10 days PEP
Pediatric Treatment[1]	7 years and older: 2 oral inhalations BID x 5 days	age > 1 year, BID: ≤ 15 kg 30 mg; 16- 23 kg 45 mg; 24- 40 kg 60 mg; >40 kg 75 mg	5 mg/kg/day- max 100 mg BID*	(ages 1-8) 4.4-8.8 mg/kg/d QD or divided BID; (ages 9-12) 100 mg BID;
Timing	if used with other inhalers, use inhaler first, then dose Relenza	with or without food food may ↓ nausea	with or without food food may ↓ nausea	with or without food food may ↓ nausea
Renal Failure	no adjustment	adjust dose (CrCl < 30 ml/min)	adjust dose (CrCl < 10 ml/min)	adjust dose (CrCl < 50 ml/min)
Hepatic Failure	no adjustment	unknown, no adjustment ?	↓ adult dose to 100 mg QD	no adjustment
Retail Cost	1 diskhaler- @ $50	10 capsules- @ $70-80 25 ml susp- @ $45-55	10 tablets- @ $30; 45 B 120 ml syrup- @ $25 B	10 tabs/caps- @ $10; 20 B 120 ml syrup- @ $15; 36 B
Side Effects	cough, bronchospasm, sinusitis, dizziness	N/V/D (usually mild), insomnia, vertigo	insomnia, HA, N/V, anxiety, CNS, anorexia	same as rimantadine, yet more CNS, EPS
Precautions	COPD, asthma, lactose hypersensitivity	renal failure- use cautiously COPD, asthma- no data	seizure Hx, CNS effects, ↓ liver fxn, ↓ kidney fxn	CHF, edema, orthostatic hypotension, liver disease
Drug Intxns	none anticipated	none anticipated	ASA, APAP, cimetidine	HCTZ/triamterene, anticholinergics, others…
Pregnancy	C	C	C	C
Lactation	unknown/use with caution	unknown	not for use during lactation	not for use during lactation

1- within 2 days of signs and symptoms of influenza B- Brand

*not indicated, but there is data and dosing recommendations

Colleen M Terriff, PharmD; WSU College of Pharmacy *2005*

Laboratory Values

Electrolytes and Chemistry

Albumin	3.5-5.0 g/dL
Ammonia	30-70 mcg/dL
Bicarbonate	24-30 mEq/L
BUN	8-18 mg/dL
Bilirubin, conjurgated	0.1-0.3 mg/dL
Bilirubin, total	0.1-1.0 mg/dL
Calcium	8.5-10.5 mg/dL
Chloride	95-106 mMol/L
Creatinine	0.6-1.2 mg/dL
Glucose	65-110 mg/dL
Magnesium	1.6-2.4 mEq/L
Phosphorous	2.6-4.5 mg/dL
Protein, total	6.0-8.5 g/dL
Potassium	3.5-5.0 mEq/L
Sodium	135 – 145 mEq/L
Uric Acid	M: 3.5-8 mg/dL; F: 2.5-6.2 mg/dL
BUN/SCr	10:1

Liver Enzymes

Alkaline Phos	M: 34-110 U/L; F: 24-100 U/L
ALT	0-35 U/L
AST	0-35 U/L

Cardiac Enzymes

CPK	M: 24-195 U/L; F: 24-170 U/L
CK-MB	<12 IU/L
LDH	100-200 U/L
Troponin T	<1.5 ng/mL
Troponin I	<0.1 ng/mL

Pacreatic Enzymes

Amylase	28-100 U/L
Lipase	4-24 U/L

Thyroid Function

FTI	0.8-2.4 ng/dL
Total T3	55-200 ng/dL
Total T4	4-12 mcg/dL
Free T4	0.8-2.7 ng/dL
TSH	0.5-5 mcU/L
RAIU	1-13% 2h 5-20% 6h 15-40% 24h

Hypothyroidism: ↓ TT4, ↓FT4, ↑TSH
Hyperthyroidism: ↑ TT4, ↑FT4, ↓TSH

Hematology

Hct	M: 39-49%; F: 33-43%
Hgb	M: 14-18 mg/dL; F: 11.5-15.5 mg/dL
MCH	27-33 pcg
MCHC	33-37 g/dL
MCV	76-96 fL
RDW	11-16%
Reticulocyte Count	0.5-2.5%
Platelets	140,000-440,000 U/L
RBC	M: 4.3-5.9 x 10^6/mm3; F: 3.5-5.0 x 10^6/mm3
WBC	4.8-10.8 x 10^3 cells/mm3
ANC	>1000

Iron Studies

TIBC	200-400 mcg/dL
Serum Iron	M: 65-175 mcg/dL; F: 50-170 mcg/dL
% Saturation	33% (Serum Iron/TIBC)
Serum Ferritin	M: 15-200 ng/mL; F: 20-120 ng/mL

Erythropoetin	10-30 mcU/L
Vitamin B-12	100-900 pg/dL (<300 pg/dL check B-12 defic.)
Folic Acid	1.8-16 ng/mL

WBC Differential

Neutrophils	50-70%
Bands	0-5%
Eosinophils	0-5%
Basophils	0-1%
Monocytes	0-7%
Lymphocytes	25-30%

Cerebrospinal Fluid (CSF):

WBC	< 10 (monocytes)
Differential	> 90% (monocytes)
Protein	< 50
Glucose	1/2 –2/3 serum

Blood Gases:

HCO_3	A: 20-26 mEq/L; V: 22-28 mEq/L
O_2 Saturated	A: 90-98%; V: 60-85%
PCO_2	A: 35-45mmHg; V: 40-52mmHg
pH	A: 7.35-7.45; V: 7.32-7.42
PO_2	A: 80-95mmHg; V: 30-50mmHg

Miscellaneous Lab Values

PTH	12-68 pg/mL
HbA1c	4-6%
Prothrombin time	10-13 sec
INR	1.0; A-fib 2-3; Prosthetic valve 2.5-3.5
aPTT	30-45 sec
ESR	M: 0-20 mm/min; F: 0-30 mm/min
BNP	0-100
D-dimer	<0.5 mcg/mL
Osmolality	285-295 mOsm/L

Urinalysis

Color	Straw
Turbidity	Clear
Specifc Gravity	1.002-1.030
pH	5-7.5
Bacteria	None
Protein	Neg
Glucose	Neg
Ketones	Neg
Bilirubin	Neg
Lkcyte Esterase	0-trace
Nitrites	Neg
Urobiligen	0-trace
WBCs	0-2/HPF
RBCs	1-2/HPF
Epithelial Cells	0-1/LPF
Crystals	Neg

Changes in Color

Green	Pseudomonas, drugs (Propofol)
Red/Orange	Blood, Drugs (phenazopyridine, rifampin, daunorubicin, doxorubicin), Dyes
Brown/Black	Cascara, Senna, Iron Salts, Dyes, Liver Failure

Metric Conversions

1 gallon = 3785 ml
1 fluid ounces = 29.57 ml
1 ml = 1 g
1 pint = 473.18 ml
10 minims = 0.616 ml

15-16 drops (gtts) = 1 ml
1 table spoon = 15 ml
1 ounce (oz) = 28.35 g
1 mcg = 1/1,000,000 g
1 cubic centimeter = 1/1000 L

1 teaspoon = 5 ml
1 pound (lbs) = 453.592 g
1 grain = 64.8 mg
1microliter =1/1,000,000 L

Solution Percentages

1:100 = 1g/100ml or 10mg/ml = 1%
1:200 = 500mg/100ml or 5mg/ml = 0.5%
1:1000 = 100mg/100ml or 1mg/ml = 0.1%
1: 5000 = 20mg/100ml or 200mcg/ml = 0.02%
1: 10,000 = 10mg/100ml or 100mcg/ml = 0.01%

Equations

ANC = %Segs + %Bands x Pts total WBCs

Corrected Calcium = [(4-Albumin)(.8)+measured Calcium]

IBW men = (ht inches > 60inches) x 2.3 + 50
IBW women = (ht inches > 60 inches) x 2.3 + 45

Adjusted BW = [(Actual BW - IBW) x .4] + IBW
(Use Adj.BW if the actual body weight is greater than 20% of the calculated IBW)

Creatinine Clearance (Cockroft-Gault):
CrCl males = [(140 - Age) x IBW kg] / (72 x SCr)
CrCl females ={ [140 - Age) x IBW kg] / (72 x SCr)} x 0.85

Anion Gap = Na - (Cl + HCO_3)
Normal Anion Gap = 8-16mEq/L plasma

Serum Osmolality = (2 x [Na] + ([Glucose] / 18 + ([BUN] / 2.8)
1 mEq = 1 mOsm

Serum Tonicity = 2 x (Na) + (Glucose / 18)

BSA* (m^2) = $\sqrt{Ht(inches)xWt(lb)/3131}$

In metric: BSA (m^2) = $\sqrt{Ht(cm)xWt(kg)/3600}$

LDL = (TC^* – HDL) – (TG^*/5); valid for TG < 400mg/dL

mEq = weight (gram)/mEq Weight (gram)
if weight is not shown:
mEq (wt) = atomic wt (g)/(valence number) x 1000

*BSA=body surface area
TC=total cholesterol
TG=triglyceride

NEUROPATHIC PAIN
Adapted from Gregory Holmquist, PharmD

Background
- Usually no discernable somatic injury
- Described as burning, tearing, electric shock, tingling
- Common features: allodynia, hyperalgesia, decreased sensitivity, worse at night when not distracted
- Can be continuous or paroxysmal

Treatment
- TCAs
  - All have similar efficacy, but desipramine and nortriptyline preferred b/c better tolerated
  - May take 4-6 wks to see benefit
  - Desipramine 10-150 mg/day
  - Nortriptyline 10-150 mg/day
  - Amitriptyline 10-150 mg/day
  - Imipramine 10-150 mg/day
- SSRIs/Atypical antidepressants
  - Especially effective when depression exists
  - Duloxetine 60 mg/day
  - Venlafaxine 150-375 mg/day
  - Mirtazapine
  - Buproprion 150-300 mg/day

  **need to affect NE to be effective for neuropathies
- Anticonvulsants
  - Usually faster effect than antidepressants
  - SE limit use esp. dizziness, drowsiness
  - Gabapentin 1800-3600 mg/day
  - Pregabalin 300-600 mg/day
  - Topiramate 100-200 mg/day
  - Carbamazepine 400-1200 mg/day
  - Phenytoin 200-300 mg/day
  - Divalproex 1000-1500 mg/day
  - Lamotrigine 200-400 mg/day
  - Valproic acid, oxcarbazepine, tiagabine, levetiracetam, zonisamide also effective
- Topical analgesics
  - Capsaicin
    - Apply 3-4x/day for 3-4 wks for benefit
    - Useful add on to TCAs
  - Lidocaine 5% patch
    - Up to 3 patches applied daily to affected area
    - 12 hrs on, then 12 hrs off
    - Works in 1-2 weeks
  - Ketamine 5% gel
    - Not FDA approved or commercially available
    - May be useful for allodynia, hyperalgesia

OPIOID ANALGESICS
Adapted from Gregory Holmquist, PharmD Wil Edwards, PharmD, and Tracy Skaer, PharmD

Types of Pain Appropriate for Opioids
- Nociceptive e.g. osteoarthritis, cancer pain, surgery recovery
- Chronic pain unresponsive to other treatments
- Combination with adjuvants for neuropathic pain

Advantages of Opioids
- No GI bleeds, renal toxicity, hepatotoxicity
- Strongest analgesics
- Quick onset
- No ceiling effect
- Work for many different pain syndromes

Disadvantages of Opioids
- CNS depression
- N/V, constipation
- Respiratory depression
- Hypersensitivity, itching
- Urinary retention
- Myoclonus

Barriers to Overcome
Tolerance: natural adaptation of the body, where drug effects diminish over time
Dependence: an adaptation that presents itself with the production of withdrawal symptoms when there is a reduction of dose/blood level, addition of an antagonist, or discontinuation of a drug.
Addiction: behaviors that include craving, compulsive use, impaired control of drug use.

Opioid Receptors and Actions
- Mu (analgesia, respiratory depression, sedation, euphoria, constipation)
- Kappa (analgesia, respiratory depression, sedation, constipation, dysphoria)
- Delta (analgesia)
- Sigma (dysphoria, hallucinations, confusion)

Immediate-release vs. Sustained-release
- Immediate-release: patient becomes dependent on peaks, tolerance develops faster, more SE, greater time spent at subtherapeutic levels
- Sustained-release: more constant drug levels with fewer SE, pain returns less frequently, fewer behavioral changes, less drug-seeking

Classification of Opioids

Phenylpiperidines	Phenanthrenes	Phenylheptanes
Meperidine	Codeine	Methadone
Fentanyl	Hydromorphone	Propoxyphene
	Levorphanol	

	Morphine	
	Oxycodone	
	Hydrocodone	
	Pentazocine	

Opioid Reversal agents		
Drug	Dose	Note
Naloxone	▪ IV: 0.4-2mg q2-3min PRN ▪ May repeat q20-60min ▪ Infusion: 0.25-6.25mg/hr	▪ If no response after 10mg question diagnosis ▪ Caution in CVD
Naltrexone	▪ PO: 25mg ▪ Range: 50mg/d-100-150mg TIW	▪ Do not give until pt is opioid-free for 7-10days ▪ Caution in Liver Dz

Opioids to Avoid

- Propoxyphene: not effective, too much euphoria
- Mixed agonist-antagonists
  - Pentazocine, butorphanol
  - Analgesic ceiling effect
  - Hallucinations, precipitate withdrawals
- Meperidine
  - Normeperidine metabolite causes seizures
  - Oral dosage form minimally effective
  - Parenteral may be useful for chills/rigors from amphotericin, blood products, cytokines
- Codeine
  - SE too severe: constipation, N/V

Opioids Available for Use

- Tramadol
  - Less risk of physical dependence, alternative to NSAIDs in geriatric patients, fibromyalgia?
  - Disadvantages: seizure potential, nausea, dizziness, interacts with antidepressants, ceiling effect
  - Dose: 25 mg QD-BID initially; increase by 25 mg q2-3 days to max dose of 400 mg (200 mg in elderly)
- Hydrocodone Combinations
  - Short-acting, immediate-release products
  - All are combined with APAP or NSAID
- Morphine
  - Available in many dosage forms, less euphoria than other opioids
  - Disadvantages: societal stigmatization, metabolites accumulate in renal dysfunction, constipation
- Oxycodone
  - Mainly affects kappa receptor, not mu
  - Women usually respond better
  - More euphoria, because more CNS penetration
- Methadone
  - Advantages: cheap, NMDA receptor blockade, less abuse potential possibly

- Disadvantages: difficult to dose (long and variable half-life, variable bioavailability, highly protein bound), drug interactions via 3A4 and 2D6, can cause Torsades, textbook conversions inaccurate
- Methadone Conversion
  - Morphine 30-90 mg/d: Use 1/4 total daily dose divided q8h
  - Morphine 90-300 mg/d: Use 1/6 total daily dose divided q8h
  - Morphine >300 mg/d: Use 1/8 total daily dose divided q8h

- Fentanyl
  - Body fat, temp, edema, patch placement affect bioavailability
  - Do not use if patient cachectic, edematous, febrile, has fluctuating pain, opiate naïve, has minor pain, or can tolerate oral sustained-release morphine
  - Fentanyl conversion guidelines often underestimate dose for cancer pain
    - 2 mg oral morphine = 1 mcg/hr fentanyl patch
- Hydromorphone
  - More potent than morphine
  - Available as injectable or short-acting oral

Recommended Starting Opioid Analgesic Dose

Drug	Dose Based on Weight	Ave. Adult Dose
Morphine Sulfate		
IV	0.05-0.07 mg/kg q2h	3-5 mg Q2h
IM	0.14-0.17 mg/kg q3h	10-12 mg Q3h
PO	0.4 mg/kg q3h	30 mg Q3h
PR	0.4-0.6 mg/kg q3h	30-40 mg Q3h
PCA		
Con	1 mg/mL	1 mg/mL
Basal	0-0.014 mg/kg/hr	0-1 mg/hr
Bolus	0.014 mg/kg/6 min	1 mg/6min
Hydromorphone		
IV	0.01-0.014 mg/kg q1h	0.75-1 mg Q2h
IM	0.02-0.03 mg/kg Q3h	1.5-2 mg Q3h
PO	0.05-0.09 mg/kg Q3h	4-6 mg Q3h
PR	0.04-0.09 mg/kg Q3h	3-6 mg Q3h
PCA		
Conc	0.2 mg/mL	0.2 mg/mL
Basal	0-0.003 mg/kg/hr	0-0.2 mg/hr

Bolus	0.003 mg/kg/6 min	0.2 mg/6 min
Oxymorphone		
IV	0.01-0.014 mg/kg Q2h	0.75-1 mg Q2h
IM	0.014-0.02 mg/kg Q3h	1-1.5 mg Q3h
PR	0.07-0.14 mg/kg Q3h	5-10 mg Q3h
Fentanyl		
IV	0.5 mcg/kg Q2h	25-50 mcg Q2h
IM	1 mcg/kg Q3h	75-100 mcg Q3h
PCA		
Conc	10 mcg/ml	10 mcg/ml
Basal	0-0.14 mcg/kg/hr	0-10 mcg/hr
Bolus	0.14 mcg/kg/6 min	10 mcg/6 min

Initial Fentanyl Transdermal Dose from Daily Oral Morphine

Oral 24-hour morphine	IM 24-hour morphine	Fentanyl transdermal
(mg/day)	(mg/day)	(mcg/hr)
45-134	8-22	25
135-224	23-37	50
225-314	38-52	75
315-404	53-67	100
405-494	68-82	125
495-584	83-97	150
585-674	98-112	175
675-764	113-127	200
765-854	128-142	225
855-944	143-157	250
945-1034	158-172	275
1035-1124	173-187	300

[1]Do not use this table to convert from Fentanyl transdermal system to other therapies

Pharmacokinetics of Narcotic Agonist Analgesics					Equianalgesic doses[2] (mg)	
Drug	***Onset*** (minutes)	**Peak** (hours)	**Duration**[1] (hours)	**$t^{1/2}$** (hours)	**Parenteral** (mg)	**Other**
Alfentanil	Immed	nd[3]	Nd[3]	1 to 2[4]	IM 0.4 to 0.8	nd[3]
Codeine	10 to 30	0.5 to 1	4 to 6	3	IM 120 to 130 SC 120	Oral 200[5]
Fentanyl	7 to 8	nd[3]	1 to 2	1.5 to 6	IM 0.1 to 0.2	TD 25 mcg/hr
Hydrocodone	nd[3]	nd[3]	4 to 6	3.3 to 4.5	nd[3]	Oral 5 to 10
Hydromorphone	15 to 30	0.5 to 1	4 to 5	2 to 3	IM 1.3 to 1.5 SC 1 to 1.5	Oral 7.5
Levomethadyl	2 to 4 hrs	1.5 to 2	48 to 72	2 to 6 days	nd[3]	nd[3]
Levorphanol	30 to 90	0.5 to 1	6 to 8	11 to 16	IM 2 SC 2	Oral 4
Meperidine	10 to 45	0.5 to 1	2 to 4	3 to 4	IM 75 SC 75 to 100	Oral 300
Methadone	30 to 60	0.5 to 1	4 to 6[6]	15 to 30	IM 10 SC 8 to 10	Oral 10 to 20
Morphine	15 to 60	0.5 to 1	3 to 7	1.5 to 2	IM 10 SC 10	Oral 30 to 60

Oxycodone	15 to 30	1	4 to 6	nd[3]	IM 10 to 15 SC 10 to 15	Oral 30[5]
Oxymorphone	5 to 10	0.5 to 1	3 to 6	nd[3]	IM 1 SC 1 to 1.5	Rectal 5-10
Propoxyphene	30 to 60	2 to 2.5	4 to 6	6 to 12	nd[3]	Oral 130[8]
Remifentanil	1	1 min	Short[9]	~ 3 to 10 min	0.5-1mcg/kg/min	nd[3]
Sufentanil	1.3 to 3[4]	nd[3]	Nd[3]	2.5	IM 0.01 to 0.04	nd[3]

[1] After IV administration, peak effects may be more pronounced but T_{DUR} is shorter. Duration of action may be longer with the oral route.
[2] Based on morphine 10 mg IM or SC.
[3] nd – No data available.
[4] Data based on IV admin.
[5] Starting doses lower (codeine 30 mg; oxycodone, 5 mg; meperidine, 50 mg).
[6] Duration and half-life increase with repeated use because of cumulative effects.
[7] Data based on intrathecal or epidural administration.
[8] Starting doses lower (propoxyphene 65 to 130 mg). In equimolar doses (100 mg of napsylate equals 65 mg of HCl).
[9] The duration of action does not increase with prolonged administration.

Solid Organ Transplants
Adapted from Zuly Eden, PharmD and Lisa Kostelac, PharmD

Immunosuppression Induction Therapy
- Older Therapies
  - MALG, Atgam, OKT3
- Current Therapies
  - Thymoglobulin, basiliximab, daclizumab
- Strategies for Improving Antibody Use
  - Reserve for high risk populations
  - Give shorter courses and use lower doses

Immunosuppression Maintenance Therapy
- Older Medications
  - Cyclosporine, Sandimmune, azathioprine, prednisone
- Current Medications
  - Tacrolimus, Neoral, mycophenolate mofetil, sirolimus
- Drug Regimens
  - Kidney:
    - tacrolimus or cyclosporine + mycophenolate + steroid +/- antibody
    - Kidney: ½ dose tacrolimus or ½ dose cyclosporine + sirolimus plus steroid (may taper off at 1 year) +/- antibody
  - Heart/Lung: tacrolimus + steroid + mycophenolate +/- antibody

Acute Rejection
- 5-15 days post-transplant, within 1 year
- Signs & Symptoms
  - Asymptomatic/non-specific: fever, malaise, fatigue, anorexia
  - Organ dysfunction
  - Biopsy to determine if acute rejection
- Risk Factors
  - Sub-therapeutic immunosuppression
  - Poor HLA match
  - Retransplant
  - Female (donor/recipient)
  - Pediatric
  - African-American
  - Cadaveric donor
- Treatment
  - Steroid pulse dose and taper
    - Pulse dose: methylprednisolone IV 0.5-1 gm QD x 3d
    - Taper: prednisone over 1-3 weeks to maintenance dose
    - Ideal dose, route, regimen unknown
    - Rapid action, reverses majority of rejections
  - Monoclonal/polyclonal antibodies
    - Pro: role in steroid resistant rejection
    - Cons: increases risk of viral infections, malignance, difficult to administer, more monitoring
    - Not first line

Long Term Complications

- Infection
  - 0-1 mo: wound/line infections, reactivation of donor infections
  - 1-6 mo: period of most intense immunosuppression
    - Immunomodulating viruses (CMV, EBV, HSV, Hep B, HepC)
    - CMV treatment: ganciclovir, valganciclovir, CMV immune globulin
    - Opportunistic infections: PCP, Candida, Toxoplasmosis
  - >6 mo: community-acquired infections
- Post-Transplant Hypertension
  - Impacts graft survival
  - Major culprits: cyclosporine, prednisone, tacrolimus
  - Treat if BP > 140/90 mmHg
  - Management:
    - Nutrition, diet, weight control
    - Anti-hypertensive agents: patient specific
      - Special Consideration: diltiazem, verapamil drug interaction via CYP3A4 inhibition
      - Requires 30-40% dose reduction of cyclosporine or tacrolimus
- Post-Transplant Diabetes Mellitus
  - Major Culprits:
    - Tacrolimus > Cyclosporine: impairs insulin secretion, decreases muscle uptake of glucose
    - Prednisone: increases hepatic glucose production, decreases muscle uptake of glucose
  - Management
    - Intensive blood glucose control similar to non-transplant diabetic patient
- Post-Transplant Dyslipidemia
  - Lipid panel: increased TC, LDL, and TG; decreased HDL
  - Major culprits: sirolimus, cyclosporine, prednisone
  - Management:
    - Nutrition, exercise, weight control
    - Statins: start at time of transplant
      - Pravastatin preferred agent: no CYP interactions
- Post-Transplant Osteoporosis
  - Major culprits: long-term steroids
  - Most bone loss occurs within first few months
  - Management
    - Before or immediately after transplant Ca 500mg elemental TID and Vit D 800mg
    - Low bone density: bisphosphonate plus Ca, Vit D

Drug	Class	MOA	Dose	Monitoring	SE	Tidbit
Cyclosporine (CsA, Neoral, Gengraf, Sandimmune)	Calcineurin Inhibitor	Inhibits IL-2 production and T-cell activation by binding CpN	PO: 5-7 mg/kg/day divided BID IV: 1/3 PO	12 hr trough 0-3 mo: 200-250 3 mo-1 yr: 175-200 >1 yr: 150-175	Nephrotoxicity, tremor, hirsutism, HTN, diabetes, gum hyperplasia, K^+ and Mg^{2+} imbalance, lipid abnormalities	▪ Various products are not interchangeable (diff. bioavailability) ▪ CYP3A4 substrate
Tacrolimus (TAC, Prograf, FK-506)	Calcineurin Inhibitor	Inhibits IL-2 production and T-cell activation by binding FKBP	PO: 0.15-0.3 mg/kg/d divided BID IV: 1/3 PO	12 hr trough 0-3 mo: 2-15 3 mo-1 yr: 10-12 >1 yr: 8-10	Nephro/neurotoxicity, HTN, diabetes, tremor, lipid abnormalities, HA	▪ Tacrolimus usually more effective and better tolerated than cyclosporine ▪ High-risk patients ▪ Rescue therapy ▪ CYP3A4 substrate
Mycophenolate mofetil (Cellcept, MMF)	Anti-metabolite	Inhibits IMP Dehydrogenase which inhibits purine synthesis	0.5-1.5 g PO or IV BID	12 hr trough: 1.5-4 mcg/ml MPAG < 100	N/V/D, blood dyscrasias	▪ MPA is active metabolite ▪ MPAG is inactive metabolite, but causes SE ▪ More GI SE than AZA ▪ More specific to T and B cells than AZA ▪ Reduced acute rejection than AZA
Azathioprine (Imuran, AZA)	Anti-metabolite	Inhibits purine synthesis	PO: 1-2 mg/kg/d IV: ½ PO		Myelosuppression, N/V, hepatotoxicity, blood dyscrasias	▪ Metabolized to active moiety by xanthine oxidase

Prednisone, methylpred-nisolone	Cortico-steroid	Inhibits T and B cell activation, among other actions	125 mg IV BID x 7d, then taper to 5-10 mg PO QD		Many incl. fluid retention, diabetes, osteoporosis, ulceration, adrenal/pituitary suppression	▪ Part of most protocols for solid organ transplants
Sirolimus (Rapamune, SRL)	TOR Inhibitor	Inhibits T-cell activation	1-5 mg PO QD	24 hr trough 3-12 Check levels q 7d	Hyperlipidemia, hepatotoxicity, blood dyscrasias, nephrotoxicity	▪ ~60 hr half-life ▪ CYP3A4 substrate and inhibitor ▪ Synergistic with calc inhibs—use ½ dose CsA or TAC ▪ Kidney sparing
Thymoglobulin			1.5 mg/kg IV x 3-5d	WBC, platelets, blood pressure	Anaphylaxis, leukopenia, thrombocytopenia, higher risk of CMV	▪ Premedicate with APAP 650 mg PO, methylprednisolone 125 mg IV, and diphenhydramine 50 mg IV
Daclizumab (Zenepax)	IL-2 Receptor Antibody	Binds IL-2 to inhibit T-cell activation	IV: 1 mg/kg q 2 weeks x 5 doses			▪ 90-120 d duration of blockade ▪ Low immunogenicity
Basiliximab (Simulect)	IL-2 Receptor Antibody	Binds IL-2 to inhibit T-cell activation	IV: 20 mg x 2 doses on day 0 and 4			▪ 30-45 duration of blockade

Otitis Media
Adapted from Mike Olds, MD

Resources
Washington State Department of Health. WSMA Practice Guideline for Judicious Use of Antibiotics. http://www.doh.wa.gov/Topics/Antibiotics/providers.htm

Definitions
- *Acute otitis media*: Acute inflammatory condition due to bacterial or viral infection w/ middle ear effusion and an intact tympanic membrane
- *Chronic Otitis Media with effusion*: persistent inflammatory fluid of greater than 3 months duration behind an intact tympanic membrane
- *Chronic Otitis Media*: chronic infection of the middle ear w/ purulent discharge through a perforated tympanic membrane

Likely Causative Organisms
- Acute Otitis media
  - *Strep pneumoniae* ~25%
  - *H. influenzae* ~20-25%
  - *M. catarrhalis* ~10-20%
- Chronic Otitis media
  - *Pseudomonas* ~56%
  - *Staph. aureus* ~18%
  - Diphtheroids ~8%

Symptoms of Acute Otitis Media
- Earache
- Irritability
- Sleep disturbance
- Fever (+/-)
- Reduced hearing
- Red, bulging tympanic membrane
- Rubbing/pulling ear

Symptoms of Chronic Otitis Media
- Painless otorrhea
- Hearing loss
- Foul odor
- Perforation

Treatment of Acute Otitis Media
- Observation
  - 50-75% of cases resolve spontaneously
  - If child > 6mo, ear pain mild, and fever <39°C, can hold drugs if diagnosis uncertain—if >2 yo can hold even if known OM
- Pain control
  - Acetaminophen or ibuprofen
  - Topical benzocaine
- Primary Antibiotic Therapy
  - Amoxicillin (80-90mg/kg/day)
  - Erythromycin plus sulfonamide
- Alternative Antibiotics
  - Amoxicillin plus clavulanate
  - Cefuroxime
  - Single dose Ceftriaxone

Treatment of Chronic Otitis Media
- Ototopical therapy:
  - Ofloxacin
  - Ciprofloxacin
  - Ototoxicity with aminoglycosides (max 7 day Tx), gentian violet, alcohol
- Alternatives
  - Neomycin/Polymyxin
  - Gentamicin ophthalmic
  - Boric acid/iodine powder
- Oral/Parenteral therapy
  - Oral ciprofloxacin +/- clindamycin
  - IV ticarcillin/clavulanate
  - IV ceftazidime +/- clindamycin
  - IV/IM gentamicin or tobramycin +/- clindamycin

Prevention: Hib and pneumococcal vaccination

Complications of Otitis Media

- Mastoiditis
- Facial nerve paralysis
- Abscess
- Petrositis
- Labyrinthitis
- Meningitis
- Lateral sinus thrombosis
- Otic hydrocephalus

Antibiotic Treatment of Acute Otitis Media

Antibiotic	Strep. pneumo	H. influen Beta-lact Negative	H. influen Beta-lac Positive	M. cat Beta-lac Negative	M. cat Beta-lac Positive	Strep. pyogenes	Staph. Aureus
Amoxicillin	+	+	-	+	-	+	+/-
Ampicillin	+	+	-	+	-	+	+/-
TMP/SMX	+/-	+	+	+	+	-	+
Erythromycin/ sulfisoxazole	+	+	+	+	+	+	+
Amox/clav	+	+	+	+	+	+	+
Cefaclor	+	+	+/-	+	+/-	+	+/-
Cefuroxime	+	+	+	+	+	+	+
Cefixime	+/-	+	+	+	+	+	-
Cefprozil	+	+	+	+	+	+	+
Cefpodoxime	+	+	+	+	+	+	+/-
Loracarbef	+	+	+	+	+	+	+/-
Clarithromycin	+	+/-	+/-	+	+	+	+

PAIN MANAGEMENT
Adapted from Gregory L. Holmquist, PharmD and Wil Edwards, PharmD

Clinical Pearls to Pain Management
- Role of medications = complement, not supplant nonpharmacological approaches
- Every patient is different, so individualize treatment
- One prescriber, one pharmacy if possible
- Must treat depression and pain together
- Sleep, diet = foundation for pain control

Treatment Goals
- Decrease the subjective intensity and duration of pain
- Decrease suffering and disability associated with pain
- Decrease psychological and socioeconomic sequelae associated with under treating pain
- Minimize ADR or the development of tolerance
- Improve quality of life and optimize the ability to perform activities of daily living.

Benefits of Preventing Pain
- Prevent memory of pain
- Prevent physiological responses to pain
- Prevent psychological responses to pain
- Prevent behavioral responses to pain
- Can use less medication
- Improve sleep
- Improve diet
- Enable exercise

Pain Definition: an unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Nociceptive: results from stimulation of common pain receptors in most tissues
- Somatic: Related to skin, muscle, and tissues of somatic origin
    - Superficial Pain: local throbbing, burning, pricking, allodynia (very sensitive skin) hyperalgesia.
    - Deep Somatic Pain: dull aching in nature (can be localized)
        - may be a radiating component
- Visceral Pain: diffuse, dull, aching pain that is poorly localized
    - noticed at the onset or early stages of disease
    - associated w/nausea and other autonomic symptoms
- Neuropathic: related to peripheral nerve or central nervous system injury or dysfunction.

Assessment of Pain
- Acute Pain: Injury/trauma to the somatic structures or viscera
    - General Rule: Intensity of acute pain is usually proportional to the degree of damage.
    - Signs/Symptoms

        - Tachycardia
        - Mydriasis
        - Hypertension
        - Pallor
        - Diaphoresis
        - Anxiety
        - Grimacing
        - Hyperventilation
    - Physical issues: Rest/fatigue (unable to sleep due to pain)
    - Psychological issues: Depression, Mood, no sympathy or understanding from others.
    - Physical Tissue Damage
    - Psychological
        - Depression
        - Anxiety
    - Social Factors
        - Stress
- Chronic Pain: rarely accompanied by autonomic symptoms
    - -pts who report chronic pain often fail to show objective evidence of the ongoing pathologic events (except the pts who have had multiple surgeries who have an ↑ scar tissue)
    - Signs/Symptoms:
        - Sleep disturbances
        - Irritability
        - Constipation
        - Social withdrawal
        - Depression
        - Appetite disturbances

Nonpharmacological Pain Management

- Heat/cold
- Physical Therapy
- Transcutaneous electro-neurostimulation
- Acupuncture
- Massage
- Distraction
- Relaxation

Patient Assessment		PQRST Characteristics of Pain
Palliative factors Provocative factors	*P*	What makes the pain better? What makes the pain worse?
Quality	*Q*	Describe the pain
Radiation	*R*	Where is the pain?
Severity	*S*	How does this pain compare with other pain you have experienced? Rate on a scale?
Temporal factors	*T*	Does the intensity of the pain change with time?

Describing Pain

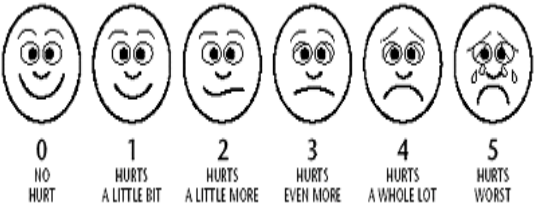
Scales for Adults

1----------5----------10

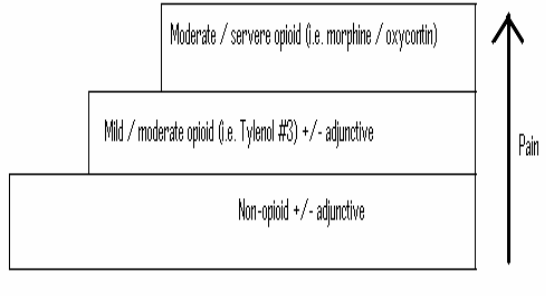
No Pain

Worst Possible Pain

Scales for Children/Elderly



WHO Pain Ladder



PNEUMONIA
Adapted from Jason Brouillard, PharmD

Likely Causative Organisms

Community-Acquired Pneumonia	Hospital-Acquired Pneumonia	Aspiration Pneumonia	Viral Pneumonia
Streptococcus pneumoniae *Haemophilus influenzae* *Moraxella catarrhalis*	*Staphylococcus aureus* Enteric gram (-) bacilli *Klebsiella pneumoniae* *Escherichia coli* Non enteric gram(-) bacilli *Enterobacteraceae* *Pseudomonas aeruginosa*	Gram (+) bacteria and anaerobes *Bacteroides fragilis* *Bacteroides melaninogenicus* *Peptostreptococci spp.* *Fusobacterium*	Cytomegalovirus Influenza / parainfluenza Adenovirus Respiratory syncytial virus (RSV)
Atypical pathogens *Chlamydia pneumoniae* *Mycoplasma pneumoniae* *Legionella pneumophilia*			**Fungal Pneumonia** *Pneumocystis carinii* (PCP) *Aspergillus spp*.

Community-Acquired Pneumonia Algorithm

OUTPATIENT	HOSPITALIZED		RISK FACTORS
	General medical ward	ICU	
▪ Macrolide* OR doxy (avoid doxy in peds) ▪ If recent antibiotic: FQ† alone OR new macrolide plus high-dose amox or Augmentin	▪ 3rd gen ceph‡ or amp/sulbactam plus new macrolide or doxy OR fluoroquinolone† alone ▪ Doxycycline/macrolide for atypical	3rd gen ceph‡ or amp/sulbactam AND new macrolide or FQ	**CAP** COPD/Smoking Alcoholism Diabetes Immunosuppression Nursing Home Resident **NOSOCOMIAL** Age >60 Mechanical Ventilation Organ Failure Prior Antibiotics Hospitalized >5 days
ASPIRATION	**NOSOCOMIAL**	**PCN ALLERGY**	
Add amox/clavulanate OR clindamycin	Ceftazidime, cefepime, Zosyn, or carbapenem PLUS FQ or AG (2-3 week therapy)	Aztreonam PLUS clindamycin PLUS FQ (or aminoglycoside)	

*Azithromycin, clarithromycin, erythromycin, telithromycin; †Levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin (any FQ with enhanced activity against *S. pneumo*); ‡Cefotaxime, ceftriaxone, or ceftazidime

Useful Resource
Infectious Diseases Society of America. CAP and HAP Clinical Practice Guidelines. http://www.idsociety.org

Treatment Principles
- Treat for 5-10 days (atypical organisms treat 14-21 days) --Always cover atypicals with empiric treatment
- Nosocomial pathogens are usually not involved until day 5 of admission to an institution
- Double-cover pseudomonas—DO NOT double-cover anaerobes (increased risk for pseudomembranous colitis)
- Pneumococcal vaccine in patients >65 yo or if >5 years since last vaccination

RENAL FAILURE
Adapted from Henry Mroch, MD

Kidney Function Overview

- Average glomerular filtration rate (GFR) is 100ml/min or 150L/day
- Creatinine (Cr) is a marker for kidney function. When GFR is normal, creatinine levels are about 1. **Every time the serum creatinine doubles, creatinine clearance drops by 50%**
- Most resorption takes place in the proximal tubules
- Aldosterone works at the distal tubule, where sodium is actively transported from urine back into the blood (water follows) and potassium passively gets excreted into the urine
  Aldosterone is critical for potassium homeostasis
  Hyperkalemia causes serious cardiac arrhythmias

Blood Pressure and Volume Regulation

- Low kidney perfusion results in **afferent arteriole vasodilation** and **efferent arteriole vasoconstriction**, in attempt to increase glomerular pressure
- Hormone response to hypotension:
  - Norepinephrine ↑
  - Renin ↑
  - Angiotensin II (AT-II) ↑
  - Aldosterone ↑
  - Vasopressin ↑
  - Atrial natriuretic peptide ↓
- Renin gets released and causes AT-II formation, resulting in direct vasoconstriction of efferent arteriole
- Prostaglandins cause afferent arteriole dilation
- Aldosterone causes sodium and water retention from the distal tubule
- Vasopressin causes water resorption via aquaporins in collecting ducts
- ACE- Inhibitors and ARBs cause efferent arteriole vasodilation (↓ GFR) **AND** NSAIDS cause afferent arteriole vasoconstriction (↓ GFR)

Acute Renal Failure

- Definition: clinical syndrome characterized by abrupt decline in GFR and rise in BUN and SCr. Occurs over days to weeks. **Reversible**
- Causes of ARF in a hospital setting:
  - Acute tubular necrosis
  - Intra- or post-renal obstruction
  - Renal artery stenosis
  - Prerenal
- Causes of PRERENAL failure:
  - Hypovolemia (hemorrhage, hypoalbuminemia, 3rd spacing)
  - Cardiac failure (myocardial dysfunction, pulmonary hypertension)
  - Systemic vasodilatation (sepsis, anaphylaxis, anesthesia)
- Notorious agents that cause acute tubular necrosis include: acyclovir, aminoglycosides, amphotericin b, ethylene glycol, cyclosporine, cisplatin, NSAIDs, and radiocontrast agents

Nondialytic Management of ATN

COMPLICATION	TREATMENT
Intravascular volume overload	Restrict salt (1-2g/day) and water (<1L/day) Diuretics
Hyponatremia	Restrict water Avoid hypotonic IV solutions
Hyperkalemia	Restrict dietary potassium (<40mmol/day) Potassium-binding resins (Kayexalate) Glucose and Insulin Sodium bicarbonate and β-agonists Calcium gluconate
Metabolic acidosis	Restrict dietary protein and give sodium bicarb if pH below 7.2
Hyperphosphatemia	Restrict dietary phosphate and give phosphate binding agents (calcium carbonate/acetate)
Hypocalcemia	Calcium carbonate of calcium gluconate
Hypermagnesemia	Discontinue Mg-containing antacids

Indications for Dialysis in Acute Renal Failure

- **A**cidosis (metabolic)

- **E**lectrolytes (K, Ca, Mg)
- **I**ngestions (dialyzable substances)
- **O**verload (pulmonary edema)
- **U**remia (encephalopathy, pericarditis)

Chronic Renal Failure

- Indicated by serum creatinine or creatinine clearance:
  - Women SCr ≥1.5mg/dL
  - Men SCr ≥ 2.0 mg/dL
  - Creatinine clearance(CrCl) <70mL/min
- The 2 major causes of CRF: diabetes (40%) and hypertension (27%)
- Consequences of CRF include:
  - Anemia
  - Protein malnutrition
  - Hypertension
  - Heart disease
  - Bone disease
- Blood pressure <125/75 slows progression of kidney disease
  - ACE-inhibitors and ARBs are first line treatment options
  - Diuretics can be used with ACE inhibitors or as 2nd-line therapy
- Anemia in CRF:
  - Can be due to erythropoietin deficiency, iron deficiency, or hyperparathyroidism
  - Treatment options:
    - Oral or IV iron
    - Epoetin-alpha, Darbepoietin

    patients need to have good iron levels for these to work
    - Red blood cell transfusion
    - Vitamins / nutritional supplements
- Elevated serum phosphorus levels can also be problematic in CRF
  - Consequences: increased calcium phosphate product, parathyroid gland hyperplasia, coronary artery calcification, myocardial fibrosis
  - Treatment options:
    - Dietary restriction
    - Dialysis
    - Phosphate binding agents
- Hyperparathyroidism in CRF:
  - Vitamin D deficiency or phosphate retention can cause hypocalcemia, which leads to hyperparathyroidism due to feedback on the parathyroid gland and increased TSH production—leads to bone loss
  - Treat with vitamin D supplements and phosphate binders
- Avoid nephrotoxic drugs (esp NSAIDs)

Care Chart for CRF

CrCl 70	CrCl 50	CrCl 30	CrCl 10-15
▪ Patient education ▪ Hypertension (ACE) and risk factor modification	▪ Parathyroid hormone monitoring ▪ Phosphate binders, monitor RBC ▪ Folate supplementation	▪ Nephrology consult ▪ Anemia: Iron and Epoetin ▪ PTH and Vitamin D ▪ Renal transplant candidate ▪ ACCESS creation	▪ Consideration of dialysis

Dialysis

- There are 2 major types: hemodialysis and peritoneal dialysis
- Indications
  - GFR < 10-15 ml/min
  - Uremic symptoms (fatigue, N/V, SOB, arthralgia, pericarditis)
  - Hyperkalemia
  - Acidosis
- HEMODIALYSIS:
  - Hospital based, accessed via a fistula in arm

    - Contraindications: thrombosed central veins, severe angina, hypotensive heart failure, resources, severe vascular disease
    - Complications: cramps, hypotension, chest pain, air embolism, hemolysis, nausea, vomiting, headache
- PERITONEAL DIALYSIS
    - Home based, accessed via pigtail catheter in peritoneal cavity
    - Contraindications: colostomy/ ileostomy, adhesions, lack of housing space, morbid obesity, poor hygiene, dementia
    - Complications: catheter related, exit site and tunnel infection, peritonitis, sclerosing peritonitis, technique failure, hernias, leaks, constipation

SINUSITIS
Adapted from Mike Olds, MD

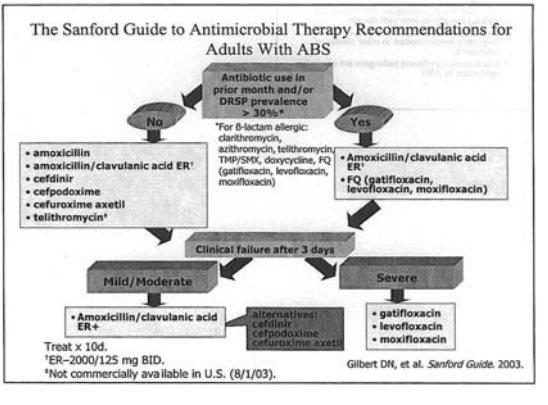
Definition
- Inflammatory disease of the paranasal sinuses
- Can be viral, allergic, fungal, or bacterial
- Viral illness is the most common predisposing factor for acute sinusitis: rhinovirus, influenza, or adenovirus

Acute sinusitis
- There is usually an initiating event—viral infection, allergy, foreign body
- Look for tenderness over the sinuses, nasal mucosal inflammation, and drainage
- Treat both infectious and drainage problems
- Most common bacterial pathogens: *Streptococcus pneumoniae* and *Haemophilus influenza*

Chronic sinusitis
- Symptoms greater than 3 months
- Look for underlying cause
- Don't be afraid to get imaging studies

Complications of Sinusitis
- Orbital cellulitis
- Abscess – many locations
- Cavernous sinus thrombosis
- Meningitis
- Pre-septal edema

Pharmacological Treatment for Acute Bacterial Sinusitis
- Recent use of systemic antibiotic (within 4-6 weeks) = risk factor for antibiotic-resistant infection
- High-dose amoxicillin +/- clavulanic acid recommended for penicillin-resistant *S. pneumo.*
- Adjunctive therapies may also be used
- Decongestants and anticholinergics for symptom relief
- Guaifenesin (except possibly at high dose), saline spray or irrigation, steam, "nonsedating" antihistamines likely not useful



SEXUALLY TRANSMITTED DISEASES
Adapted from Jason Iltz, PharmD

Clinical Practice Guidelines Centers for Disease Control and Prevention website: http://www.cdc.gov/std/treatment

Disease	Causative Organism	Signs and Symptoms	Diagnostic Tests	Complications	Treatment
Syphilis	*Treponema pallidum*	▪ Primary: ulcer and chancre at infection site lasting 1-8wks (10-90 days after exposure) ▪ Secondary: rash, fever, arthralgia, HA, mucocutaneous lesions (hands, feet, lips, mouth, genitals), lymphadenopathy lasting 4-10wks (17 days-6 months after exposure) ▪ Latent syphilis: often no symptoms, but still contagious ▪ Neurosyphilis (tertiary): CNS involvement, other organs	▪ Rapid Plasma Reagin (RPR) used for screening and to monitor successfulness of drug therapy ▪ Fluorescent Treponemal Antibody-Absorption Test (FTA-ABS) used as a confirmatory test	▪	▪ 1st Choice: Benzathine Penicillin G: 50,000U/kg IM up to adult dose 2.4 million units (1 dose/wk for 1-3wks) ▪ Aqueous Crystalline Pen. G: 18-24 million units/day intermittent or continuous for 10-14 days ▪ Aqueous Procaine Pen. G: 2.4 million units IM QD PLUS Probenecid 500mg PO QID, both for 10-14 days ▪ **Oral penicillin desensitization protocol if allergic and pregnant
Gonorrhea	*Neisseria gonorrheae*	▪ Dysuria ▪ Urinary frequency ▪ Urethral discharge ▪ Urethritis	▪ Gram-negative diplococci with kidney bean morphology within PMNs ▪ HIV test to rule out	▪ Epididymitis Prostatitis ▪ Inguinal lymphadenopathy ▪ Urethral stricture	▪ Treat both gonorrhea and chlamydia ▪ Possible treatments o Ceftriaxone 125mg IM/IV once o Cefixime 400mg PO once o Ciprofloxacin 500mg PO once o Levofloxacin 250mg PO once o Ofloxacin 400mg PO once ▪ PLUS agent for Chlamydia if not ruled out

Chlamydia	*Chlamydia trachomatis*	▪ N/V/D ▪ White mucopurulent and non-odorous vaginal discharge ▪ Diffuse abdominal pain ▪ Anorectal pain with bleeding ▪ Very tender inguinal adenopathy ▪ Cervix is red and inflamed	▪ Endocervical or urethral wall scrapings show intracellular parasites	▪ Infertility ▪ Ectopic pregnancy	▪ Possible treatments: o Doxycycline 100mg PO BID for 7 days o Azithromycin 1gm PO once ▪ Alternative agents (ALL taken for 7 days): Levofloxacin 500mg PO QD, Amoxicillin 500mg PO TID, ofloxacin 300mg PO BID, erythromycin base 500mg PO QID, erythromycin ethylsuccinate 800mg PO QID
Trichomoniasis		▪ Greenish-yellow discharge ▪ Malodor ▪ Itching/burning genitals	▪ Wet mount reveals pear-shaped flagellated organisms ▪ Basic pH of vaginal discharge (>5)		▪ Metronidazole 2gm PO once OR ▪ Metronidazole 500mg PO for 7 days **must treat partner
Scabies	*Sarcoptes scabei*	▪ Severe pruritis ▪ Dark colored (reddish) lines on the affected areas			▪ *Permethrin 5% cream (Elimite) applied from neck down and washed off after **8-14** hrs ▪ Alternatives: o Lindane 1%, applied from the neck down and washed off after **8** hrs o Ivermectin (Stromectal) 200mcg/kg orally, repeated in 2 wks

Pubic Lice	*Pediculosis pubis*	▪ Itching			▪ Lindane 1% shampoo applied to affected area and washed off after **4** minutes o Lindane is most toxic – contraindicated in pregnancy ▪ Permethrin 1% crème rinse (Nix) applied to affected area and washed off after **10** minutes ▪ Pyrethrins 0.3% w/ piperonyl butoxide 3-4% (Rid, Pronto) applied to affected area and wash off after **10** minutes **must wash linens, clothing, etc. to prevent reinfestation

TUBERCULOSIS
Adapted from Carol Vanevenhoven, PharmD

Resources
Centers for Disease Control and Prevention website http://www.cdc.gov/nchstp/tb
Horsburgh C, Feldman S, Ridzon R. Practice Guidelines for the Treatment of Tuberculosis. *Clinical Infectious Diseases*. 2000; 31:633-9

Tuberculosis Types	Signs and Symptoms	Risk factors	Causative Organism
▪ Pulmonary ▪ Extrapulmonary (larynx, lymph nodes, pleura, kidneys, brain, bone, joints) ▪ Miliary Tb: generalized infection	Pulmonary Tb: coughing (80%), pain in chest when breathing or coughing, coughing up sputum or blood Nonspecific symptoms: weight loss, fatigue, malaise, fever, night sweats	▪ HIV infection (100X risk for active disease) ▪ Immunocompromisation ▪ Injection drug users ▪ Close contact with Tb patient ▪ Elderly ▪ Homeless ▪ Healthcare workers ▪ Born in area where Tb common (Asia, Africa, Latin America) ▪ Live or work in residential facilities	*Mycobacterium tuberculosis* ▪ acid fast bacillus ▪ slow growing ▪ waxy outer coating (can stick to dust)

Mantoux TB Skin Test
- Tests for PPD (purified protein derivative)
- Two tests are required
- An immunocompromised person may not have accurate test
- Interpretation of results depends on patient's risks factors
  - (diagnosis at 5mm induration for highest risk people versus 15 mm induration for people with no risk factors)

Primary Infection
- *M. tuberculosis* inhaled, then immune system engulfs it
- *M. tuberculosis* is viable in immune cells, which travel through lymphatics to lymph nodes
- Cell-mediated immunity established

- Bacteria go dormant in macrophages—immune system can't attack
- After ~16 weeks, patient is PPD positive

Reactivation of Disease
- Only 7-10% will have reactivation. (most patients will remain asymptomatic)
- Greatest risk in first 2 years after exposure
- Factors favoring reactivation: old age, immunocompromisation, alcoholism, malnutrion

Bacille Calmette-Guerin (BCG):
TB vaccine developed in 1921. Not recommended in U.S., but still used in many countries. Vaccine is 0-80% effective. BCG will result in positive skin test

Tuberculosis Therapy

Post-Exposure Prophylaxis (known exposure or positive PPD)	**Active Disease**	**Multi-drug Resistant TB**	**Adjunctive Steroids**
▪ <u>INH sensitive</u>: INH 300mg PO QD for 9 months. If compliance problem: INH 900mg PO twice weekly directly observed therapy for 9 months ▪ <u>Presumed INH Resistance</u>: RIF 600mg PO QD for 4 months ▪ <u>Multi-drug resistant TB</u>: PZA + EMB or EMB + Levaquin/Ofloxacin for 6-12 months although regimens are unproven	**isolation is essential (5-7 days), patients should only be around others in well ventilated places, INH and RIF are backbone of therapy ▪ <u>Non-HIV patients</u>: **INH+RIF**+PZA+/-EMB ▪ <u>HIV positive patients</u>: o *Not on NNRTI's or PI* INH+RIF+PZA+EMB for 9-12mo o *On NNRTI's or PI* INH+PZA+EMB+rifabut x 9-12mo	▪ No standard regimen. Base drug choices on susceptibility data, previous treatment history, and exposure history ▪ Avoid monotherapy and avoid adding only a single agent ▪ Always change two or more drugs when adjusting therapy ▪ Drugs added should not have been given previously	▪ <u>Severe pulmonary TB</u>: faster radiological response, no survival benefit ▪ <u>TB meningitis</u>: faster resolution of CSF labs, ↓sequelae, improved survival but depends on stage of dz ▪ <u>TB pericarditis</u>: improved symptoms/survival but depends on stage of dz ▪ <u>TB pleuritis</u>: improved acute symptoms, no efficacy to prevent fibrosis w/ restrictive lung dz

Drugs Used to Treat Tuberculosis Infections

Drug	Dosage	MOA	Drug interaction	Toxicities	Side Effects/Comments
Isoniazid (INH)	Adult daily dose 5mg/kg (300mg max) on empty stomach	▪ Bactericidal, acts on cell wall ▪ Good CSF penetration	▪ Inhibits metabolism of phenytoin, carbamazepine, primidone, and warfarin. ▪ Weak MAO inhibitor ▪ Avoid w/ antacids	▪ Hepatitis (toxic effect in elderly and alcoholic) ▪ Peripheral neuropathy	▪ Give w/ pyridoxine (Vit. B_6) 25-50mg QD to prevent/treat peripheral neuropathy (reversible) ▪ Monitor LFT 1,3,6 months-d/c if ↑3-5X normal
Rifampin (RIF)	Usual adult daily dose 10mg/kg (600mg max)	▪ Bactericidal, acts on intracellular targets ▪ CSF penetration (inflamed meninges only)	Potent *inducer* of CYP2C9, 3A4 (↑clearance of warfarin, estrogen, NNRTI, PI, theo, anticonvulsants, CSA, ketoconazole, steroids, antiarrhythmics etc…)	▪ Liver dysfunction and skin eruption (toxic effect), ↑transaminases ▪ Intermittent admin (>1 week between doses) associated w/ flu-like symptoms(severe), thrombocytopenia, hemolytic anemia, renal failure = must d/c permanently	▪ SE: GI upset, ORANGE urine, contact lenses, tears, and sweat ▪ Variable absorption with AIDS, CF, DM, GI problem patients
Pyrazinamide (PZA)	Daily dose based on lean body wt: 40-55kg: 1000mg 56-76kg: 1500mg >76kg: 2000mg	▪ Exact MOA not elucidated, bactericidal in acidic pH of macrophage ▪ Good CSF penetration		Liver dysfunction (↓EtOH)	▪ SE: hyperuricemia ▪ Uric acid level – can use to track compliance
Ethambutol (EMB)	Daily dose based on lean body wt. 40-55kg: 800mg 56-76kg: 1200mg >76kg: 2000mg	▪ Interfere with RNA synthesis, **Bacteriostatic** ▪ Poor CSF penetration		Retrobulbar neuritis (dose related) - s/s blurred vision, red-green color blindness	▪ Monitor SCr ▪ Monitor drug level in AIDS, DM, CF, GI problems (variable absorption) ▪ Used to prevent resistance ▪ Often d/c after 2 months

URINARY TRACT INFECTIONS
Adapted from Mark Garrison, PharmD

UTI Classifications	Signs and Symptoms	Risk factors	Likely Causative Organisms
▪ Lower: cystitis / bladder infection ▪ Upper: pyelonephritis / kidney infection ▪ Complicated: structural abnormality ▪ Uncomplicated: no structural abnormality	▪ Dysuria ▪ Frequency ▪ Urgency ▪ Incomplete voiding ▪ Suprapubic pain ▪ Hematuria* ▪ Flank pain* ▪ Fever* ▪ Chills* *more indicative of upper UTI—pyelonephritis	▪ Female (shorter urethra) ▪ Obstruction (stone, BPH) ▪ Pregnancy ▪ Recent instrument-tation (catheters) ▪ Neurogenic bladder ▪ Sexual intercourse ▪ History of infection ▪ Immuno-compromis-ation	▪ *E. coli* (80% of cases) ▪ *S. sapro-phyticus* (5-15%) ▪ *Proteus* / *Klebsiella* (5%) ▪ *Enterococci*

Management

- Uncomplicated or first episode—no culture necessary, just treat clinically
- Recurrent UTI requires culture (need clean catch) and is likely to be more stubborn/complex organism
- Push fluids for natural flushing effect
- Urinary analgesics like phenazopyridine 200 mg TID x 2d
- Pregnancy: typically use 7 day course of therapy (avoid TMP/SMZ in 3rd trimester)
- If risk factors for STD present: doxycycline 100 mg BID x 7d and azithromycin 1 g once

Sanford's Recommended UTI Therapy

Infection	Preferred Therapy	Second-Line Therapy
Uncomplicated Lower UTI	▪ TMP/SMX 1 DS tab BID x 3d ▪ Nitrofurantoin 100 mg QID x 7d ▪ Fosfomycin 3 g PO once	▪ Ciprofloxacin 250 mg BID x 3d ▪ Ciprofloxacin ER 500 mg QD x 3d ▪ Gatifloxacin 200 or 400 mg QD x 3d ▪ Levofloxacin 250 mg QD x 3d ▪ **Avoid moxi or gemifloxacin
Recurrent Infections	▪ 1 SS tab QD x 6 mo	▪ Nitrofurantoin 50 mg QD x 6 mo
Childhood Uncomplicated Lower UTI	▪ TMP/SMZ (2mg TMP/10mg SMZ/kg) QD x 10-14d max dose: 20 mg/kg/day TMP ▪ Nitrofurantoin 2 mg/kg PO QD max dose: 7 mg/kg/day	▪ Ciprofloxacin 10-20 mg/kg BID x 10-21d max dose: 750 mg
Uncomplicated Pyelonephritis Outpatient	▪ Ciprofloxacin 500 mg BID x 7d ▪ Ciprofloxacin ER 1000 mg QD x 7d ▪ Gatifloxacin 400 mg QD x 7d ▪ Levofloxacin 250 mg QD x 7d ▪ Ofloxacin 400 mg BID x 7d	▪ Amoxicillin/Clavulanate 875/125 mg BID or 500/125 mg TID ▪ Oral cephalosporins (cephalexin, cefaclor, cefprozil, cefuroxime, loracarbef, cefdinir, cefixime, etc.) ▪ TMP/SMZ 1 DS tab BID x 14d
Uncomplicated Pyelonephritis Hospitalized **Treat IV until afebrile 24-48 hrs then switch to 2 weeks oral therapy	▪ Ciprofloxacin IV 400 mg BID x 14d ▪ Gatifloxacin IV 400 mg QD x 14d ▪ Levofloxacin IV 500 mg QD x 14d ▪ Ampicillin + Gentamicin x 14d ▪ Antipseudomonal penicillin x 14d ▪ 3rd generation cephalosporin x 14d (except *Enterococcus*)	▪ Ticarcillin/clavulanate x 14d ▪ Ampicillin/sulbactam x 14d ▪ Piperacillin/tazobactam x 14d ▪ Ertapenem x 14d (except *Enterococcus*)
Complicated UTI **Switch to oral fluroquinolone or TMP/SMZ when possible	▪ Ampicillin + Gentamicin x 2-3 weeks ▪ Piperacillin/tazobactam x 2-3 weeks ▪ Ticarcillin/clavulanate x 2-3 weeks ▪ Imipenem/cilastin x 2-3 weeks ▪ Meropenem x 2-3 weeks	▪ Ciprofloxacin IV 400 mg BID x 2-3weeks ▪ Gatifloxacin IV 400 mg QD x 2-3 weeks ▪ Levofloxacin IV 500 mg QD x 2-3 weeks

ACUTE CORONARY SYNDROMES
Adapted from Carol Vanevenhoven, PharmD

Guidelines
- Antman et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol*. 2004 Aug 4; 44(3): 671-719.

Pre-Hospital/Early ER Care For Everyone
- Obtain IV access
- ECG and fax to hospital
- Draw labs
- MONA
- Early beta-blocker

MONA
- Morphine 2-8 mg IV q5-15 min after NTG
  - Slows HR, decreases anxiety, decreases myocardial oxygen demand, peripheral arterial dilation
- Oxygen 2-4 L/min by nasal cannula for 1st 6 hrs
  - Continue treatment if O_2 sat. <90% on room air
- Nitroglycerin 400 mcg SL or spray q5 min up to 3 doses
  - Peripheral vasodilation to lower myocardial oxygen demand
  - Lower mortality days 0-1; after 1st day only relieves symptoms
  - IV infusion: 5-10 mcg/min up to max of 200 mcg/min
    - Avoid if hypotensive, brady/tachycardia, PDE inhibitor
- Chewable aspirin 162-325 mg within 1st 24 hrs unless bleeding

Early Beta-blocker
- Decrease mortality, arrhythmias, re-infarction
- Give oral β-blocker to all except low-risk unstable angina patients unless contraindication
  - Metoprolol 50-100 mg BID
- IV β-blocker reasonable for all STEMI patients esp. if hypertension or tachyarrhythmia
  - Metoprolol 5 mg slow IV over 5 min to max dose 15 mg
  - Target HR: 60-90 bpm
- Contraindications
  - HR < 50 bpm
  - Systolic BP <100 mmHg
  - Peripheral hypoperfusion/shock
  - 2nd or 3rd degree heart block
  - COPD and asthma are relative
    - Use lower dose and beta-1 selective agent

Unstable Angina
- Signs and Symptoms
  - Mild to severe chest pain (may be absent though)
  - No increase in cardiac enzymes
  - ST-segment depression or T-wave inversion
  - Coronary occlusion lasts <20 min
  - 10-20% progress to MI
- Presentation: chest discomfort, lightheadedness, neck discomfort, numbness in hands
- Treatment

- Possible ACS: monitor
- Likely or Definite ACS:
  - LMWH or IV heparin
    - Heparin preferred because shorter half-life
- Definite ACS with high-risk features or planned PCI
  - IV heparin
  - IV GP IIb/IIIa antagonist unless signs or history of bleeding, stroke, surgery
    - Abciximab (ReoPro®)
    - Eptifibatide (Integrilin®)
    - Tirofiban (Aggrastat®)
- PCI if high risk

Non-ST Elevation MI

- Signs and Symptoms
  - Mild to severe chest pain (may be absent though)
  - Increased cardiac enzymes
  - ST-segment depression or T-wave inversion
  - Coronary occlusion lasts 20 min – 2 hrs
- Treatment
  - IV Heparin
  - IV GP IIb/IIIa antagonist
  - PCI if high-risk

ST Elevation MI

- Signs and Symptoms
  - Mild to severe chest pain (may be absent though)
  - Increased cardiac enzymes
  - ST-segment elevation
  - Coronary occlusion persists without reperfusion
- Presentation: N/V, indigestion, fainting
- Treatment
  - PCI within 90 min of arrival
  - Thrombolytic within 30 min of arrival if cath lab unavailable
    - Streptokinase (SK)
    - Alteplase (t-PA)
    - Tenecteplase (TNK)
    - Reteplase (r-PA)

    Many contraindications to thrombolytics—look up!

    **Unsuccessful in 22-30% of patients
  - Unfractionated Heparin in patients receiving thrombolytic (except streptokinase unless high risk of systemic emboli)

Percutaneous Coronary Intervention

- PCI for all STEMI patients if possible
- PCI for high risk unstable angina or NSTEMI patients:
  - Persistent symptoms
  - Prior AMI/CABG/PCI
  - Widespread ECG changes
  - Recurrent ischemia
  - LV dysfunction
- Clopidogrel following stent placement
  - 300-600 mg loading dose, then 75 mg/day
  - Use in combo with ASA or alone if ASA intolerance

Medications 24 Hrs Post-MI

- Aspirin
- Beta-blocker
- Oral ACE-inhibitor (avoid IV because BP drops too much)

Post-MI Meds for Discharge

- Aspirin 75-162 mg QD indefinitely
  - Avoid ibuprofen because blocks ASA antiplatelet effect
- Beta-blocker indefinitely
- Oral ACE-inhibitor indefinitely (or ARB if intolerant)
  - Prevents ventricular remodeling and heart failure
- Cholesterol lowering therapy
- Lifestyle: smoking cessation, weight management, physical activity, BP control, blood sugar control

Cardiac Markers Used to Diagnose an MI

Cardiac Marker	Normal Values	Time for levels to increase after MI	Return to Normal Levels	Other information
CK-MB	10-13 units/L	3-6 hours	3-4 days	▪ Can rule out an MI ▪ Other disorders can elevate readings ▪ Magnitude of peak ~size of infarct
Myoglobin	< 100 ng/mL	1-2 hours	20-24 hours	▪ Helps make a rapid diagnosis ▪ Other disorders can elevate readings
Troponin T	< 0.1 ng/mL	3-4 hours	Several weeks	▪ Can diagnose MI up to 1 wk after event ▪ Angina may elevate levels
Troponin I	< 1.5 ng/mL	4-6 hours	6-7 days	▪ Very cardiac specific ▪ Not affected by non-cardiac factors ▪ Can diagnose MI for 6-7 days after event

ATTENTION DEFICIT HYPERACTIVITY DISORDER
Adapted from Clarke St. Dennis, PhD, BCPP

ADHD Characteristics

- Core Trinity—medications can help
  1. Inattention
  2. Impulsivity
  3. Hyperactivity (high gross motor activity)
- Other symptoms: low frustration tolerance, distractibility, emotionality, intrusiveness/destructiveness
- Conduct usually worsens in situations requiring sustained attention and ability to stay on task
- *DSM IV Requires at least **6 months duration** in **2 different environments**
- DSM IV Subtypes
  - Inattentive (females and adults)
  - Hyperactive/impulsive (rarest)
  - Combined (most common)
  - Not Otherwise Specified
- Comorbid Conditions Very Common
  - Conduct/Oppositional Disorders (30-50%)
  - Mood Disorders (15-75%)
  - Anxiety Disorders (25%)
  - Learning Disorders (20-25%)
  - Up to 60% of Tourette's patients have ADHD

  **always treat other disorders before ADHD

  **bipolarism is very hard to distinguish from ADHD—if patient gets worse on stimulants, probably bipolar

FDA Approved ADHD Medications

	Onset	**Peak** (hrs)	**Dura-tion** (hrs)	**Daily Doses**
Immediate Release				
Methylphenidate Ritalin® Methylin® Metadate®	20 to 60 min	~2	3 to 5	2 to 3
d-amphetamine Dexedrine® Dextrostat®	20 to 60 min	1 to 2	4 to 6	2 to 3
Methamphetamine Desoxyn®	20 to 60 min	1 to 2	4 to 6	2
First Generation Sustained Release				
Methylphenidate Ritalin SR® Metadate ER® Methylin ER®	60 to 90 min	~5	3 to 8	2
d-amphetamine Dexedrine Spansule®	60 to 90 min	NA	6 to 10	1 to 2

d,l-amphetamine Adderall®	30 to 60 min	1 to 2	6 to 8	1 to 2
Second Generation Sustained Release				
methylphenidate Metadate CD® Ritalin-LA®	30 min to 2 hrs	Bi-modal Pattern	6 to 8	1 to 2
methylphenidate Concerta®	30 min to 2 hrs	Bi-modal Pattern	12	1
d,l-amphetamine Adderall XR*®	1 to 2 hrs	Bi-modal Pattern	10 to 12	1
Stimulant Stereo-Isomers				
Dexmethyl-phenidate Focalin®	30 to 60 min	1 to 1.5	4 to 5	2
Norepinephrine Reuptake Inhibitors				
*Atomoxetine*** Strattera**®	1 to 3 days	NA	24	1
Other ADHD Medication				
Modafanil Provigil®	NA	NA	NA	1 to 2

*Adderall XR® caused sudden death in patients with cardiac abnormalities
**FDA required warning of increased teen suicide risk

Efficacy of Stimulants
- No evidence that one stimulant product is any more effective than another dosed properly
- Many children show short-term improvement, but long-term studies are lacking
- Up to 25% of children and 37% of adolescents fail therapy

Treatment with Stimulants
- Titrate dose slowly to target range
- If anorexia, give with or after meals
- If sleep disruption, give last dose before 4-6 PM
- Noon doses at school—not necessary with ER products
- Improvement seen in days to weeks

Side-Effects of Stimulants
- Anorexia
- Insomnia
- Nausea
- HA
- Dizziness
- Drowsiness
- Impaired coordination
- Irritability
- Anxiety
- Euphoria
- Sadness
- Withdrawal
- Maybe growth suppression

Non-FDA Approved Treatments for ADHD
- Antidepressants:

    - MAOIs (rarely)
    - TCAs: desipramine, nortriptyline, imipramine
        - Better for hyperactivity than attention deficiency
        - Used for stimulant non-responders because SE and overdose potential
    - Bupropion
        - May be as effective as Ritalin®, but seizure SE
    - Venlafaxine (high dose)
- Alpha-2 Agonists: Clonidine, Guanfacine
    - Better for behavioral problems, and not as effective for distractibility or inattentiveness
    - Used in stimulant non-responders or as adjunct to stimulants in ADHD patients with aggression, tics, hyperarousal, oppositionality

Atomoxetine (Strattera®)
- First non-stimulant for ADHD in children > 6 yo and first drug for adult ADD
- Mechanism
    - Inhibits NE reuptake; weak SSRI, very weak DARI
- May be given with or without food, but causes GI upset
- CYP2D6 substrate—reduce dose if concurrent 2D6 inhibitor like fluoxetine, paroxetine
- Not a controlled substance—starter packs available, refills/phone-in prescriptions available, no stimulation in drug abusers
- Similar efficacy to methylphenidate, but no insomnia or increased tic frequency
- Adult Dose: 40 mg/d for >3 days; target dose: 80 mg/day, max dose: 100-120 mg/day
- Child Dose: 0.5 mg/kg/d for >3 days; target dose: 1.2 mg/kg/day; max dose: 1.4 mg/kg/day

**much slower to work than amphetamines—must give 2 week trial at minimum before switching drugs

ACUTE DECOMPENSATED HEART FAILURE
Adapted from Carol Vanevenhoven, PharmD

Useful Reference
- DiDomenico RJ, et al. Guidelines for Acute Decompensated Heart Failure Treatment. *The Annals of Pharmacotherapy*. April 2004. 38: 649-60.

Hemodynamics of ADHF
- Venous filling pressures
  - Wet vs. Dry
  - Signs of elevated filling pressures ("wet"): orthopnea, JVD, S3 gallop, edema, ascites
- Vital organ perfusion
  - Warm vs. Cold
  - Signs of poor organ perfusion ("cold"): hypotension, weak puls, cool forearms/legs, altered mental status, decreased urine volume, increased BUN/SCr ratio

Timeline for Treatment of ADHF
- 0 hrs: initial ED contact
- 2 hrs: Establish diagnosis
- 4 hrs: Initiate IV therapy
- 6 hrs: assess response, add treatment as needed
- 8 hrs: Reassess response
- 8-12 hrs: Determine disposition—admit or send home

Warm and Wet Patients
- ~2/3 of patients with ADHF
- Aggressive diuresis to reduce fluid overload
  - On PO furosemide at home
    - Give total daily dose as IV bolus
  - No PO furosemide at home
    - SCr < 2 mg/dL: give 40 mg IV bolus
    - SCr > 2 mg/dL: give 80 mg IV bolus
  - Adequate response: > 500 ml urine output after 2 hrs or > 250 ml if SCr > 2.5 mg/dL
- Add IV vasodilator if moderate to severe volume overload
  - Volume overload: inadequate response to IV diuretics, pre-renal azotemia, supplemental oxygen, outpatient Furosemide > 100 mg/d
  - IV nitroglycerin
    - Venous dilator—reduces preload
    - 5-10 mcg/min infusion; titrate by 10-20 mcg/min increments every 5-10 min until response
  - IV nesiritide
    - Recombinant human BNP
    - Avoid if aortic stenosis, cardiogenic shock, hypertrophic cardiomegaly
    - IV Bolus 2 mcg/kg then 0.01 mcg/kg/min infusion
    - If no response after 3 hr, rebolus 1 mcg/kg and add 0.005 mcg/kg/min to infusion
    - Maximum infusion: 0.03 mcg/kg/min
- Optimize β-blocker, ACE-inhibitor, digoxin, diuretic, lifestyle

Cold and Wet Patients
- ~30% of patients
- IV nitroglycerin or nesiritide as described above

- IV nitroprusside
  - Mixed arterial and venous dilator, not a direct inotrope
  - 0.1-0.25 mcg/kg/min initially; titrate by 0.1-0.2 mcg/kg/min increments q 5-10 min
  - Usual effective dose 0.5-3 mcg/kg/min
- Positive Inotrope to increase cardiac output
  - Dobutamine
    - β-1, β-2, α-1 agonist
    - Avoid in patients on β-blocker
    - 2-5 mcg/kg/min; titrate by 2.5 mcg/kg/min q 5-15 min to max of 20 mcg/kg/min
    - May require vasopressors for support
  - Milrinone
    - Avoid in patients with hypotension, ischemic HF
    - 0.375 mcg/kg/min infusion
    - Titrate slowly because long half-life
- Optimize β-blocker, ACE-inhibitor, digoxin, diuretic, lifestyle

Cold and Dry

- ~5% of patients, relatively stable
- Dobutamine or milrinone short-term
- Optimize β-blocker, ACE-inhibitor, digoxin, diuretic, lifestyle

ADRENAL DISORDERS
Adapted from Ken Cathcart, DO

Cushing's Disease
- Excessive glucocorticoid secretion
- Causes: exogenous steroid use, ACTH secreting tumors
- Presentation
  - Unexplained osteoporosis
  - Unexplained hypokalemia
  - Proximal muscle weakness
  - Wide, purple striae
  - Thin skin
  - Virilization
  - Rapid baldness
- Treatment of choice: inferior petrosal sinus surgery
- Medications that decrease steroid synthesis
  - Ketoconazole 200-400 mg TID
  - Metyrapone 250 mg TID
  - Aminoglutethimide 250 mg TID-QID for adrenal tumors
  - Mitotane off-label for Cushing's

medications buy time until surgery or radiation (6 mo-1 year)

Addison's Disease
- Cortisol deficiency
- Causes: excessive prednisone use (as little as 5 mg QD x 1 mo), HIV infection, autoimmune disorder
- Presentation
  - Weakness/lethargy
  - Anorexia
  - N/V
  - Hypoglycemia
  - Hyperkalemia
  - Hyperpigmentation
- Treatment
  - Hydrocortisone 12.5 mg/m^2
  - Fludrocortisone 0.05 – 0.2 mg QD

Hyperaldosteronism
- Causes: aldosterone-secreting tumor, diuretic overuse, high potassium intake, low rennin activity, BCPs, CHF, pregnancy
- Accounts for ~25% of HTN, esp. in younger patients, refractory HTN, or hypokalemia with ACE/ARB, K salts
- Presentation
  - Hypertension
  - Muscle weakness
  - Hypokalemia
  - Hypernatremia
  - Polydipsia
  - Nocturnal polyuria
  - Tetany
  - Paresthesia
- Treatment
  - Remove tumor if present
  - Spironolactone 25 – 400 mg QD x 4-8 weeks

ADVANCED CARDIAC LIFE SUPPORT (ACLS)
Adapted from Lisa Kostelac, PharmD

ACLS Scenarios

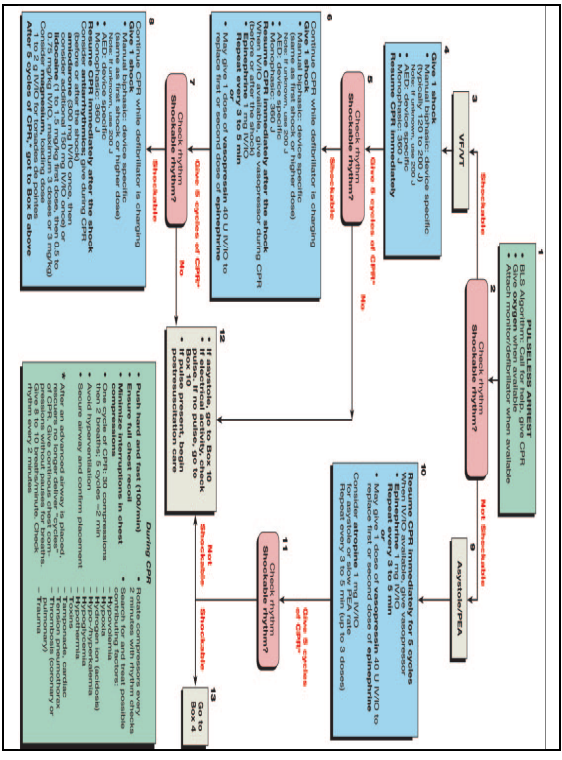
- Pulseless Arrest
  - Ventricular fibrillation/ventricular tachycardia
  - Pulseless electrical activity (PEA)
  - Asystole
- Bradycardia
- Tachycardia
  - Atrial Fibrillation (A fib) and atrial flutter (Aflutter)
  - Paroxysmal supraventricular tachycardia (PSVT)
  - Ventricular Tachycardia (VT): stable/unstable
- Acute Coronary Syndrome
  - Myocardial infarction
- Ischemic stroke
- Hypotension/shock
- Respiratory Compromise
  - SOB, respiratory arrest
- Hypothermia

Routes of Administration

- IV preferred
  - Predictable absorption/rapid onset of action
- IO (intraosseous) emphasized as an alternative
  - Predictable absorption/pharmacological effect
- Some medication may be given down the ET
  - BUT, variable absorption and dosing not well defined
  - Medication that may be given through ET
    - **N**aloxone
    - **A**tropine
    - **V**asopressin/**V**alium
    - **E**pinephrine
    - **L**idocaine
  - Give 2-2 ½ times the IV dose with 5-10 ml of water/NS

Pulseless Arrest Algorithm

- **Come, Shock Shock, Everybody, Shock and Let's Move**
- Medication
  - Do not have to wait until completion of shocks
  - May be given as soon as rhythm is checked (before, during or after CPR)
  - CPR – Rhythm Check – CPR
  - Prepare next drug dose before rhythm check



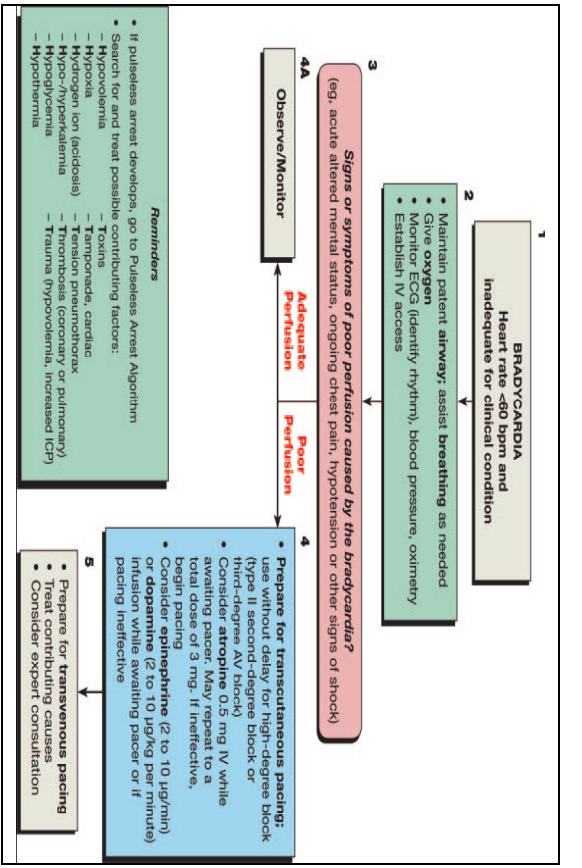
Asystole/PEA

- Check me in another lead and **EVAL**uate
- Causes of PEA
    - Assess during CPR and treat

6 H's	5 T's
Hypovolemia	Toxin/Table overdose
Hypoxia	Tamponade, cardiac
Hydrogen ions (acidosis)	Tension pneumothorax
Hypo/Hyperkalemia	Thrombosis (coronary or pulmonary)
Hypoglycemia	Trauma
Hypothermia	

Bradycardia Algorithm

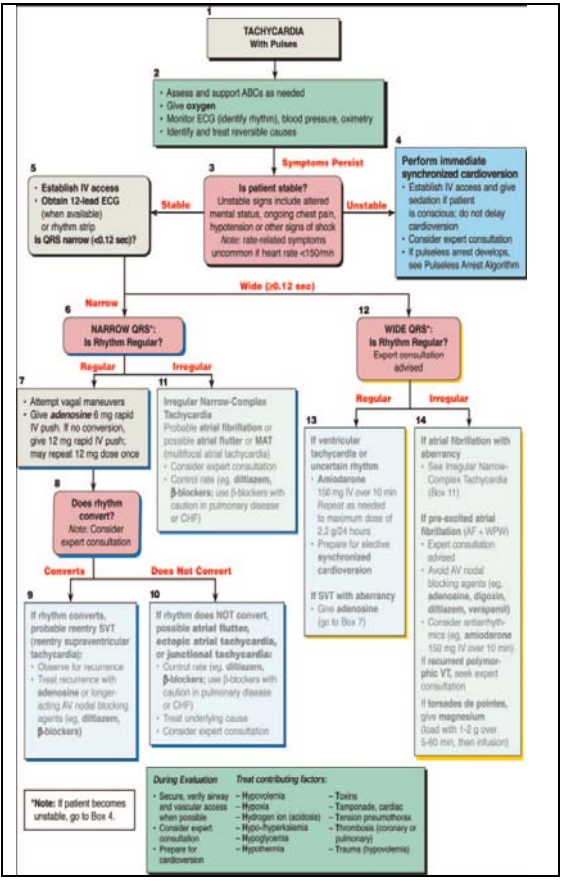
- Definition
  - o < 60 bpm or relative bradycardia w/ serious symptoms
  - o symptoms: chest pain, SOB, loss of consciousness
  - o signs: hypotension, pulmonary edema, CHF, shock
- **A**ll **T**rained **D**ogs **E**at



Tachycardia Algorithm

- Definition
  - o HR > 100 bpm
  - o Not a normal response to stress/external stimuli
  - o Unstable: altered mental status, ongoing angina, hypotension
    - ▪ Synchronized cardioversion
  - o Stable: obtain ECG to characterize QRS

- Narrow (<0.12 sec): PSVT, A fib, Aflutter
- Wide (>0.12 sec): VT, Torsades de Points



Synchronized Cardioversion Algorithm

- Indication: Unstable Tachycardia
  - Unstable A fib, Aflutter, SVT, VT
  - S&S: hemodynamic instability, CHF, angina
- Pre-medicate when possible
  - Midazolam 0.03 mg/kg IV
  - Fentanyl 0.05-1 mg/kg IV

Adjunctive Medications for ACLS Situations

- Midazolam
  - Class: benzodiazepine
  - Use: short-term conscious sedation, amnestic, anxiolytic
  - Onset (IV): < 1 min; Duration (IV): 20-60 min

    - Dose: 0.03 mg kg (0.5-2 mg)
    - Caution:
        - Additive effect with opiates (reduce dose by 30%)
        - Prolonged use of high doses: excessive sedation
            - Wait for effect then repeat dose with ½ initial dose
- Flumazenil (Romazicon®)
    - Antidote: Competitive antagonist at GABA/benzo receptor
    - Use: reverses CNS/resp depression from benzos
    - Onset (IV): 1-3 min; Duration (IV): ~ 1 hour
    - Dose: 0.2 mg IV repeat every 60 sec up to a total of 3 mg
    - Caution:
        - History of seizures (Withdrawal/seizures)
        - Chronic use of benzodiazepines (Withdrawal/seizures)
        - Head injury (Seizures)
        - TCA/polydrug overdoes (Seizures)
- Fentanyl (Sublimaze®)
    - Use: conscious sedation, pain relief
    - Onset (IV): 1-2 min; Duration (IV): 10 – 60 min
    - Dose: 0.5-2 mcg/kg IV/IM plus additional 25-100 mcg. Titrate as needed
    - Adverse effects:
        - Respiratory/CNS depression
        - Hypotension
        - Broncho/laryngeal spasm: give over 3-5 minutes
        - Caution: Concomitant benzodiazepines
            - Reduce dose of both ~30%
- Naloxone (Narcan®)
    - Antidote: Competitive opioid receptor antagonist
    - Use: reversal of CNS/resp. depression caused by opioids
    - Onset (IV): 1-2 min; Duration (IV): 20 – 60 min
    - Dose: 0.04-0.2 mg IV/IM/SC, may repeat every 2-3 min.
    - Caution:
        - Chronic use of opioids (withdrawal)
        - Underlying pain issues
- Glucagon (GlucaGen®)
    - Antidote:
        - Promotes hepatic glycogenolysis and gluconeogenesis
        - Increases cardiac contractility
    - Use: hypoglycemia, beta-blocker/calcium channel blocker reversal
    - Onset (IV): 5-20 min; Duration (IV): 60-90 min
    - Dose: 1 mg IV/IM/SC (hypoglycemia)
    - Caution: IV Incompatibilities

ADVERSE EFFECTS OF PSYCHOTROPICS
Adapted from Brandy Singer, RPh

Weight Gain
- Worst Offenders
  - Antidepressants: TCAs, SSRIs, mirtazapine
  - Mood Stabilizers: lithium, divalproex, carbamazepine
  - Antipsychotics: clozapine > olanzapine > quetiapine > risperidone > aripiprazole = ziprasidone
  - Clozapine and olanzapine can also increase risk for diabetes and cause dyslipidemias
- Treatment
  - H_3-blockers, amantadine, metformin, topiramate have limited evidence for efficacy

Acute EPS
- Occurs hours/weeks after starting or increasing antipsychotic
- Definitions
  - Dystonia = abnormal posture
  - Pseudo-Parkinsonism = Parkinsonian symptoms
  - Dyskinisia = poor ability to move voluntarily (can be from withdrawal of antipsychotic as well)
  - Bradykinisia = extremely slow movements
  - Rigidity = “cogwheeling”, “lead pipe”
- Complications of EPS: breathing difficulties, COPD, increased fall risk, akathisia mistaken for anxiety/psychosis
- Medications that cause EPS
  - Metoclopramide
  - SSRIs
  - Lithium
  - Typical antipsychotics > atypicals
  - Typicals with low anticholinergic activity > typicals with high anticholinergic activity
  - Risper > Olanz > Zipras > Quet = Aripip = Cloz
- Treatment
  - Reduce dose or switch drugs
  - Anticholinergics—may worsen akathisia, dyskinesia
  - Dopamine agonists: amantadine, bromocriptine
  - GABA agonists—benzos, Divalproex®
  - Beta-blockers: Propranolol
  - **If EPS with any atypical, can still use clozapine

Akathisia
- Inner feeling of restlessness
- Treatment
  - Reduce dose or switch drugs
  - Benzodiazepines
  - **Avoid anticholinergics

Neuroleptic Malignant Syndrome
- Occurs in ~0.5-1% of patients on neuroleptic drugs
- Signs/Symptoms: hyperthermia, tachycardia, rigidity
- Usually develops rapidly
- High mortality (~30%)
- Complications: respiratory failure, rhabdomyolysis, seizure, DIC, V. tach, aspiration, pulmonary embolism
- Treatment: D/C offending agent, supportive measures
  - Bromocriptine QID
  - Dantrolene 2-3 mg/kg/d NTE 10 mg/kg/d

Tardive EPS

- Related to length of time exposed to drug
- Only 50% are reversible
- Symptoms: lip smacking, tongue movements, facial tics, limb movements
- Prevention is key!
- Treatment: D/C offending agent
    - May try dopamine antagonists/agonists
    - Beta-blockers, lithium, cholinergics
    - GABA-agonists: benzos, Divalproex®
    - **Avoid anticholinergics

ALZHEIMER'S DISEASE
Adapted from Steve Setter, PharmD, CGP, DVM

Resources
Alzheimer's Disease Education and Referral Center Sponsored by the National Institue of Health: www.nia.nih.gov/alzheimers
US Alzheimer's Association: www.alz.org
Inland NW Alzheimer's Association (509) 483-8456

Characteristics
- Progressive, degenerative disease
- Loss of memory and other cognitive function
- Decline in ability to perform activities of daily living
- Changes in behavior and personality
  - Delusions (incl. paranoia)
  - Hallucinations
  - Aggression
  - Combativeness
  - Hyperactivity (incl wandering)
  - Disinhibition
  - Increased vocalization
- Increased need for resources leading to eventual nursing home placement

Alzheimer's vs. Age-related Memory Loss

	Alzheimer's	Age-related
Memory Loss	Forgets entire events	Forgets parts of events
Verbal reminders and recall	Usually cannot get memories back	Usually remember with reminders
Handwritten notes as reminders	Are progressively less helpful	Notes are useful reminders
Memory loss and thinking problems	Worsen with time	Stable
Independence	Less able for self-care	Usually independent

Drugs with Anticholinergic Properties
- TCAs
- Amantadine
- Clozapine
- Cyclobenzaprine
- Disopyramide
- Sedating H-1 Blockers
- Orphenadrine
- Phenothiazines
- Dimenhydrinate

**may increase plaques and tangles in brain, antagonizing anti-AD medications and facilitating disease progression

Pharmacological Therapy
- NMDA antagonists
  - Possible MOA: prevent neurotoxicity from overexcitation via glutamate signaling
  - Memantine (Namenda®)
    - Start dose at 5 mg; titrate 5 mg q week, max 10 mg bid. (10 mg qd if CrCl is 40-60)
    - Minimal hepatic metabolism

        - SE include diarrhea, insomnia, dizziness, HA.
        - Caution with Parkinson's, organic brain syndrome, neuropathic pain, neurogenic bladder
        - DI's include amantadine, ketamine, dextromethorphan, and drugs that alkalinize the urine (carbonic anhydrase inhibitors, sodium bicarb, etc.)
- Cholinesterase Inhibitors
    - Increase acetylcholine in synaptic cleft
    - Goal = improve, maintain, or slow cognitive decline, control behavioral problems, ease caregiver burden, maintain independence, delay admission to long-term care facility
    - Use with caution if concurrent PUD, urinary tract obstruction, general anesthesia with succinylcholine, pancuronium, or vecuronium, bradycardia, sick sinus syndrome, conduction abnormalities, asthma, COPD, or seizures.
    - Quote from Dr. Setter: "Treatment should be initiated and supervised by a prescriber experienced in the diagnosis and treatment of Alzheimer's dementia and the elderly."
    - Donepezil (Aricept®)
        - Dose 5 to 10 mg QD
        - Well tolerated
        - CYP3A and 2D6 substrate
    - Rivastigmine (Exelon®)
        - Dose 3 to 12 mg per day divided BID
        - GI SE are common, including weight loss
        - Little hepatic metabolism via CYP450 enzymes
    - Galantamine (Reminyl®, Razadyne®)
        - Dose 8 to 24 mg per day divided BID
        - Renal excretion, so if CrCl is 10-70 ml/min dose NTE 16 mg/day. Contraindicated if CrCl is less than 10.
        - CYP3A4 and 2D6 substrate
        - SE: N/V, anorexia, agitation
- Other Potential Treatments
    - Antioxidants, anti-inflammatory agents, estrogen

THROMBOEMBOLIC DISEASE
Adapted from Louise Achey, PharmD

Resources
- ACCP Guidelines: *Chest* 2004; Vol. 126: http://www.chestjournal.org/content/vol126/3_suppl/

Risk Factors for Venous Thromboembolism
- Virchow's triad
  - Venous stasis
    - Prolonged bed rest
    - Immobility
    - Late stage pregnancy
    - Shock, severe MI
  - Vascular injury
    - Trauma
    - Surgery
    - Chemical Irritation
  - Hypercoagulability
    - Inherited states (protein C or S deficiency)
    - Malignancy
    - Estrogen Use
    - Pregnancy
    - Cardiomyopathy
    - History of DVT or PE
    - Polycythemia Vera

Diagnosis
- Clinical signs and symptoms
  - DVT: palpable cord, leg swelling, pain in calf with dorsiflexion
  - PE: SOB, decreased perfusion
- Doppler ultrasound—misses smaller DVTs
- D-dimer test
  - Highly sensitive, but not specific to DVT/PE
  - D-dimer fragments cleaved from clots by plasmin
  - If negative, rules out thrombus—avoids ultrasound, V/Q
- Ventilation-perfusion Scan (V/Q Scan)
  - Areas that are ventilated, but not perfused suggest PE
  - Reported as low, intermediate, or high probability of PE

Treatment Overview (DVT or PE)
1. Anticoagulants in PE and DVT above the popliteal vein.
2. Heparin 1st, then oral anticoagulants for 6 months.
3. Changing to oral anticoagulation
   a. Continue both heparin AND warfarin for at least 4 days PLUS INR is at least 2.
   b. Can substitute LMWH 1mg/kg SC q12h or 1.5 mg/kg q24h for heparin infusion in outpatient (q12h more common for treatment, q24h more common for prophylaxis
4. Reduction in risk factors to prevent recurrence

Guidelines for Anticoagulation: Heparin Infusion

Disease	Guideline
Suspected VTE	▪ Obtain baseline APTT, PT, CBC ▪ Check for contraindication to heparin theapy ▪ Give heparin 5,000 units IV

	▪ Order imaging study
Confirmed VTE	▪ Rebolus with heparin, 80 units/kg IV, and start maintenance infusion at 18 units/kg/h ▪ Check aPTT at 6h to maintain a therapeutic heparin level ▪ Check platelet count daily ▪ Start warfarin therapy on day 1 ▪ D/C heparin after 4-5 days of combined treatment when INR > 2 on 2 consecutive days ▪ Anticoagulate with warfarin for at least 6 mo (goal INR 2-3)

Sample Protocol for Heparin Infusion Adjustments

aPTT (sec)	Heparin Bolus	Infusion Hold Time	Infusion Rate Adjustment	Next aPTT (hr)
< 40	50 U/kg	0	↑ by 4 U/kg/hr	6
40-60	25 U/kg	0	↑ by 2 U/kg/hr	6
60-100	0	0	No change	6
100-120	0	0	↓ by 1 U/kg/hr	6
120-140	0	30 min	↓ by 2 U/kg/hr	6
>140	0	60 min	↓ by 3 U/kg/hr	6

******varies with institution

Reversal of Heparin Activity

- 1mg Protamine reverses about 100units of heparin or LMWH if caught early
- If 30 min – 1 hr after heparin/LMWH given use 0.5 mg protamine/100 units heparin remaining
- If >2 hr after heparin/LMWH given use 0.25 mg protamine/100 units heparin remaining
- Use 2 hr half life for heparin to determine amount remaining
  - Heparin's half-life varies with dose, though
  - More heparin = longer half-life

Guidelines for Anticoagulation: LMWH

Disease	Guideline
Suspected VTE	▪ Obtain baseline aPTT, PT, CBC ▪ Check for contraindication to heparin ▪ Give unfractionated heparin 5,000 units IV ▪ Order imaging study
Confirmed VTE	▪ Give LMWH (enoxaparin) 1 mg/kg SC q12h or 1.5 mg/kg SC q24h ▪ Start warfarin therapy on day 1 ▪ Consider platelet count between days 1 and 5 ▪ Stop LMWH after at least 4-5 days of combined therapy with INR > 2 for 2 consecutive days ▪ Anticoagulate with warfarin for at least 6 mo (goal INR 2-3)

Warfarin Therapy

- MOA: inhibits production of vitamin K dependent clotting factors in liver (factors VII, IX, X, and II)
- Big 3 drug interactions: amiodarone, septra, metronidazole
- SE: bleeding, skin necrosis, purple toes syndrome
- Contraindications: pregnancy, hemorrhage, malignant hypertension, thrombocytopenia, recent eye/CNS surgery

Determining Warfarin Sensitivity/Starting Dose

	Warfarin Sensitive	**Not Warfarin Sensitive**
Age	> 60 yo	< 60 yo
Clinical History	Multiple medical problems Prophylaxis only	Few medical problems Clot present
Medications	Multiple interacting medications	Few to no other medications
Size	< 60 kg	> 60 kg
Initial Dose	Usually 5 mg or less	Either 5, 7.5, or 10 mg depending on patient
Average Daily Dose	5 mg or less	5 mg or more
Gender	Females need 10-15% less	Males need 10-15% more

Therapeutic Range for INR is 2-3 unless Mechanical valve 2.5-3.5

Guidelines for Adjusting Warfarin by INR

INR	Dose change
1.1-1.4	▪ Increase TWD by 10 – 20% ▪ Return: 1week
1.5-1.9	▪ Increase TWD by 5 – 10% ▪ Return: 1 week
2.0-3.0	▪ No change ▪ If 2-3 stable readings, ▪ Return: q 4 weeks
3.1-3.9	▪ Day 1:Hold warfarin dose ▪ Reduce TWD by 10 – 20% ▪ Return: 1-2 weeks
4.0-5.0	▪ Day 1:Hold dose x 1-2d ▪ Weekly: Reduce TWD by 10 – 20% ▪ Return: 1 week
>5.0	▪ Stop warfarin until INR<3.0 ▪ Decrease TWD by 20 – 50% ▪ Return Daily

TWD= Total Weekly Dose

Managing Patients with High INR values

Clinical Situation	Guidelines

INR> therapeutic range but < 5.0, no clinically significant bleeding, rapid reversal not indicated for reasons of surgical intervention	▪ Lower dose or omit next dose ▪ Resume warfarin therapy at a lower dose when the INR approaches desired range. ▪ If INR is only minimally above therapeutic range, dose reduction may not be necessary.
INR > 5.0 but < 9.0, no clinically significant bleeding	▪ *Pt with no additional RFs for bleeding:* omit the next dose or two of warfarin, monitor INR more frequently, and resume warfarin therapy at a lower dose when the INR is in therapeutic range. ▪ *Pts at increased risk of bleeding;* omit the next dose of warfarin, and give Vit K (≤5mg po). ▪ *Pts requiring more rapid reversal before urgent surgery or dental extraction:* Vit K (2-4 mg po); ▪ If the *INR remains high at 24 hr;* an additional dose of 1-2 mg.
INR > 9.0, no clinically significant bleeding	▪ Hold warfarin and give higher dose Vit K (5-10mg) PO with expectation INR drop in 24-48 hrs.
Serious bleeding at any elevation in INR	Hold warfarin and give Vit K 10mg by slow IV infusion, supplemented with FFP. Vit K can be repeated every 12 hrs.
Life-threatening bleeding or serious warfarin overdose	▪ Prothrombin complex concentrate, with Vit K 10mg IV in 50 ml NS infused over 60 min); ▪ Repeat if necessary, based on INR
Continuing warfarin therapy indicated after high doses of Vit K	Heparin, until the effects of Vit K have been reversed, and pt is responsive to warfarin.

ANXIETY DISORDERS
Adapted from Angelo Ballasiotes, PharmD

Panic Disorder
- Biological Basis:
  - Neurotransmitter dysregulation (NE, GABA)
  - Respiratory hypothesis (CO_2 and lactate hypersensitivity, or false suffocation alarm)
- Clinical Presentation: (must have 4 of 13 identified symptoms)
  - Increased Heart Rate
  - Dizzy or faint
  - Sweating
  - Paresthesias
  - SOB
  - Chills or hot flashes
  - Chest Pain
  - Feelings of unreality
  - N/V
  - Trembling/Shaking
  - Feeling of choking
  - Fear of dying
  - Fear of losing control of going crazy

Obsessive-Compulsive Disorder (OCD)
- Characterized by obsessions and compulsions that last at least 1 hr/day and interfere with daily functioning
- Biological Basis:
  - Related to serotonin, dopamine, or both
- Clinical Presentation:
  - Common Compulsions
    - Checking
    - Cleaning/washing
    - Counting
    - Repeating
    - Ordering/arranging
  - Common Obsessions
    - Contamination
    - Safety/harm
    - Aggression
    - Religion
    - Need for exactness

Generalized Anxiety Disorder (GAD)
- Excessive worry about events that is difficult to control and lasts at least 6 mo
- Clinical Presentation (Must have 3 of the following along with worry and anxiety):
  - Restlessness
  - Easy fatigability
  - Difficulty concentrating
  - Irritability
  - Muscle tension
  - Disturbed Sleep

Post-Traumatic Stress Disorder (PTSD)
- Exposure to traumatic event that involves actual or threatened death/serious injury to person or others—involves intense fear, helplessness, or horror

- Biological Basis:
  - Over active noradrenergic nervous system
  - Reduction in the volume within the hippocampus
- Clinical Presentation:
  - Persistent experiencing of trauma
  - Avoidance of trauma-associated stimuli
  - Hyperarousal

Acute Stress Disorder
- Like PTSD, but symptoms last for 2 weeks after trauma and resolve in 4 weeks
- Biological basis: overactive sympathetic nervous system

Social Phobia
- Generalized social phobia: fear all social situations where embarrassment can occur when exposed to unfamiliar people
- Specific social phobia: fear specific social situation like public speaking
- Biological Basis:
  - Still remains obscure
  - Possibly noradrenergic over-activity
- Clinical Presentation:
  - Tremor
  - Tachycardia
  - Blushing
  - Typically early onset = 11 – 15 years old

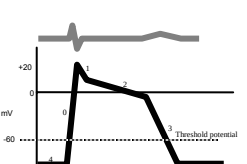
Anxiety Disorder Treatment

	PD	OCD	GAD	PTSD	Phobia
SSRIs	X	X		X	X
Atypical Antidepressant	X		M/N/T	N	V/N
TCAs	X			X	
MAOIs	X			X	
Benzodiazepines	X	X	X		X
Barbiturates and meprobamate			X		
Mood Stabilizers				X	
*Beta-Blockers			X	X	X
*Alpha 2 Agonists			X		X
*Antihistamines			X		
Alpha-1 antagonists				X	

*Indicates adjunctive therapy
M = mirtazapine
N = nefazodone
T = trazodone
V = venlafaxine
Meds in addition to counseling = additive effect
**Avoid benzodiazepines in MICA patients

CARDIAC ARRYTHMIAS
Adapted from Carol Lyn Vanevenhoven, PharmD

Myocardial Action Potential



- Phase 0: Rapid Ventricul. Depolarization. Cell receives impulse, rapid Na entry, depolarization
- Phase 1: Early Repolarization. Na channels inactivated, partial repolarization.
- Phase 2: Plateau Phase. Ca re-entry, absolute refractory period.
- Phase 3: Late & Rapid Repolarization. Rapid K+ exit. Relative refractory period.
- Phase 4: Diastolic Depolarization. Resting Membrane Potential. Slow Na leak leads to next ventricular depolarization

Cardiac Arrythmias

- *Abnormal Impulse Generation*
  - Automatic tachycardias (ectopic beats).
    - Increased slope of phase 4—regions of heightened automaticity (compete with SA node)
    - Caused by catecholamines, hypoxemia, hypokalemia, fiber stretch, edema.
  - Triggered automaticity.
    - Repolarization in phase 3 is interrupted by "afterdepolarizations" causing a 2nd depolarization before 1st one is done
    - Caused by abnormal Ca+ and Na+ influx, hypoxemia, hypokalemia, catecholamines, digoxin OD, high pCO2.
- *Abnormal Impulse Conduction* – re-entry
  - Requires 2 pathways: an area of unidirectional block and slow conduction in the other pathway
  - Allows repetitive excitation
  - A single circuit induces a premature contraction and continuous cycling results in tachycardia

Antiarrhythmics

- Treat or prevent arrhythmias by:
  - Increasing threshold potential--Decrease phase 4 slope
  - Increasing absolute refractory period (facilitates conduction in the area of block, allowing conduction when re-entry is occurring)
- Primary targets are ion channels (Na, K, Ca)
- Secondary targets are receptors that modulate these channels (adrenergic, cholinergic, adenosine)

Class I Antiarrhythmics

- MOA: primarily block fast sodium channels
- Class Ia Agents
  - Depress phase 0 depolarization (↓ conduction velocity). Prolong action potential & refractoriness.
  - Useful for SVT, VT, symptomatic premature ventricular beats & prevention of V-fib.(atrial & vent. tachy).

    - Drugs: disopyramide, procainamide, quinidine.
- Class Ib Agents
    - Fast onset & offset (no effect on slow HR)
    - Shorten action potential duration and ↓ refractoriness.
    - Improves antegrade conduction, eliminating unidirectional block.
    - Useful for VT, prevention of V-fib, & symptomatic premature vent. beats. (ventricle only).
    - Drugs: lidocaine, mexiletine.
- Class Ic Agents
    - Slow on/off (slowed conduction at normal HR)
    - Profoundly slows conduction velocity
    - Refractoriness unaltered
    - Useful for VT/V-fib (risk of proarrythmia), refractory SVT
    - Drugs: flecainide, propafenone, moricizine.
- SE of Class I:
    - *ALL* have ventricular proarrhythmia risk.
    - Quinidine (diarrhea 30-40%, DI)
    - Procainamide (drug-induced lupus 50%, active metabolite accumulates in renal failure)
    - Disopyramide (anticholinergic 70%, strong negative inotrope).
    - Lidocaine (CNS, seizures, psychosis, sinus arrest, aggravation of underlying conduction disturbances).
    - Flecainide (CHF, blurred vision, dizziness, HA).
    - Propafenone (dizziness 25%, GI upset 25%, bronchospasm, strong negative inotrope).

Class II Antiarrhythmics
- MOA: β-blockers—antiadrenergic action on SA & AV nodes
- Useful for abnormally automatic nodal tissue or nodal reentrant loop.
- Slow ventricular response

Class III Antiarrhythmics
- MOA: Block K+ channels
- Prolong repolarization & refractory period
- No change in conduction velocity
- Drugs in this class vary widely in their indications
    - Amiodarone (VT, VF, SVT)
    - Sotalol (VT, SVT, AV re-entry)
    - Ibutilide (acute conversion of A fib)
- Side Effects:
    - Amiodarone: CNS, GI, Torsades, pulmonary fibrosis (5-10%), hepatitis, photosensitivity (blue-grey discoloration), hypotension, corneal deposits, optic neuritis, thyroid
    - Bretylium: hypotension, GI
    - Dofetilide: Torsades
    - Ibutilide: Torsades, hypotension
    - Sotalol: Torsades, depression, GI, bronchospasm, worsening CHF, fatigue

Class IV Antiarrhythmics
- MOA: Ca Channel Blockers—↓ conduction, prolong refractoriness, ↓ automaticity of SA & AV node
- Good for automatic tachyarrhythmias originating in nodes

Atrial Fibrillation

- Pathophysiology
  - Supraventricular tachyarrhythmia with uncoordinated atrial activation & deterioration of atrial mechanical function (poor filling & poor pumping resulting in desynchronization)
  - Loss of atrial kick, which indicates ↓ blood flow (↓ cardiac output)
  - Irregular vent. activation which leads to irregularly irregular rhythm (AV node is allowing some conduction to go thru periodically)
  - 400-650 atrial bpm, 120-180 ventricular bpm. No P wave on ECG
- Epidemiology
  - Most common sustained rhythm seen in practice
  - Risk increases with age (0.4% overall, 6-10% if >80),
  - More common in men.
  - Ischemic stroke rate 5% per year.
  - Common comorbidity in pts with heart disease/failure
- Types of Atrial Fibrillation
  - Acute Onset: onset <48 hours
  - Paroxysmal: terminates spontaneously in 7 days
  - Recurrent: more than 2 episodes
  - Persistent: duration >7 days, doesn't terminate spontaneously
  - Permanent: No termination w/ cardioversion
  - Lone: no cardiac risk factors or known cause
- Etiology
  - Acute: alcohol intake (holiday heart syndrome), post-surgery, electrocution, AMI, myocarditis/pericarditis, pulmonary embolism, hyperthyroid, emotional stress, exercise.
  - Cardiac: valvular heart disease, atrial septal defect, cardiomyopathy, CAD, HTN, sinus node disease
  - Systemic: COPD, CVA, electrolyte abnorm., fever, thyrotoxicosis
  - Neurogenic: heightened vagal or adrenergic tone from ANS
- Symptoms
  - Asymptomatic
  - Palpitations
  - Dyspnea
  - Light-headedness
  - Chest discomfort
  - Hypotension
  - Syncope (uncommon & serious)
- Consequences of Atrial Fibrillation
  - Hemodynamic: loss of synchronous atrial activity; irregular ventricular response; rapid HR; worsening CHF (loss of atrial kick, ↓ filling time)
  - Precipitating angina: ↑ O_2 demand; reduced coronary filling time
  - Systemic arterial emboli:
    - Risk Factors: age>60, left atrial enlargement, low EF, previous embolic event, CAD, HTN, DM

- Treatment Strategies
  - **Rhythm Control** (restore normal sinus rhythm w/ drugs or electrical)
  - **Rate Control** (allow A-fib, but control ventricular rate)

- Prevention of thromboembolism with anticoagulation

**Rhythm control shown more harmful than Rate control (AFFIRM trial)

- Can treat severe symptoms (ischemic chest pain or acute pulmonary edema) with Direct Current Cardioversion (DCC)

- Pharmacological Control of Rate
  - Goal 60-80 bpm at rest, 90-115 bpm at mod. exercise
  - Two mech. for rate control: slow conduction or ↑ refractoriness of AV node.
  - **CCB**: more effective than placebo or digoxin at reducing vent. rate at rest and exercise. Use w/ caution in HF patients (dilt. appears safer). IV admin. results in rapid HR reduction (4-5 min)
    - *Diltiazem* dose: bolus: 0.25mg/kg IV over 2 min, if poor response at 15 min, repeat 0.35 mg/kg IV. Maintenance: 5-15mg/hr
    - *Verapamil* dose (not used much): Bolus: 5-10 mg IV over 2 min, Maintenance: 5-10mg/hr. Causes more hypotension.
  - **Beta Blockers**: best results in trials w/ metoprolol & atenolol. Improve resting/exercise HR. First choice in states of high adrenergic tone and lone a-fib.
    - *Metoprolol* dose: (5-10 min onset, duration 2-4 h) bolus: 2.5-5mg (1mg/min) up to 3 doses. Maint: PO 25-100mg BID
    - *Esmolol*: (2-5 min onset, duration 20-30 min) Bolus: 0.5 mg/kg IV over 1 min. Maint: 50-300mcg/kg/min continuous infusion w/ boluses between increases
    - *Propranolol*: Bolus: 0.5-1mg IV q 2 min (up to 0.15mg/kg). Maint: 0.04mg/kg/min IV or 10-120 mg TID po.
  - **Digoxin**: no longer 1st line. Slow onset >2hr. Full control (HR<100) in 24-48hrs. Only effective at rest. Useful for HF pts.
    - Load: 10-15mcg/kg LBW up to 1-1.5mg (usual dose 1mg with 0.5 mg initially, then 0.25mg q6h).
    - Maint: 0.125-0.25mg/day (adjust for renal).
  - **Amiodarone**: antiarrythmic, but slows conduction thru AV node

- Cardioversion
  - **Goal:** restore NSR. Must address reversible CV & non-CV precipitants of a-fib first. Normally not indicated in pts w/ A fib >1yr or in pts w/ large atrial size. Best pts: symptomatic A-fib & pts w/ low chance of reoccurrence
  - **Antiarrythmic**: low dose amiodarone drug of choice: Load 800mg/day for 1 week, then 400mg/day for 1 month, then maint. OR 600-800mg/day until 10g total then maint. Maintenance dose: 100-200 mg/day
    - 2nd line: sotalol or dofetilide
    - Flecainide & propafenone 1st line for pts w/ no evidence of organic heart disease.

  **NEVER give type Ia or III antiarrythmics alone to pts with A fib. w/o an AV blocker on board—you will incr. vent. rate. (amiodarone is exception).

  - **Electrical conversion**: quick & effective. Restores NSR in 85-90%. Failure/immediate recurrences in 25% and another 25% have recurrence in 2 weeks. Requires

general anesthesia (versed or fentanyl). May repeat in combo w/ antiarrhythmics.
    - **Safe elec. conversion**: 1) ensure adequate anticoag (INR 2-3) for 3 weeks prior to cardioversion and 4 weeks afterwards. 2) If within 48 hours can perform Trans-esophageal echocardiogram (TEE) which permits the visualization of valves and atria to assess presence of thrombi. Recommend IV heparin or LMWH at presentation.
- Stroke prevention: Risk of stroke with no therapy (4.5-5%), aspirin (4%), warfarin (INR 2-3) (1.4%). Overall A-fib accounts for 15% of all strokes in the US. Everyone should be on anticoag unless they have a true contraindication to warfarin or are non-compliant. Warfarin/ASA should be continued until sinus rhythm has been maintained for at least 4 weeks. Continue indefinitely in pts w/ perm. A fib or documented recurrent paroxysms.

Atrial Flutter
- Similar to A fib in precipitating factors, consequences, drug therapies but less common.
- 300 atrial bpm, HR is 300, 150, 100, 75, or 60 bpm.
- Regular rhythm, saw tooth pattern from atrial waves on ECG

Paroxysmal Supraventricular Tachycardia
- Can be transient or prolonged. Caused by reentrant mechanisms, usually AV node re-entry or AV re-entry (anomalous AV pathway). Can also be caused by SA node re-entry or intra-atrial re-entry.
- Presentation: sudden onset & termination. HR 180-200 bpm.
- Symptoms: Palpitations, nervousness, anxiety, dizziness, syncope, maybe shock
- Treatment for PSVT:
    - Valsalva maneuver (like bearing down for a bowel movement)
        - Results in ↓ sympathetic tone and ↑ vagal tone which ↑ refractoriness & slows conduction in AV node.
        - Terminates PSVT 10-30%.
    - Adenosine is drug of choice.
        - Negative chronotrope & slows conduction thru nodal tissue.
        - Rapid, brief effect.
        - 6mg IV bolus over 1-3 secs, wait 2 min & repeat w/ 12 mg IV bolus (max 30mg). Follow each dose w/ saline flush because drug degrades quickly
    - 2nd line is diltiazem (85% conversion rate).
        - Verapamil should be avoided in wide complex tachycardia (WPW)
    - 3rd line is beta blocker or digoxin
- Long-term treatment of PSVT
    - Goal: slow conduction and ↑ refractoriness of AV node.
    - Use verapamil, diltiazem, BB, digoxin.
    - If conduction pathway identified can use radiofrequency catheter ablation which prevents recurrence in 85-98%.

Ventricular Arrhythmias

- Arise from ectopic foci in vent. myocardium leading to premature vent. complexes (PVCs). Frequent PVCs can lead to sudden cardiac death.
- Don't treat asymptomatic PVCs w/ antiarrhythmics
- Only beta blockers have been shown to prevent mortality.
- Causes: organic heart dz, exercise, ischemia, metabolic/electrolyte imbalance, drugs (dig tox)

Ventricular Tachycardia

- Classifications
  - Nonsustained VT: ≥3 consecutive PVCs in <30 sec. Rate ≥100bpm. Stops spontaneously.
  - Sustained VT: Consecutive PVCs >30 sec. Rate 150-200 bpm. P waves indiscernible. Can degenerate into V-fib (no effective CO).
  - Monomorphic VT: consistent QRS configuration
  - Polymorphic VT: varying QRS (unstable or Torsades(wide QRS))
- Acute Treatment
  - Severe symptoms: Direct Current Cardioversion.
    - If transient initiating factor (MI, dig tox) then no long-term antiarrythmic.
  - Mild symptoms: IV amiodarone: 150mg IV push over 10 min, then 1mg/min for 6 hours then 0.5 mg/min infusion.
    - Have DCC readily available.
    - May need Transvenous Pacing.
- Long Term Treatment: Implantable Cardioverter-Defibrillator
  - *Indications* for ICD: **1)** Recurrent VT or VF. **2)** Pts resuscitated from cardiac arrest due to unidentifiable/irreversible cause. **3)** Syncope w/ sustained VT/VF induced at electrophysiologic study by programmed stimulation. **4)** NSVT, CAD (remote MI), LV dysfunction and sustained VT/VF induced at electrophysiologic study by programmed stimulation. **5)** Heritable polymorphic VT. **6)** Severe LV dysfunction (EV<30%) and remote MI
  - Antiarrhythmics are added to ICD to prevent shocks and prolong battery. Amiodarone is 1st line, sotalol is 2nd line.
- Treatment of NSVT
  - Conservative: beta blocker
  - Empiric: amiodarone.
  - Aggressive: Electrophysiologic studies +/- ICD.

Ventricular Proarrhythmia

- Drug induced (new or worsening arrhythmia).
  - Ex. Quinindine induced Torsades

Torsades De Pointes

- Risk factors: female, hypokalemia/hypomagnesemia. HF/LV dysfunction, ischemic heart disease, anorexia/liquid protein diets, neurological injury
- CV drug causes:
  - Class Ia (quinidine, procainamide, disopyramide)
  - Class III (dofetilide, ibutilide, sotalol, amiodarone (lowest risk – 1%)
  - CCB (bepridil)
  - Diuretics (via electrolyte depletion).

- Non-CV drug causes:
  - Psychotropics (Haldol, phenothiazines, TCAs)
  - -azole antifungals (inhibit metabolism of other agents)
  - Antibiotics (EES, biaxin, amantadine, septra, quinolones)
- Torsades prevention:
  - Avoid certain drugs and drug interactions in patients with prolonged QT interval
  - Maintain normal K+ and Mg+ levels
  - Torsades treatment: recognition of arrhythmia, d/c offending agent, correct electrolytes, DCC if unstable.
  - Drug of choice is IV magnesium 2 grams.
    - Other options include temporary transvenous pacing, isoproterenol, or epinephrine.

Ventricular Fibrillation

- Non-perfusing rhythm (no pulse), not conducive to life.
- Goal is to resuscitate and keep neurologically intact
  - CPR and defibrillation

**The longer in V Fib, the greater the chance of asystole.

BIPOLAR DISORDERS
Adapted from Clarke St. Dennis, PhD, BCPP

Resources
- DBSA Mood Disorder Questionnaire
  http://www.dbsalliance.org/questionnaire/screening_intro.asp

Background
- Highly individual disorders involving mania or hypomania that are difficult to treat and even harder to diagnose
- Usually diagnosed after antidepressant failure, substance abuse, or antidepressant-induced hypomania/mania
- Lifetime suicide risk ~20% with ~50% attempting sometime

Always treat bipolarism first if CC mental illness because suicide potential

Spectrum of Bipolar Disorders
- Mania
  - Need abnormally high or irritable mood for >1 week
  - Signs/symptoms (need >3 or >4 if irritable mood)
    - Inflated self-esteem
    - Decreased need for sleep
    - Pressured speech
    - Flight of Ideas
    - Distractibility
    - Increased goal-directed activity/psychomotor agitation
    - Excessive involvement in high-risk activities
- Hypomania: like mania, but only need symptoms for 4 days
  - Uncharacteristic change in functioning, observable by others, but doesn't impair functioning; no psychosis
- Mixed Episodes
  - Manic episode + major depressive disorder
  - Highest rate of suicide of any mental disorder
  - Big concern with unprotected antidepressant
    - Must use DBSA mood disorder questionnaire to screen for bipolarism before starting AD

Bipolar Types
- Bipolar I: at least one manic episode ± depression
- Bipolar II: recurrent major depressive episodes with at least one hypomanic episode—no major manic or mixed episode
- Cyclothymia: recurrent hypomania with minor depression for at least 2 years in adults (1 year in kids/adolescents)

Bipolar Descriptors
- Rapid cycling: at least 4 episodes in last 12 mo
- Seasonal pattern: depression in fall or winter regularly
- Post-partum onset: start mood stabilizer right after birth

Monotherapies for Bipolarism
- Lithium
  - Approved for acute mania and maintenance
  - Works best for Bipolar I, not as useful for Bipolar II, mixed episode, substance abuse, juvenile onset bipolar
  - Kinetics
    - Therapeutic range usually 0.5-1.5 mEq/L
    - ↑ dose 300 mg, ↑ levels 0.2-0.4 mEq/L
    - Treat for response first, then blood levels

        - Excretion influence by renal function, sodium levels
        - ~7 days to reach steady state
        - Draw levels 12 hrs after last dose
    - Take with food and water for GI side effects
    - SE: tremor, loose stools, fatigue, polydipsia/uria, anorexia, muscle weakness, confusion, thyroid
    - Toxicity: Slurred speech, stupor, coarse tremor, arrythmias, anuria, coma, seizure, death
    - Get ECG, CBC, SCr, thyroid, BMP before starting
    - Interactions: diuretics, NSAIDs
- Divalproex
    - More effective than lithium for Bipolar II, mixed episodes, rapid cycling, substance abuse, head trauma
    - Serum levels not useful: but aim for 125-150
    - Always taper off if need to D/C
    - SE: liver failure, pancreatitis, hair loss, sedation, tremor, confusion, rash, thrombocytopenia, teratogen
    - Monitor: thyroid, BMP, CBC, LFTs, lipids, BG q 3-6 mo
- Carbamazepine
    - Slow dose titration because more CNS effects than divalproex
    - Hepatic inducer (esp. 3A4) including own metabolism—check levels 4-6 wks after starting
    - Black box like divalproex for pancreatitis
- Lamotrigine
    - Useful in rapid-cycling disorders and bipolar depression for maintenance
    - Not useful for acute mania
    - Must follow package insert titration to avoid Stevens-Johnson and TEN
- Atypical antipsychotics

Useful Adjuvant Therapies

**most patients require two or more therapies

- Atypical antipsychotics
    - If lithium or divalproex not effective, add atypical
    - Especially useful if using SSRI to prevent mania
- Gabapentin/pregabalin
    - mostly for sleep, anxiety, neuropathy in bipolar
- Topiramate
    - Must draw bicarb level to avoid non-anionic hyperchloremic acidosis (it's a mild carbonic anhydrase inhibitor)
    - Very sedating—requires slow titration
    - Weight loss only at high doses (with many SE)
- Tiagabine, zonisamide, levetiracetam likely not effective or too dangerous to use

Bipolar Indications

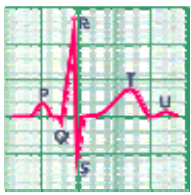
Drug	Acute Mania Monotherapy	Acute Mania Co-Therapy (w/ Lithium or Divalproex)	Maintenance of Mania	Bipolar Depression
Chlorpromazine (Thorazine®)	Yes			
Lithium	Yes	Yes	Yes	
Divalproex (Depakote® and Depakote ER®)	Yes	Yes	Yes (off-label)	Yes
Carbamazepine (Tegretol®)	Yes		Yes (off-label)	
Olanzapine (Zyprexa®)	Yes	Yes	Yes	
Quetiapine (Seroquel®)	Yes	Yes	Soon	
Lamotrigine (Lamictal®)			Yes	Yes (mainly prophylaxis)
Fluoxetine/Olanzapine (Symbiax®)				Yes
Risperidone (Risperdal®)	Yes	Yes		
Aripirazole (Abilify®)	Yes		Yes	
Ziprasidone (Geodon®)	Yes			

*Depakote appears more effective than lithium for several types of bipolar spectrum disorders

CARDIAC CONDUCTION
Adapted from Jason Brouillard, PharmD

Cardiac Conduction System

- *Sinoatrial Node*: located in upper right atrium, primary pacemaker, fastest automaticity (60-100 bpm) (automaticity means can depolarize spontaneously)
- *Atrioventricular Node*: located near tricuspid valve, 2° pacemaker if SA fails (40-60 bpm). Slows conduction of impulse from atria.
- *Bundle of His*: Located between tricuspid and mitral valve. Divides into right and left branches
- *Purkinje Fibers*: At the end of right and left bundles. Carries impulse to ventricular muscle cells. Automaticity 15-40 bpm



Normal PQRST Complex

EKG Components

- *P wave:* represents depolarization (contraction) of both atria
- *PR interval:* represents AV conduction time (filling time)
  - Normally 0.12-0.20 sec. If longer may indicate AV block.
- *QRS*: depolarization of ventricles (normal is 0.06-0.10 sec)
  - *Q wave*: first negative deflection from baseline
  - *R wave*: first positive deflection from baseline
  - *S wave*: negative deflection following R wave
- *QT interval:* duration of ventricular systole
  - Normally 0.30-0.45 sec
- *T wave*: ventricular repolarization (resting period).
  - Wave goes opposite of depolarization wave
  - Peaked T wave indicates hyperkalemia
  - Inverted T wave indicates MI or ischemia
- *ST segment*: time between ventricular depolarization and repolarization.
  - Elevation/depression indicates myocardial injury/ischemia
  - Causes of ST segment or T wave changes
    - Electrolyte abnormalities
    - Post-cardiac surgical state
    - Acidosis or alkalosis
    - Anemia
    - Fever
    - Catecholamines
- *U wave*: small, smooth hump sometimes following the T wave. If there may be normal or may indicate hypokalemia

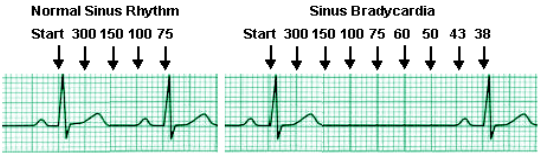
Determining if Rhythm is Normal

- Is the HR fast (>100 bpm is tachy) or slow (<60bpm is brady)?
- Are the RR intervals evenly spaced?
- Do P waves look normal, 1:1 with QRS's?
- Is QRS complex widened?
- Is PR interval shortened or lengthend?
- Is the ST segment elevated?

Grid method for HR

If the peaks are regular, the HR can be estimated using the EKG grid. To do this, locate a QRS complex on a bold line. If the next QRS complex is separated by:

i. One large box, the heart rate is 300 BPM (300/1)
ii. Two large boxes, the heart rate is 150 BPM (300/2)
iii. Three large boxes, the heart rate is 100 BPM (300/3)
iv. Four large boxes, the heart rate is 75 BPM (300/4) ...and so on.

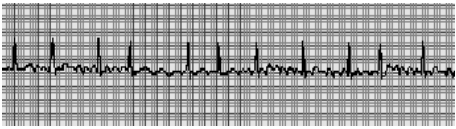


Wolfe-Parkinson-White

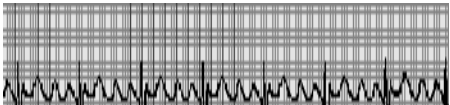
- Accessory conduction pathway bypasses AV node and directly connects atria and ventricles
- EKG shows shortened PR interval (widened QRS) and extra bump (delta wave) due to pre-excitation
- Rare: 0.15 - 0.25% in gen. population
- Some experience severe palpitations / tachycardia. Only treat patients w/ symptoms
- Treatment: catheter ablation of accessory pathway.
- Risk of sudden cardiac death in asymptomatic pts is 1 in 1000 patient years.
- *Avoid* Beta Blockers, Calcium Channel Blockers, Adenosine, digoxin because unchecked accessory pathway conduction can occur if you block AV node. Use of adenosine can aid in diagnosing WPW.

Arrythmia Patterns

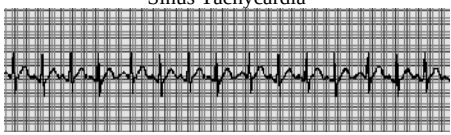
Atrial Fibrillation



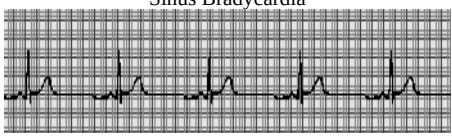
Atrial Flutter



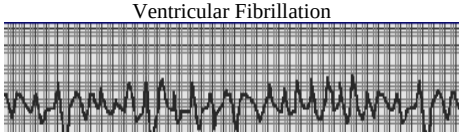
Sinus Tachycardia



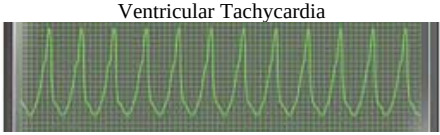
Sinus Bradycardia



Ventricular Fibrillation



Ventricular Tachycardia



Torsades de Pointes

DEPRESSION
Adapted from Clarke St. Dennis, PhD, BCPP

Resources
- NAMI website for childhood depression and black box warnings: www.ParentsMedGuide.org.

Risk Factors for Depression
- Gender: women 2x more likely than men
- Age: peaks at 20-40 yo
- Family History: 1.5-3x risk
- Marital status
  - Higher risk if separated/divorced
  - Married women more likely than single
  - Single men more likely than married
- Early parental death
- Postpartum within 6 months of delivery
- Negative life events

Epidemiology
- If 1 episode of depression: ~50% chance of recurrence
- If 3 episodes of depression: >95% chance of recurrence
- ~15% of recurrent depressives successfully commit suicide

Diagnosis of Major Depressive Episode
- Five or more of the following symptoms present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (a) depressed mood or (b) loss of interest or pleasure.
  - Depressed mood most of the day nearly everyday
  - Diminished interest or pleasure in all, or almost all, activities, nearly everyday.
  - Significant weight loss when not dieting or weight gain (5% change from baseline in one month).
  - Insomnia or hypersomnia, nearly everyday
  - Psychomotor agitation or retardation, nearly everyday.
  - Fatigue or loss of energy, nearly everyday.
  - Feelings of worthlessness or excessive/inappropriate guilt, nearly everyday.
  - Diminished ability to think or concentrate or indecisiveness, nearly everyday.
  - Recurrent thoughts of death, recurrent suicidal ideation without plan, or suicide attempts, or specific plans of committing suicide.
- Symptoms don't meet criteria for mixed episode (mania and depression)
- Symptoms cause significant distress or impairment. Required for diagnosis.
- Symptoms not due to substance or general medical condition like diabetes, MI, or stroke.
- Symptoms not explained by bereavement—greater than 2 months since loss

Treatment Options for Depression
- Counseling (cognitive behavioral therapy)
- Medications
- Support groups
- Diet/exercise
- Electro-convulsive therapy, vagal stimulation

**counseling + medications = additive benefit

Evaluating Therapy Effectiveness
- Response = 50% reduction in HamD or MADRS score during 6-8 week trial—industry standard for drug approval
- Remission = HamD ≤ 7 or MADRS ≤ 10—clinical standard

Monoamine Oxidase Inhibitors
- Irreversible MAO A and B Inhibitors:
  - Available agents = Tranylcypromine (Parnate®) and phenelzine (Nardil®)
  - Drug interactions = sympathomimetics, meperidine (possibly fatal), tyramine rich foods
  - Used for =*refractory* or *atypical* depression; panic disorder; phobias
  - SE = weight gain, orthostatic hypotension, sexual dysfunction.
- Reversible Type B MAOIs
  - Selegiline (Eldepryl®) and Emsam® (patch-form)
  - Used in Parkinsonism @ doses of 5-10 mg /day
  - High doses = antidepressant (same problems as tranylcypromine and phenelzine)

Tricyclic Antidepressants
- *TCA Advantages:*
  - Neuropathic pain = Requires NE (superior to SSRIs)
  - Hypnotics = Esp. amitriptyline, sinequan (H1 blockers)
  - Generic/cheap, but studies say higher total costs
  - Biphasic = higher remission than SSRIs
    - NERIs and SSRIs: imipramine, amitriptyline, doxepin
    - NERIs: desipramine, nortriptyline, protriptyline, maprotiline
    - SSRIs: clomipramine
- *TCA Disadvantages*
  - Sodium channel blockers = effect on heart rhythm
  - 10-14 day supply can be lethal
  - Interact with alcohol, and 2D6 inhibition can be lethal
  - Triad of receptor blocking effects:
    - M-1 blockade = Anti-cholinergic side effects
    - Alpha-1 blockade = Anti-adrenergic side effects
    - H-1 blockade = Anti-histaminic side effects

SSRIs
- Trazadone (Desyrel®) = SSRI, H-1 blocker, 5HT2 blocker, M-1 blocker, alpha 1 and 2 blocker
  - Less anti-cholinergic activity than TCAs
  - Sedating, used as hypnotic
  - Anti-adrenergic: α1= postural hypotension; α2 = priapism
- Celexa® = SSRI + H -1 blocker (20% sedation)
  - Relatively free of activation SEs and well tolerated
- Lexapro® = Most selective SSRI.
  - Little sedation (no H-1 effect)
  - 10 mg Lexapro® ~ 40 mg Celexa®
  - Minimal CYP inhibition, faster onset than Celexa®
- Prozac® = SSRI + 5HT2c antagonist (raises DA, NE)
  - Effective in eating disorders
  - High activation—most of SSRIs

    - Strong CYP2D6 inhibitor, mild-mod CYP 1A2, 3A4, 2C9/19 inhibitor
    - Longest t 1/2 (10d) of SSRIs
    - Weight neutral
    - Only AD for childhood depression or bulimia.
    - 1st AD indication for PMDD
- Zoloft® = SSRI + DARI+ Sigma opiate antagonist,
    - Improved cognition and lowest prolactin secretion of SSRIs because DARI
    - Less negative effect on sleep architecture and high rate of GI side effects because sigma antagonist
    - Moderate withdrawal risk—1/2 dose x 3 d to taper
    - Weight neutral
    - DOC for nursing moms, high functioning patients
- Paxil® = SSRI + M-1 Blockade + NERI + NO synth. inhibitor
    - STRONG 2D6 inhibition, moderate 1A2 inhibitor
    - NERI at high doses may help with anxiety
    - M-1 blockade impairs cognition
    - Most sexual dysfunction of SSRIs because NO synthetase inhibition
    - Most weight gain of SSRIs
    - Highest rate and most severe withdrawal of SSRIs
- Luvox® = SSRI + high sigma opiate blockade.
    - Most sedating of SSRIs.
    - Highest rate of GI ADRs among SSRIs
    - Strong 1A2 and 3A4 inhibition, mod. 2C9/19
    - Used for OCD mostly, and not depression

Atypical Antidepressants

- Venlafaxine (Effexor®, Effexor XR®) = SSRI, NERI, DARI
    - No Anti-cholinergic, alpha-1, or H-1 blocking effects and few CYP-450 interactions
    - SSRI <150 mg, NERI > 150mg, and DARI >300 mg/d
    - Higher remission rates than traditional SSRIs
    - SE: Nausea, dry mouth, constipation, sleepiness, nervousness, dizziness, sweating, asthenia, sexual dysfunction, sustained increases in diastolic B.P., withdrawal reactions severe.
    - Monitor BP—esp. >300 mg/day
    - Uses: severe refractory depression, neurologic pain control at 160 mg/day, anxiety disorders, and treatment of hot flashes secondary to tamoxifen
- Nefazadone (Serzone®) = SSRI, slight NERI, 5HT2 blocker
    - Advantages: anxiolytic effect, improved sleep architecture, sexual side effect incidence ~ placebo
    - Unique SE = blurred or abnormal vision (vapor trails)
    - FDA BLACK BOX WARNING 2002 - Potential for LIVER FAILURE
    - Indications: Agitated & refractory depression, mixed anxiety/depression, fibromyalgia, PTSD
    - BID dosing, usually get away with QD dosing HS
- Mirtazapine (Remeron®) = alpha-2 blocker (increases NE and 5HT release), H-1 blocker, 5HT2 and 5HT3 blocker
    - Efficacy: Equal to amitriptyline for depression and superior to placebo for anxiety.
    - Higher remission rates than traditional SSRIs
    - SE: somnolence (68%), wt. gain (32%), dry mouth (18%), and constipation (14%)

    - Increasing dose up to 60 mg/day early in therapy may DECREASE sedation or wt. gain.
        - Being used as sleeper drug at the 7.5 mg dose
    - Indications: Agitated or refractory depression, fibromyalgia, good for pts. with GI problems
- Bupropion (Welbutrin® products / Zyban®) = NERI and DARI
    - ADRs: highly activating (to point of stimulation). Seizure potential (less with SR dosage form).
    - Absolute contraindication with history of seizures.
    - Mild drug interaction potential.
    - Indications: Retarded and refractory depression, augmentation with SSRIs (for sexual dysfunction), ADHD, smoking cessation (Zyban®), and weight loss possible.
- Duloxetine (Cymbalta®) = 60/40 SSRI:NERI
    - Indications: Depression, 1st to get IND for diabetic pain, IND for stress incontinence, trials for fibromyalgia.
    - SE: Similar to Effexor® = nausea (start at 20-30 mg/day, then increase), less sexual dysfunction, high withdrawal potential, avoid in hepatic insufficiency, may worsen liver disease.
    - Drug interactions: Substrate for 1A2 and modestly for 2D6. Mild 1A2 & moderate 2D6 inhibitor.

Adverse Effects of SSRIs and Other Antidepressants

- CNS side effects
    - Sedation, activation / sleep issues (caution with fibromyalgia patients)—usually resolve in 4-6 weeks
    - Headache usually goes away in 1-2 weeks
    - Withdrawal reactions: Paxil=Effexor>>Luvox>Zoloft>Lexapro>>Prozac
    - Tremor and EPS with SSRIs
- GI Side effects = 2nd highest ADR in SSRIs (20-40%)
    - Dose-related. Effect can be immediate. Luvox® > Zoloft® for highest GI distress
    - Usually resolves in 1-2 weeks
- Sexual dysfunction (30-75% incidence).
    - Worst with Paxil!
    - May not resolve with time
    - Treatment
        - lower dose / ride it out (not recommended)
        - switch to AD less likely to cause
        - Welbutrin®, Serzone®, Remeron® have no more incidence than placebo.
        - Add therapies to counter-act sexual dysfunction (i.e. add on Welbutrin® or Viagra®)
        - Rhythmic methods (not recommended)
- Pregnancy
    - All category C and all secreted in breast milk. Zoloft® is drug of choice for moms.

Activation Among Antidepressants

Prozac > Zoloft > Paxil < Lexapro < Celexa <Luvox
(Activating) (Sedating)
Welbutrin > Effexor/Cymbalta << Serzone Remeron

Treating Refractory Depression

- Switch to biphasic antidepressant first (venlafaxine, TCA, sertraline, MAOI, mirtazapine)

- Most common and best studied additions
  - Lithium = most predictable, but insurance may not cover
  - Also: thyroid products (T3 - Cytomil®); stimulants like Ritalin®, Dexedrine®, or Adderall®; buspirone (Buspar®) - good for highly anxious patient, pindolol - works well to speed up onset.
- Potential augmentation strategies:
  - AD combos (SSRI + Welbutrin® most studied)
  - *Atypical anti-psychotics = increasingly popular! May even be used in depression alone. I.e. Seroquel®.
  - Also: Other DA agonists like pramipexole and amantadine, estrogen for peri- or post-menopausal women (now less common), testosterone for refractory depression in men, glucocorticoid synthesis inhibitors like ketoconazole not recommended, and mood stabilizers like Lithium.

TYPE II DIABETES MELLITUS
Adapted from R. Keith Campbell, RPh, CDE

ADA Standards of Care

Physician Visits	2-4 per year
A1C	2-4 per year
FBG	4-6 per year
Foot Exams	Every Visit
Urine Protein	Yearly
Lipid Panel	As needed to control
BP	As needed to control
Dilated Pupil	Yearly
Flu, pneumococcal vaccine	As needed

98% of diabetic patients not meeting standards

Diabetes Targets by ADA and AACE

	American Diabetes Association	American Association of Clinical Endocrinologists
Target HbA1c	< 7%	< 6.5%
Target Fasting Glucose	< 90-130 mg/dL	< 110 mg/dL
Peak PPG	< 180 mg/dL	< 140 mg/dL
When to screen	> 45 yo	> 30 yo

AACE = American Assoc. of Clinical Endocrinologists
ADA= American Diabetes Association

Lipid/Blood Pressure Goals from NCEP and JNCVII
TC: < 200 mg/dL
LDL: < 100 mg/dL
TG: < 150 mg/dL
HDL: > 45 mg/dL
BP: < 130/80 mmHg

HbA1c Relation to Average Blood Glucose

HbA1c %	Blood Glucose (mg/dl)
6	135
7	170
8	205
9	240
10	275
11	310

Signs of Hypoglycemia
- Sudden Onset
- Staggering, Poor Coordination
- Anger, Bad Temper, irritability
- Pale Color
- Confusion, Disorientation
- Sudden Hunger
- Sweating
- Eventual Stupor or Unconsciousness

Signs of Hyperglycemia:
- Gradual Onset
- Drowsiness

- Extreme thirst
- Very Frequent Urination
- Flushed Skin
- Vomiting
- Fruity or Wine-Like Breath (due to ketones)
- Heavy Breathing
- Eventual Stupor or Unconsciousness

Foot Care:
4 mechanical ways to damage feet: direct injury, ischemia, repetitive stress, and infection

1. Inspect feet daily for blisters, infections & cuts.
2. Keep feet clean. Wash daily with warm water (NOT HOT). Dry especially between toes.
3. Cut toenails straight across. Talk to doctor about how to treat corns or calluses. Don't treat w/ chemicals.
4. Avoid exposing your feet to extreme hot or cold.
5. Avoid walking barefoot.
6. Wear properly fitted clean socks or stockings.
7. Shoes must be properly fitted.
8. Do not apply hot water bottles or heating pads to your feet if they feel cold.
9. Avoid smoking.
10. Do not cross your legs.

Have feet checked by physician at every visit; patient should examine daily and report any changes immediately.

Diabetic Ketoacidosis

- Common DKA Findings:
  - Elevated BG: 250-600 mg/dL
  - Dehydration
  - Hypotension
  - N/V
  - Acetone breath
  - Rapid shallow breaths
  - Polyuria (initially)
  - Hyperkalemia
  - Low serum pH
- Treatment of DKA:
  1. Fluid replacement with NS or 1/2NS.
  2. Electrolyte replacement especially potassium; Bicarbonate and phosphate replace if indicated.
  3. Regular insulin SQ (10-20% of total daily dose). In children 0.25-0.5 units/kg q4-6h.
  4. Regular insulin IV is used in more serious cases (bolus = 0.1 units/kg, drip = 0.1 units/kg/hr). SQ insulin can be started as hyperglycemia corrects (250-300 mg/dL) and pH rises above 7.2.
  5. Vigilant monitoring of vital signs & cardiac activity.
  6. ECG indicates for all adults.

Chronic Complications of Diabetes:

- Accelerated macrovascular diseases
- Retinopathy
- Nephropathy
- Dermopathy
- Neuropathy
- Diabetic foot problems
- Gastropathy
- Erectile dysfunction
- Peripheral painful neuropathy

How Excess Glucose Causes Complications

- Basement membrane thickening
- Advanced glycosylated end products
- The polyol pathway; Increased aldose reductase
- Increased Protein Kinase C
- Coagulation disorders
- Macrovascular problems
- Oxidative stress resulting in increased levels of ROS
- Faulty lipid metabolism yields hypercholesterolemia and hypertriglyceridemia
- Impairment of phagocytosis (affects ability to fight infection)
- Increased neonatal morbidity and mortality
- Increased BP, Coronary Artery Disease, and weight
- Increased incidence of cataracts, glaucoma, gum disease, and dental cavities
- Many hemorrheologic factors affected adversely

Treatment for complications:

- Neuropathy: normalized BG, Capsaicin, Neurontin, Cymbalta, Lyrica, preventive foot care
- Retinopathy: normalized BG and BP, annually dilated pupil eye exams, laser therapy and vitrectomy if needed.
- Nephropathy: normalized BG, assess serum creatinine and urine proteins, ACE inhibitors
- Cardiovascular diseases: normalize BG, Statins, niacin, Lopid, Zetia, ACEIs, ARBs, diuretics, ASA, diet, and exercise.
- Other drugs: NSAIDs, Vitamin C, D, and E, beta-carotene, zinc, selenium, alpha-lipoic acid, Coenzyme C-Q10, folic acid, B vitamins, Chromium, Calcium, Magnesium, Reglan, PPI, antacids, Trental, Cialis, and caution with use of Beta blockers and Calcium blockers
- Future Medications: PKC-inhibitors, Pulmonary Insulin, and Rimonabant

Treatment Options for Type II Diabetes

- Start first with oral medications then add insulin and/ or incretins later on.
- Oral meds include: metformin (1st med to use), sulfonylureas, thiazolidinediones, meglitinides, and alpha glucosidase inhibitors.
- Combination Therapy Regimens in Type 2 Diabetes:
  - Usual Patient: secretagogue + insulin sensitizer
  - Initially most simple and cost-effective:
    - Low-dose, once daily sulfonylurea and metformin
    - Full-dose, once daily sulfonylurea and metformin
  - For marked insulin resistance: metformin + glitazone
  - If target A1c<7% not achieved: try triple therapy or add basal insulin with oral therapy

Therapeutic Options for Managing Type 2 Diabetes:

- Affect postprandial glucose and HbA1c
  - Insulin/insulin analogs
  - Alpha-glucosidase inhibitors (AGI)
  - Meglitinides
  - Exenatide or pramlintide
- Affect fasting glucose and HbA1c
  - Sulfonylureas
  - Biguanides

    - Thiazolidinediones
    - Basal Insulins

Treating the metabolic Syndrome:

- Stop smoking
- Eat less
- Take magnesium
- Take aspirin
- Take and ACEI or and ARB
- Take a statin
- Take pioglitazone, metformin, rimonabant to reduce insulin resistance

Contraindications to the Oral Hypoglycemics:

- Sulfonylureas:
    - Type 1 diabetes
    - Pregnancy or lactation
    - Severe renal or liver disease
    - Stressful concurrent conditions
    - Diabetic ketoacidosis
    - Sulfonylurea allergy
    - Note: Use chlorpropamide cautiously in elderly or patients with renal insufficiency
- Meglitinides:
    - Type 1 diabetes
    - Pregnancy or lactation
    - Stressful concurrent condition (e.g. severe infection or surgery)
    - Diabetic ketoacidosis
    - Use caution in: Patients with liver damage, elderly or debilitated patients
- Metformin:
    - Pregnancy
    - Congestive heart failure
    - Hepatic dysfunction
    - History of alcohol abuse or binge drinking
    - Tissue hypoxia (e.g., acute MI, dye tests)
    - Renal dysfunction
    - Serum creatinine greater than or equal to 1.5 mg/dl in men
    - Serum creatinine greater than or equal to 1.4 mg/dl in women
    - Age >80 years (without adequate renal function or creatinine clearance
- Alpha-Glucosidase Inhibitors:
    - Cirrhosis
    - GI disease: IBD, colonic ulceration, partial intestinal obstruction or risk of obstruction
    - Pregnancy or lactation
    - Creatinine clearance <25 ml/min
    - Serum creatinine >2 mg/dl
    - Warnings (acarbose): Elevated serum transaminase levels (AST and/or ALT); effect is dose related >100mg TID
- Thiazolidinediones:
    - Pregnancy or lactation
    - Heart failure (NYHA Class III and IV)

- Hepatic dysfunction (use with caution), monitor liver enzymes; discontinue if ALT levels >3 times upper limit of normal

New Diabetic Medications:

- Exenatide (Byetta ®)
  - New class of antidiabetic medications called Incretin mimetics, similar to endogenous glucagon-like peptide 1 (GLP-1)
  - Subcutaneous injection used to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea
  - No dose adjustment needed with metformin alone, however the sulfonylurea dose needs to do reduced by approx. 50% to decrease risk of hypoglycemia
  - Exenatide mimics the enhancement of glucose-dependent insulin secretion and other antihyperglycemic actions of incretins.
  - Simple to initiate, convenient fixed-dose pens
  - Initially 5 mcg SC twice daily, can increase to 10 mcg twice daily if needed for glycemic control
  - Most common adverse effects: hypoglycemia (esp. with sulfonylureas) and dose-related nausea
  - Renally excreted, do not use with CrCl< 30ml/min
- Rimonabant (Acomplia®)
  - First antagonist of the cannabinoid type 1 (CB1) receptor helps normalize endocannabinoid system.
  - EC system plays a key role in energy balance, glucose and lipid metabolism, tobacco dependence, both centrally and peripherally.
  - Looking for indication to modify 4 CV risk factors: smoking dependency, obesity, dyslipidemia, and insulin resistance.
  - Appears effective in tobacco cessation
  - Significantly reduces weight and insulin resistance
  - Improves waist circumference, HDL-C, and triglycerides
  - Proposed dose: 20mg/day by mouth
  - Well tolerated with an acceptable safety profile
- Ruboxistaurin (Arxxant®)
  - In Phase III trials for treatment DR/DME
  - PKC-ß inhibitor that slows progression of pre-proliferative to proliferative diabetic retinopathy
  - Being studied to treat underlying cause of DR/DME (hyperglycemia-induced microvascular dysfunction) rather than treating the symptoms
  - Shown to block hyperglycemia-induced expression of VEGF at multiple points along the pathway
  - Results in ameliorating effect on diabetes-induced vascular complications

Oral Antidiabetic Medications				
		MOA	DOSING	SIDE EFFECTS
Second Generation Sulfonylureas				
Glimepiride	Amaryl® SAFE FOR ELDERS	Stimulates the release of insulin from pancreatic beta cells. Glimepiride: less weight gain, greater extra-pancreatic effect, selective effects on K_{ATP} channels in the heart, less hypoglycemia. Glipizide: less hypoglycemia.	1-2mg QD; Max dose of 8mg/day. Freq: once/day; Duration: 24 hrs	Hypoglycemia, GI, blood dyscrasias, cholestatic jaundice, elevated LFTs, blurred vision, disulfiram reaction
Glipizide	Glucotrol®, Glucotrol XL® SAFE FOR ELDERS		5mg QD; Max dose of 40mg/day (divided) Freq: 1-2 times/day; Duration: 12-24 Hrs	Weight gain, hypoglycemia GI, dermatological, blood dyscrasias, cholestatic jaundice, disulfiram reaction
Glyburide	Diabeta®, Micronase®, Glynase®(micronized) DiaBetic®(Canada)		2.5-5mg QD; Max dose of 20mg/day. Freq: 1-2 times/day; Duration: 12-24 Hrs Glynase®: 1.5-3mg QD; Max dose 12mg/day	Weight gain, hypoglycemia GI, visual changes, blood dyscrasias, hyponatremia, cholestatic jaundice, hepatitis

		MOA	DOSING	SIDE EFFECTS
Alpha-glucosidase Inhibitor				
Acarbose	Precose®	Competitive and reversible inhibition of intestinal alpha-glucosidases and less effect on pancreatic alpha-amylase resulting in delayed carbohydrate digestion and abs; reducing postprandial hyperglycemia	25mg TID with first bite of food of each main meal; titrate every 4-8 weeks to a maintenance dose of 50-100mg TID. Max doses: ≤60kg: 50mg TID or ≥60kg: 100mg TID	GI, most common during initiation of drug, flatulence, diarrhea, and abdominal pain; increase in LFTs
Miglitol	Glyset®		25 mg TID with first bite of food of each main meal; titrate over 4-8 weeks up to maintenance dose of 50-100 mg TID. If not at A_{1c} goal in 3 mos., titrate up to 100 mg TID. Max dose: 100 mg TID	GI *For both drugs slower dose titration and 25 mg once daily dosing minimizes GI side effects

		MOA	DOSING	SIDE EFFECTS
Biguanide				
Metformin	Glucophage® / Glucophage XR®/ Fortamet®/ Glumetza® Riomet® 100 mg/ml	Improves insulin sensitivity by reducing insulin resistance: decreases hepatic glucose production, increases peripheral insulin uptake, and decreases intestinal abs of glucose-minor effect MONITOR RENAL FUNCTION	Initially start with small dose (500mg) for less GI problems; then 500mg BID or 850mg QD; titrate up 500mg weekly to a or 850mg every two weeks to a max dose of 2550mg/day (2000mg/day effective max dose, less SEs and same benefit)	GI-related complaints (diarrhea, nausea, vomiting), lactic acidosis (serious, but rare event), unpleasant or metallic taste, reduction in serum vitamin B12 (rarely associated with anemia) *Improves Lipid panel: decreased triglycerides, and LDL-C *May aide in weight reduction or maintenance; usually does not cause hypoglycemia

		MOA	DOSING	SIDE EFFECTS
Thiazolidinediones				
Pioglitazone	Actos® *Glitazone of Choice	Directly reduces insulin resistance by activating PPAR-gamma nuclear receptors; increase glucose uptake in skeletal muscle and fat cells and lowers hepatic glucose output. CV effects independent of glycemic control. No risk of hypoglycemia when used alone.	Use as monotherapy or in combo with metformin, sulfonylurea, or insulin. Initially 15 or 30mg; Max of 45 mg QD (45 mg usually only used in monotherapy)	Weight gain, edema, fluid retention, anemia, slightly increased LDL, increased hepatic enzymes, N/V, abd pain Positive effect on lipid profile: increased HDL, decrease in TG and small dense LDL. Always once daily dosing
Rosiglitazone	Avandia®		Use as monotherapy or in combo with metformin, sulfonylurea, or insulin. Initially 2mg or 4mg QD, if not at goal titrate to 4 mg BID or 8mg QD after 3 months (40% of patients require BID)	Weight gain, fluid retention, edema, anemia, increased hepatic enzymes, N/V, abd pain, heart failure May increase TG, LDL, HDL, decrease small dense LDL

Meglitinides/Phenylalanines				
		MOA	DOSING	SIDE EFFECTS
Repaglinide (Meglitinide)	Prandin®	Increases glucose-stimulated insulin secretion by the pancreas; Chemically unrelated to sulfonylureas	Hypoglycemic-naïve patient: 0.5mg 15 minutes prior to meals, up to 4 mg before every meal; Max daily dose 16mg	Hypoglycemia, weight gain, GI disturbances, upper respiratory infection or problems, arthralgia, headache
Nateglinide (Phenylalanine)	Starlix®		60-120 mg TID 1-30 minutes prior to meals Max daily dose: 120 mg before meals; Combo with metformin or a thiazolidinedione, if monotherapy is insufficient to normalize BG	Hypoglycemia, weight gain, dizziness, rash
Combination				
Glipizide+ Metformin	Metaglip®	See glipizide and metformin above	2.5/250, 2.5/500, 5/500. Naïve patients: 2.5/250 QD w/meal. FPG > 280-320 mg/dL: 2.5/500 BID. One tab per day q 2 wks: Max: 10/1000 or 10/2000 per day divided. Previously treated: 2.5/500 or 5/500 BID Max: 20/2000	See glipizide and metformin above.
Glyburide+ Metformin	Glucovance®	See glyburide and metformin above.	Initial starting dose of 1.25mg/250mg BID with meals and can be increased to 10mg/2000mg. Previously treated pts starting dose 2.5/500 or 5/500 BID w/ meals; can increase to 20mg/2000mg.	See glyburide and metformin above.
Rosiglitazone+ Metformin	Avandamet®	See rosiglitazone and metformin above.	1/500, 2/500, 4/500 BID Max dose: 8/2000	See rosiglitazone and metformin above.

EATING DISORDERS
Adapted from Brandy Singer, RPh

Anorexia Nervosa (AN)
- Diagnosis: <85% of normal body weight, may or may not have bingeing episodes, absence of 3 consecutive menses if female
- Causes
  - 56% linked to genetic causes
  - Neurotransmitter related (5HT, NE, DA, Vasopressin)
  - Environmental (Family, stress, personality, etc.)
  - Elevated cortisol levels in brain
- Clinical Presentation:
  - Body Weight (<85% normal)
  - Amenorrhea
  - Lack of Satiety
  - Hunger pains
  - Dry, cracked Skin
  - Hair loss
  - Fine, downy hair growth
  - Brittle nails
  - Intense fear & obsession over weight gain and being fat
  - Commonly associated with other mood disorders

Bulimia Nervosa (BN)
- Diagnosis: binge eating averaging 2x/week for at least 3 mo, may or may not purge
- Causes
  - 56% linked to genetic causes
  - Neurotransmitter related (5HT, NE, DA, Vasopressin)
  - Environmental (Family, stress, personality, etc.)
  - Elevated cortisol levels in brain
- Clinical Presentation:
  - Binge Eating
  - Weight Sensitivity
  - Inconspicuous eating
  - Food Choices
  - Often occurs in athletes
  - Commonly associated with other mood disorders

Binge Eating Disorder
- Binge eat 5,000-20,000 calories once or more/day
- Obesity and weight fluctuations common
- Increased risk of dyslipidemia, HTN, DM, gallbladder disease, certain cancers

Eating Disorder Not Otherwise Specified
- AN symptoms, but regular menses
- AN with weight loss, but still within normal limits
- BN with less frequent episodes
- Repeatedly chewing and spitting out large amounts of food

Treatment
- *Behavioral & Psychological therapy* = cornerstone
- Always check CV Status (EKG) before initiating Rx therapy

	AN	BN
Cyproheptadine (Periactin®)	X	
SSRIs (1st line therapy)	X	X
TCAs	X	X
Bupropion	X	
Ondansetron	X	
Anti-convulsants		X
Anti-Psychotics	X	
Lithium	X	X
Metoclopramide	X	
Benzodiazepines	X	X
Fenfluramine		X
TPN (Only in serious cases)		X

Additional Drug Notes:
- Ondansetron: 4mg ac or when feel urge to binge
- Anti-psychotics: weight gain, ↓ anxiety & obsessions
- Metoclopramide: ↑ gastric emptying, ↓ bloating/abdom pain
- BZ's: Take with meals to ↓ anxiety associated with eating
- Check blood levels of TCAs & MAOIs in BN due to decreased absorption from purging.

Evaluation of Therapeutic Outcomes

AN	BN
Diary	"recovery"
Weigh-ins	continued treatment
Monitor med side effects	Limit toxic med supply
	Watch for large/frequent purchase or use of OTCs

SLEEP DISORDERS
Adapted from Brandy Singer, RPh

Insomnia
- Patient complains of difficulty falling asleep, staying asleep, or getting enough sleep
- Causes:
  - Stress, life events
  - Medical (cardio pain, GI, neurological)
  - Psychiatric (mood disorders, substance abuse)
  - Medications
    - SSRIs (Prozac, Zoloft)
    - Prednisone
    - Theophylline/caffeine
    - Ritalin (stimulants)
    - Clonidine

- Bupropion
- Antineoplastics
- Clonidine
- Beta-blockers
- Diuretics
- Anticonvulsants

Non-pharmacological Treatment = Sleep Hygiene

1. Exercise routinely, 3-4 times per week, though not within 2 hours of bedtime as this may cause arousal
2. Create a comfortable sleep environment free of distractions such as loud noises, lights, temperature, etc.
3. Use the bed only for sleeping
4. Alcohol, caffeine or nicotine are all commonly encountered substances that should be avoided
5. Avoid feelings of fullness or hunger
6. Eat a healthy meal and eat only a light dessert at least 2 hours prior to sleep
7. Avoid drinking large quantities of liquids in the evening to prevent frequent restroom trips in the night.
8. Do something relaxing before engaging in sleep.

Pharmacologic Treatment Options

- **Antihistamines**: diphenhydramine (↑ SE), meclizine
- **Herbals** Melatonin (1-10mg), Valerian (2-3g, takes 2-4 weeks), L Tryptophan (not recommended due to ↑ eosinophils)
- **BZ's** Use only short-term, rebound insomnia common
- **Barbiturates**
- **Chloral Hydrate** "Mickey Finn", knock-out drops
- **Anti-depressants** TCAs (many SE), trazodone, low dose mirtazapine, SSRIs (citalopram), trazodone
- **Non-BZ hypnotics** zolpidem (Ambien®), zaleplon (Sonata®), eszopiclone (Lunesta®)
- **Ramelteon (Rozerem®)**: MT1 & MT2 agonist, 1st hypnotic to be non-scheduled, may be used long-term

******watch falls, rebound insomnia, hangover effect, amnesia, dependence

Sleep Apnea

- Cessation of airflow from nose/mouth during sleep lasting >10s
- Results in broken sleep, ↓ daytime function, HA, poor memory, irritability
- Causes:
  - Occlusion of airway
  - Idiopathic
  - Comorbid medical conditions
- Non-pharmacological Treatment Options:
  - Weight loss (limited benefit)
  - Treat underlying cause
  - Change in sleep position
  - Nasal CPAP
  - Tracheostomy
- Pharmacological Treatment Options:
  - Non-sedating antihistamines

- Avoid CNS depressants (EtOH, hypnotics, BZ's)
- Protriptyline (10-30mg/day)
- Fluoxetine (20mg/day)
- Theophylline/clonidine (respiratory stimulants)
- Medroxyprogesterone (60mg/day, unknown efficacy)
- Modafinil (200mg qAM)

Narcolepsy
- Irresistible attacks of refreshing sleep that occur daily over at least 30 days (DSM-IV criteria)
- Cause: abnormality in regulation of REM sleep, possibly involving cholinergic system
- Non-pharmacological Treatment Options:
  - Encourage good sleep hygiene (see insomnia)
  - 2 or more BRIEF daytime naps
- Pharmacological Treatment Options (use lowest effective dose):
  - Stimulants: for excessive daytime drowsiness, ↑ NE release
    - Dextroamphetamine, Methamphetamine, Methylphenidate, Modafinil)
  - TCAs (Imipramine, protriptyline, nortriptyline)
  - Sodium Oxybate (Xyrem®): Sodium salt of Gamma Hydroxybutyric acid; C-III, restricted distribution in the US. Also known "GHB", a date rape drug.

Restless Leg Syndrome
- Complaints of discomfort in legs or arms, frequently keeping patient awake at night
- Causes:
  - Pregnancy
  - Renal failure
  - Iron deficiency
- Treatment:
  - Walking
  - Movement
  - Reassurance
  - BZ's
  - Bromocriptine
  - Opiates
  - Clonidine
  - Carbamazepine
  - levodopa

Jet Lag, Shift Work
- Circadian Rhythm disruption by travel, work schedule
- Treatment:
  - Acclimation prior to travel
  - BZ's (short-acting)
  - Melatonin
  - Modafinil
  - Avoid EtOH

Nocturnal Myoclonus
- Repetitive, stereotypic limb movement, 20 – 40 second frequency, 10 minute duration
- Treatment:

- Clonazepam 0.5 – 2mg
- Baclofen 20 – 40mg
- Lamotrigine 100mg
- Opiates
- Levodopa

Sleep Disorders (Pharmacological Tx Chart)

	IN	SA	NA	RLS	JLW	NM
Antihistamines (1st-generation)	X					
Antihistamines (2nd generation)		X				
Melatonin	X				X	
Valerian	X					
Barbiturates	X					
Benzodiazepines	X			X	X	X
Chloral Hydrate	X					
SSRIs (activating)		X				
SSRIs (sedating)	X					
TCAs	X	X	X			
Trazodone	X					
Non-BZ Hypnotics	X					
Ramelteon®	X					
Stimulants			X			
Modafinil		X	X		X	
Bromocriptine				X		
Clonidine		X		X		
Opiates				X		X
Carbamazepine				X		
Levodopa				X		X
Baclofen						X
Lamotrigine						X

IN = Insomnia
SA = Sleep Apnea
NA = Narcolepsy
RLS = Restless legs Syndrome
JLW = Jet Lag/Work
NM = Nocturnal Myoclonus

HEADACHE AND MIGRAINE
Adapted from Carol Vanevenhoven, PharmD

Resources

- Goadsby PJ, et al. Migraine—Current Understanding and Treatment. NEJM. 2002 Jan 24; 346(4): 257-70.
- Snow V, et al. Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache. *Ann Intern Med*. 2002 Nov 19; 137(10): 840-9.

Migraine

- Pathophysiology
  - Activation of the trigeminal sensory nerves may trigger the release of vasoactive substances such as substance P, neurokinin A, and calcitonin gene-related peptide. These induce an inflammatory reaction around the cerebral and meningeal blood vessels, inducing vasodilation. There is also a disturbance in 5-HT activity.
  - Lasts 4-72 hours. Associated with N/V, photo-or phono-phobia, and aggravation upon movement. Many proposed triggers. With or without aura.
- Presentation
  - Prodrome (~60% migraine sufferers): neurologic, psychologic, autonomic, and constitutional
  - Usually begins as dull ache and increases with each arterial pulse to an intense throbbing headache. Most often affects frontotemporal region
  - 90% have nausea and 1/3 experience emesis
  - Systemic symptoms: anorexia, food cravings, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and edema localized to face, scalp, or periorbital region
  - Postdromal phase: exhaustion, malaise, irritability, and recurrence of pain with sudden head movement
  - Average 1-4 attacks per month

Cluster Headache

- Pathophysiology
  - Similar to migraine.
  - Triggers are poorly understood, but hypothalamic dysfunction and hypoxemia may play a role, as may alcohol, vasodilators, stress, warm weather, missed meals, and excessive sleep.
  - One of the most severe types, but relatively uncommon. Men 4-7 times more likely to experience. More common in spring, and fall, and usually occur at night.
- Presentation
  - Attacks occur suddenly and reach max intensity over 5-15 minutes
  - Described as searing, burning pain behind one eye
  - No aura, N/V
  - Pain lasts 15 min to 3 hrs, often recurs at same time each day
  - Patients may rub or beat heads against objects to alleviate pain

- Usually not sensitive to movement or stimuli

Tension Headache:

- Pathophysiology
  - **o** Unknown. Excessive muscle contraction? Abnormal vascular reactivity?
  - **o** Chronic tension headaches show some similarities to migraine pathophysiology.
- Presentation
  - **o** Characterized by bilateral dull aching pain (hatband distribution
  - **o** Pain is usually mild to moderate
  - **o** Often occurs after or during periods of stress
  - **o** No aura, N/V
  - **o** May include photophobia or phonophobia

Medication Overuse Headache (secondary cause):

- Also known as "rebound" headache.
- Overuse of caffeine, aspirin, NSAIDS, Tylenol, opiates, ergotamine tartrate, decongestants or benzdiazepines.
- Presentation
  - Usually experience gradual worsening of headache symptoms
  - Occurs daily or almost daily, often in early a.m.
  - Headache varies in type, severity, and location
  - Other symptoms may include: N/V, anxiety, irritability, depression, memory problems, or difficulty concentrating
  - Slow improvement occurs after discontinuation of precipitator (may take 6-8 weeks)
  - Preventative medications are ineffective while pt continues to use excessive amounts of precipitants

Treatment

- Abortive Treatments - refer to tables
- Preventative Treatments:
  - Tension
    - TCA's: amitriptyline, doxepin, imipramine, maprotiline, protriptyline, and desipramine
    - SSRI's: fluoxetine
  - Cluster
    - Verapamil, lithium, ergotamine, methysergide, corticosteroids, valproate,indomethacin, melatonin, methylergonovine
  - Migraine
    - Beta blockers, antidepressants, anticonvulsants, methysergide, CCB's, NSAIDS

Abortive Migraine Treatments

Agent	Adult Dose	Max Dose	Headache Type
Analgesics			
Ibuprofen	200-800 mg q6h	Avoid > 2.4 g/day	Migraine
Naproxen sodium	550-825 @onset, 220mg in 3-4 hrs prn	Avoid > 1.375 g/day	Migraine, tension
Diclofenac potassium	50-100 mg @ onset, 50 mg in 8 hrs prn	Avoid > 150 mg	Migraine
Ketorolac	15-60 mg IM @ onset, repeat q6hr	160 mg/day	Migraine, tension
Aspirin	500-1000 mg q4-6 hr	4 gm	Migraine, tension
Acetaminophen	1 gm q 4-6 hr	4 gm	Migraine, tension
Midrin (isometheptene, dichloral phenazone, APAP)	2 caps @onset, then 1 cap q1hr	6 caps/day and 20 caps/month	Migraine, tension
Fiorinal (butalbital, caffeine, ASA)	1-2 tabs q 4-6 hr	4 tabs/day for 2 days/week	Migraine
Fioricet (butalbital, caffeine, APAP)	1-2 tabs q 4-6 hr	4 tabs/day for 2 days/week	Migraine
Excedrin (APAP, ASA, caffeine)	2 tabs q 6 hr	8 tabs/day	Migraine

Intranasal Lidocaine			
Lidocaine 4 % solution	.5-1 ml intranasal q 15 min	3 doses max	Cluster, migraine
Corticosteroids			
Prednisone	40-60 mg, taper over 7-21 days	--	Intractable migraine, cluster
Dexamethasone	4-16 IM (*8 mg oral)	--	Intractable. migraine (*cluster)
Hydrocortisone	no recommendation	--	Intractable migraine
Narcotic analgesics			
Meperidine	50-100 mg (PO, IV, IM, rectal)	Intractable migraine	
Morphine	5-10 mg (PO IV IM rectal)	Intractable migraine	
Hydromorphone	2-4 mg PO	Intractable migraine	
Butorphanol	1 mg intranasal, repeat q60-90 min	Intractable migraine	
Butalbital, asa, caffeine, codeine (Fiorinal w/codeine)	1-2 caps q 4hr, up to 6 caps/day	Migraine, tension	
Inhaled Oxygen			
100 % oxygen	7-10 L/min for 15 minutes		Cluster

Antiemetics			
Metoclopramide (Reglan)	10 mg IV/PO at onset		Migraine
Prochlorperazine	10 mg IV or IM at onset		Migraine
Chlorpromazine	1 mg/kg IM		Intractable migraine
Ergot compounds			
Dihydroergotamine, 1 mg/ml	.5-1 ml IV or IM q1hr	max 2 mg/day IV, 3 mg/day IM (total 6 mg/week)	Migraine, cluster
Ergotamine tartrate with caffeine (Cafergot, Ercaf)	Suppositories: 1 q 1 hr 2 tabs stat, then 1tab q 30min	max 2 supp./attack or 12/mo. max 6 tabs/attack or 10/wk	Migraine, cluster
Ergotamine tartrate (Ergostat, Medihaler)	SL: 1 q 30 min nasal: 1 puff q 5min	SL: max 3 tabs/day or 5tabs/wk Nasal: 6 puffs/day or 15/week	Migraine, cluster
5-HT agonists			
Sumatriptan (Imitrex)	SQ: 6 mg, rpt 1 hr Tab:25-100 mg, rpt 2 hr Nasal: 5,10,20 mg in one nostril, rpt q 2hrs	SQ: 12 mg/day max Tab: 300 mg/day max nasal: 40 mg/day max	Migraine, cluster
Zolmitriptan (Zomig)	1.25-5 mg stat, repeat q 2hrs	Max 10 mg/day	Migraine, cluster

Naratriptan (Amerge)	1-2.5 mg stat, repeat q 2hrs prn	5 mg/day	Migraine, cluster
Rizatriptan (Maxalt)	5-10 mg stat, repeat q 2hrs	Max 30 mg/day	Migraine, cluster
Almotriptan (Axert)	6.25-12.5 mg stat, repeat q 2hrs	Max 2 doses/24 hr	Migraine, cluster
Frovatriptan (Frova)	2.5-7.5 mg stat, repeat q 2hrs	Max 7.5mg/24 hr	Migraine, cluster
Eletriptan (Relpax)	20-40 mg stat, rpt q2hr	max 80 mg/day	Migraine, cluster

HEART FAILURE
Adapted from Carol Vanevenhoven, PharmD

Resources
- ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult
- ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary 2001. *J. Heart Lung Transplant*. 2002; 21: 189-203
- Jessup M et al. Heart Failure. NEJM 2003; 348: 2007-18.

New York Heart Association Classification
Class I – patients with cardiac disease but no limitations of physical activity
Class II – symptoms from ordinary exertion
Class III – comfortable at rest, but less than ordinary activity leads to symptoms
Class IV – inability to carry on physical activity without discomfort and symptoms are present at rest

New Classification System
Stage A – high risk for developing heart failure, no apparent structural abnormality
Stage B – have a structural abnormality of heart, no symptoms of heart failure
Stage C – have a structural abnormality of heart and current/previous symptoms of heart failure
Stage D – end stage symptoms of heart failure refractory to standard treatment

Etiology of heart failure
- Ischemic Causes
  - History of AMI (responsible for ~ 2/3 of systolic HF)
- Non-ischemic Causes:
  - Hypertension
  - Dilated cardiomyopathy
    - Idiopathic
    - Toxins (illicit drugs, alcohol, etc)
    - Viral

Diagnostic Tests for Suspected HF
- Electrocardiogram
  - Ischemia
  - Old MI
  - Arrhythmias
- Chest X-ray
  - Heart size
  - Pulmonary congestion
- Echocardiogram
  - Assess LV function

Lab Assessment
- CBC – anemia (Hct < 25) mimics HF symptoms
- Urinalysis – excess protein suggests disorders that may cause peripheral edema
- SCr – renal dysfunction may cause volume overload
- Thyroid function tests (TSH) – hypothyroidism/hyperthyroidism produces S/S of HF
- BNP – produced by left ventricle when stretched

- BNP < 100, HF unlikely; neg pred. value 90%
- BNP > 500, HF likely; pos pred. value 90%

**If GFR < 60: BNP > 200 suggests HF

**BNP can be unexpectedly low if obese (BMI > 30) or flash pulmonary edema and labs drawn too soon

Describing Heart Failure

- Systolic: inadequate contracting muscle
  - 60-70% of all HF
  - Left ventricular ejection fraction <40%
  - Causes: CAD, HTN, arrhythmias, cardiomyopathy
- Diastolic (isolated): normal contracting muscle
  - ↑ resistance to filling
  - Causes: valvular stenosis, pericardial dz, ventricular stiffness after AMI, hypertrophy, etc.
- Right ventricular dysfunction
  - Signs/Symptoms
    - Peripheral edema, JVD, ascites, abdominal pain/bloating, constipation, nausea
- Left ventricular dysfunction (most common)
  - Signs/Symptoms
    - Rales, S3 gallop, pulmonary edema, Cheyne-Stokes respiration, dyspnea on exertion, orthopnea, cough, tachypnea
- Non-specific Signs/Symptoms
  - Tachycardia, pallor, cyanosis of digits, cardiomegaly, fatigue, nocturia, exercise intolerance, CNS disturbance

Treatment Goals

- Improve quality of life:
  - Reduce symptoms
  - Improve exercise capacity
  - Increase/maintain physical autonomy
- Prolong life
  - Decrease arrhythmias
  - Slow/Stop progression of pump failure

Non-Pharmacologic Management of Heart Failure

- Dietary Recommendations
  - Reduce salt intake (2 gm/day)
  - Moderate water intake (2 L/day)
  - Alcohol abstinence
  - Weight management
- Regular exercise (walking, cycling)
- General
  - Stress adherence to treatment plan
  - Smoking cessation
  - Influenza and pneumococcal vaccination

Meds used in heart failure therapy

- **ACE inhibitors** – Cornerstone of therapy
  - ↓ mortality, enhanced functional status, reduced hospitalization with chronic heart failure
  - Adverse effects: hypotension, ↑ SCr, ↑K^+, cough, angioedema, neutropenia, hepatotoxicity
  - Monitor: BP, SCr, K^+ 1-2 wks after starting
  - Hold or slow titration if SCr increases > 0.3 mg/dl, symptomatic hypotension, or K^+ > 5.5 mEq/L

- Caution if SCr ≥3, $K^+ \geq 5.5$, systolic BP < 90
- Pregnancy category X
- ARB reasonable alternative if intolerant to ACEI
- Renal dysfunction is a "hemodynamic" effect, not a "toxic'" effect

- **Hydralazine/Nitrates** – ↓ mortality, for patients contraindicated or intolerant to ACEI or used in combination with ACEI, dig, diuretic
- **Beta blockers**
  - Use in patients with stable HF due to left ventricular systolic dysfunction, or with symptomatic heart failure unless contraindicated
  - ↓ Mortality, ↑ EF, ↓ incidence of sudden death, ↓ remodeling/progression, improved symptoms (long term), ↓ rate of hospitalization
  - Adverse effects: fluid retention, fatigue, bradycardia & heart block, hypotension
  - Contraindications:
    - Relative: asthma, diabetes
    - Absolute: bradyarrhythmias or heart block without pacemaker, symptomatic hypotension, decompensated heart failure
  - Starting Therapy
    - Begin with low doses in stable patient already on ACEI or diuretic (symptoms may worsen on β-blocker)
    - Monitor closely 2 hrs after 1st dose, then double dose at weekly intervals as tolerated

Dosing Guidelines

Drug	Initial Dose	Target Dose
Metoprolol	5 mg BID	50-75 mg BID
Metoprolol XL	12.5-25 mg QD	200 mg QD
Carvedilol®	3.125 mg BID	25-50 mg BID

  - Monitor for signs of decompensation: fluid retention, frequent fluid retention unresponsive to diuretics, incipient cardiogenic shock
- **Diuretics** – never use as monotherapy, important adjunctive tx, ↓ intravascular volume, improve symptoms, no long-term increase in QOL, exercise tolerance, or mortality
  - *loops* – most commonly used, dosed qd (single large dose preferred to smaller multiple doses) for HF (dosed bid for HTN)
  - *thiazides* – "gentle diuresis" only use in mild HF, CrCl > 25 ml/min, ineffective with renal insufficiency, max dose HCTZ 50mg
  - Adverse effects (thiazides and loop): ↓ K^+ & Mg^+, ↓ Na^+, stimulation of neurohormonal activity, hyperuricemia, hypotension, ototoxicity, GI, metabolic alkalosis
- **Digoxin** – no decrease in mortality, trend toward ↑ death due to worsening HF, only improves symptoms
  - Usually given to patients w/ no adequate response to ACEI, + diuretics + beta-blockers, or in combination w/ ACE-I + diuretics if persistent symptoms
  - Loading dose not generally needed for HF
  - HF therapeutic range ≤ 0.9 ng/ml
  - Adverse effects: anorexia, N/V, visual disturbances, disorientation, confusion, ventricular arrhythmias, AV block, sinus bradycardia, junctional escape rhythms

    - Monitor: baseline EKG, K^+ and renal function, drug levels
- **Ca^{2+} channel blockers** – place in therapy not yet established; use amlodipine (Norvasc®), felodipine (Plendil®)
- **Aldosterone Inhibitors** (Eplerenone,Inspra, Spironolactone)
    - Spironolactone indicated for class III & IV HF with symptoms despite standard therapy, $K^+ < 5$, SCr < 2.5
    - Reduces mortality and hospitalization in severe HF
    - Start ACEI first, then try 12.5-25 mg QD
    - Adverse effects: gynecomastia, hyperkalemia
    - Eplerenone indicated for HF post-MI with K^+ <5.5 and CrCl > 30

Meds that can worsen heart failure

- Negative inotropes
    - Antiarrhythmics (disopyramide, sotalol, propafenone, flecainide)
    - High dose β-blockers
    - Calcium channel blockers (verapamil, diltiazem)
- NSAIDs – salt and water retention
    - Decreased effectiveness of diuretics and ACE-I
- Corticosteroids – salt and water retention (hydrocortisone > prednisone > dexamethasone)
- Chemotherapy - cardiotoxic

HYPERLIPIDEMIA
Adapted from Jason Iltz, PharmD

Guidelines

- Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004; 110: 227-39.
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001; 285 (19): 2486-97.

NCEP Guidelines for Cholesterol Classification

Cholesterol	Level (mg/dL)	Classification
Total	< 200	Desirable
	200-239	Borderline-High
	> 240	High
HDL	< 40	Low
	> 60	High
LDL	< 100	Optimal
	100-129	Near-Optimal
	130-159	Borderline-High
	160-189	High
	> 190	Very High
Triglycerides	< 150	Normal
	150-199	Borderline-High
	200-499	High
	> 500	Very High

NCEP Major Risk Factors for CHD (exclusive of LDL-C)

- Cigarette smoking
- HTN (BP ≥ 140/90 mm Hg or on antihypertensive medication)
- Age (men ≥ 45yrs; women ≥ 55)
- Low HDL (≤ 40 mg/dL)
- Diabetes (CHD risk equivalent)
- Family history of premature CHD (CHD in male first-degree relative < 55yo or CHD in female first-degree relative < 65yo)

***Negative Risk Factor: High HDL (> 60 mg/dL)

Emerging Risk Factors

- Obesity
- Physical Inactivity
- Atherogenic Diet
- Alcohol intake
- Lipoprotein A
- Insulin Resistance
- Homocysteinemia
- Hypertriglyceridemia

**not counted in NCEP treatment guidelines, but might encourage more aggressive therapy than guidelines suggest

NCEP Treatment Guidelines

Patient	Start Diet	Start Drugs	LDL Goal
No CHD	≥ 160	≥ 190 mg/dL	< 160

0-1 risk factor	mg/dL		mg/dL
No CHD ≥ 2 risk factors	≥ 130 mg/dL	≥ 130 mg/dL if 10-year risk 10-20%* ≥ 160 mg/dL if 10-year risk < 10%	< 130 mg/dL
CHD or Risk Equivalent**	> 100 mg/dL	≥ 130 mg/dL	≤ 100 mg/dL

*Framingham risk assessment
**Diabetes, Atherosclerotic Disease (PAD, abdominal aortic aneurysm, or symptomatic carotid artery disease), or multiple risk factors that confer a 10-year risk for CHD at greater than 20%

Calculations
LDL = (TC – HDL) - (TGs / 5)
*TG must be <400 for equation to be valid

VLDL = TGs / 5

1 mmol/L cholesterol = 38.67 mg/dL
1 mmol/L triglyceride = 88.57 mg/dL

Medication/Disease-Induced Hyperlipidemia

- Increase LDL
  - Anabolic steroids
  - Progestins
  - Thiazides
  - Isotretinoin
  - Hypothyroidism
  - Nephrotic Syndrome
  - Obstructive liver disease
- Increase Triglycerides
  - Diabetes mellitus
  - Alcohol
  - Hypothyroidism
  - Obesity
  - Renal Insufficiency
  - Glucocorticoids
  - Protease Inhibitors
  - Oral estrogens
  - Bile acid-binding resins
  - Ticlodipine
  - β-blockers w/o ISA
- Decrease HDL
  - Diabetes mellitus
  - Smoking
  - Hypertriglyceridemia
  - Menopause
  - Obesity
  - Male puberty
  - Uremia
  - Anabolic steroids
  - Progestins
  - β-blockers w/o ISA

Dietary Therapy of High Blood Cholesterol

Component	TLC Recommended Intake
Total fat	25% - 35%
Saturated fatty acids	<7%
Polyunsaturated fats	≤10%
Monounsaturated fats	≤20%
Carbohydrates	50% - 60%
Protein	~15%
Cholesterol	<200 mg./day
Total calories	To achieve and maintain desirable weight

Pharmacotherapy Used in Hyperlipidemia

Drug Class	Total Cholesterol	LDL-Cholesterol	HDL-Cholesterol	Triglyceride	Mechanism of Action
Niacin	↓ 25%	↓ 10-15%	↑ 15-35%	↓ 20-50%	Increases VLDL clearance. Decreases LDL/VLDL production, VLDL secretion, and HDL catabolism
Bile Acid Sequestrants	↓ 20%	↓ 10-20%	↑ 3-5%	↑ or Neutral	Binds bile acids in intestine and decreases enterohepatic recirculation. Cholesterol = bile-acid precursor, and demand for cholesterol in liver increases as bile-acid production increases. Liver removes LDL from blood to make bile acids.
Fibric Acid Analogs	↓ 15%	Transient ↑ then ↓ 5-15%	↑ 6-15%	↓ 20-60%	Decrease VLDL synthesis. Increase VLDL/triglyceride removal, lipoprotein lipase (LPL) activity, HDL stability
Ezetimibe (Zetia®)	↓ 18%	↓ 12-22%	↑ 1-3%	↓ 7-11%	Inhibits cholesterol transport across intestinal wall. Metabolite remains active in intestinal wall via enterohepatic recirculation.
Omega-3-Fatty Acids	↑ 10%	↑ 10%	Neutral	↓ 25-50%	Triglyceride lowering not understood. Decrease platelet aggregation. May lower blood pressure, have antiarrythmic effects
HMG-CoA Reductase Inhibitors	↓ 15-60%	↓ 20-65%	↑ 3-15%	↓ 10-50%	Increases LDL receptors in liver. Blocks rate limiting enzyme in cholesterol synthesis. Increases catabolism and decreases synthesis of VLDL and LDL.

Niacin

- Use immediate-release OTC or prescription extended-release products—OTC ER products are hepatotoxic
- Dose ~2-3 gms/day—must titrate slowly
- Avoid taking with hot beverages, alcohol
- SE: flushing, itching, hyperglycemia, gout symptoms, increased LFTs, myopathy with statins and fibrates
- Monitoring: LFTs, blood glucose, and urate at 0, 6 weeks, then q3 mo until stable dose, then q6 mo after stable dose, lipids q6-8 weeks until stable then q6-12 mo
- If LFTs >3x upper limit of normal, have patient stop alcohol use and repeat LFTs in 2 weeks
- Contraindications: gout, significant liver damage, history of PUD, caution with coronary, gallbladder, liver disease

Niacin Titration Protocol

Week	Breakfast	Lunch	Dinner	Evening Snack
1			250 mg	
2	250 mg		250 mg	
3	250 mg	250 mg	250 mg	
4	250 mg	250 mg	250 mg	250 mg
5	250 mg	250 mg	500 mg	250 mg
6	500 mg	250 mg	500 mg	250 mg
7	500 mg	500 mg	500 mg	250 mg
8	500 mg	500 mg	500 mg	500 mg

**may take ½ aspirin before niacin if flushing/itching

Bile Acid Sequestrants

- Products: cholestyramine (Questran®), colestipol (Colestid®), colesevelam (WelChol®)
- SE: dyspepsia, bloating, constipation
- Cholestyramine and colestipol decrease absorption of many drugs, but colesevelam doesn't (except verapamil)
- Monitoring: lipids q6-8 weeks until stable then q6-12 mo, watch for vitamin deficiency with long-term use
- Start with 1 dose QD and titrate to 2-4 doses/day
- Premixing doses in water and storing in refrigerator helps with dyspepsia and palatability
- Drink 6-8 glasses of water/day, and consider psyllium if significant constipation
- Questran Light (sugar-free) tastes best

Fibrates

- Products: gemfibrozil (Lopid®), fenofibrate (Tricor®)
- SE: increased LFTs, myopathy, transient increase in LDL, dyspepsia (take with food), gallstones, increased mortality with clofibrate (not used)
- Drug interactions: displaces warfarin, increased nephrotoxicity with cyclosporine and fenofibrate
- Monitoring: LFTs at 0, 6 weeks, 3 mo, then q3 mo; renal function at baseline and yearly
- If LFTs >3x upper limit of normal, have patient stop alcohol use and repeat LFTs in 2 weeks
- Contraindicated in pregnancy

Ezetimibe

- Mainly used as adjunct to statins in refractory patients
- SE: headache most common, angioedema possible

Omega-3 Fatty Acids
- Omacor® 4 gms QD or 2 gms BID
- Very little data to support use
- SE: halitosis, N/V/D, dyspepsia, increased LDL/TC, weight gain, prolonged bleeding time
- Decreases triglycerides, but many patients don't respond (withdraw if no response in ~2 mo)

HMG-CoA Reductase Inhibitors
- SE: HA, dyspepsia, increased LFTs, myopathy, hematuria, proteinuria
- Drug interactions: myopathy with niacin, gemfibrozil, cyclosporine, certain antibiotics; CYP3A4 or 2C9 inhibitors
- Monitoring: LFTs at 0, 6 weeks, 3 mo, then q6-12 mo if normal; CPK at baseline and in patients on interacting drug
- **Use 25% of maximum statin dose when combining with interacting drug to prevent myopathy

Combination Therapy
- Indications
  - Diet + single agent does not achieve goal (at least 3 mo trial on monotherapy)
  - High dose single agent therapy is not tolerated
  - Very large reduction in TC, LDL are needed
  - Combined hyperlipidemia
- Options
  - Statins + Resins (lower LDL by 40-50%, safest combo)
  - Niacin + Resin (lower LDL by 30-40%, poorly tolerated)
  - Statins + Niacin (increase risk of myopathy – lower dose statin to ↓ risk)
  - Statins + Fibrate (increase risk of myopathy – lower dose statin to ↓ risk, combined hyperlipidemia)
  - Ezetimibe + Statins (for extra LDL reductions)

Statin Comparison

Name (Brand/Generic) **Metabolism**	Crestor® Rosuvastatin CYP2C9	Lipitor® Atorvastatin CYP3A4	Zocor® Simvastatin CYP3A4	Mevacor® Lovastatin CYP3A4	Pravachol® Pravastatin N/A	Lescol® Fluvastatin CYP2C9
Equivalent Dosing in milligrams (mg)	N/A	5	10	20	20	40
	2.5	10	20	40	40	80
	5	20	40	80	N/A	N/A
	10	40	80	N/A	N/A	N/A
	20	80	160	N/A	N/A	N/A
	40	N/A	N/A	N/A	N/A	N/A

**Potency decreases from Left to Right.

Administration
Fluvastatin & Pravastatin – Take at Bedtime
Lovastatin and Simvastatin - Take with evening meal.
Atorvastatin and Rosuvastatin – Take anytime

HYPERTENSION
Adapted from Angela Lam, PharmD

Definitions
- Blood Pressure – force of blood against walls of arteries
- Systolic BP – force of blood in arteries when heart beats
- Diastolic BP – force of blood arteries when heart relaxes
- Isolated Systolic HTN: SBP>/= 140mmHg or DBP< 90 mmHg
    - Usually in elderly due to stiffer arteries

Causes of Primary Hypertension
- Idiopathic
- RAAS
- Neurological/receptor abnormalities
- Autoregulatory abnormalities
- Vasodilation/Vasoconstriction imbalances

Causes of Secondary Hypertension
- Sleep apnea
- Chronic kidney disease
- Primary aldosteronism
- Cushing's syndrome
- Thyroid or parathyroid disease
- Pheochromocytoma
- Drug induced or related causes (NSAIDS, alcohol, caffeine, steroids, ergot alkaloids, pseudoephedrine)

Key Messages of JNCVII Guidelines
- For patients >50 yo, SBP is more important CVD risk factor
- Thiazide diuretics should be initial therapy for most cases of hypertension either alone or in combo with other drug classes.
- Most patients will require two or more combinations of antihypertensive drugs to reach BP goal

Blood Pressure Classification

BP Classification	SBP mmHg	DBP mmHg
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	>160	>100

*Hypertension is an asymptomatic disease

CVD Risk
- The BP relationship to risk of CVD is continuous, consistent, and independent of other risk factors.

CVD Risk Factors
- Hypertension
- Smoking
- Physical inactivity
- Dyslipidemia
- Diabetes Mellitus
- Age (older than 55 for men, 65 for women)
- Family History
- Obesity (BMI >30 kg/m^2)
- Microalbuminuria or GFR <60 ml/min

Evaluation of patients with Hypertension

- Assess lifestyle and identify other CV risk factors or disorders that affect prognosis and guide treatment.
- Reveal causes of high BP
- Assess presence or absence of target organ damage/CVD

Goals of Therapy
- Reduce CVD and renal morbidity and mortality.
- Treat BP to <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or chronic kidney disease.
- Achieve SBP goal in patient over 50 years old.

Lifestyle Modifications to Reduce Blood Pressure
- Weight reduction (10kg)
- Adopt DASH eating plan
- Dietary sodium reduction (<2g a day)
- Physical activity (30 min 3 times weekly)
- Decrease alcohol intake

Follow-up and Monitoring
- Patients should return for follow-up and adjustment of medications until BP goal is reached.
- More frequent visits for stage 2 HTN or with complicating comorbid condition
- Serum potassium and creatinine monitored 1-2 times/year.
- After goal is stable, follow-up visits at 3 – 6 month intervals.

Hypertension in Women
- BP should be checked in women taking older oral contraceptives with high estrogen content. Hormone Replacement Therapy does not raise BP.
- Pregnant women with HTN should be followed carefully.
    - Methyldopa, BBs, and vasodilators are preferred for the safety of the fetus
    - ACEI and ARBs are contraindicated in pregnancy

Causes of Resistant Hypertension
- Excess sodium intake
- Inadequate diuretic therapy
- Excess alcohol intake
- Medications
- OTC drugs and herbal supplements

Compelling Indications for Individual Drug Classes

Indication	Initial Therapy Options
Heart failure	THIAZ, BB, ACEI, ARB, ALDO ANT
Postmyocardial infarction	BB, ACEI, ALDO ANT
High CAD	THIAZ, BB, ACEI, CCB
Diabetes	THIAZ, BB, ACEI, ARB, CCB
Chronic kidney disease	ACEI, ARB
Recurrent stroke prevention	THIAZ, ACEI

BP Classification	SBP mmHg	DBP mmHg	Lifestyle Change	Without compelling indication	With compelling indications
Normal	<120	<80	Encourage		
Prehypertension	120-139	80-89	Yes	No antihypertensive drugs indicated	Drug(s) for compelling indications
Stage 1 Hypertension	140-159	90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ACE, ARB, BB, CCB, or combination	Drugs for compelling indications
Stage 2 Hypertension	>160	>100	Yes	Two-drug combination for most (usually thiazides-type diuretic and ACEI or ARB or BB or CCB)	Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

Thiazide Diuretics

- Drugs: Hydrochlorothiazide, Chlorthalidone, Metolazone
- MOA: Inhibit Na+/Cl- reabsorption in distal tubule -> vasodilation
- Advantages
  - Inexpensive
  - Synergy with ACEI, Beta Blockers
  - Benefits with osteoporosis—less Ca wasting
  - Metolazone beneficial in low GFR
- Disadvantages
  - Hypokalemia/natremia/magnesemia
  - Hyperglycemia/lipidemia/uricemia/calcemia
  - Ineffective in renal insufficiency (<30ml/min)
    - Except metolazone
  - Cross sensitivity with sulfa allergy
  - Sexual dysfunction
- Counseling Tips
  - Take in the morning
  - Watch for potassium supplementation
  - Monitor input/output water and electrolytes

Loop Diuretics

- Drugs: Furosemide, Bumetanide, Torsemide, Ethacrynic Acid
  - Equivalent dosing 40:1:10:100mg
- MOA: Inhibit reabsorption of Cl- in ascending loop of Henle
- Advantages
  - Potent, rapid and short acting
  - Can be used in renal insufficiency
- Disadvantages
  - Hypokalemia/natremia/calcemia/magnesemia
  - Ototoxicity, phototoxicity
  - Dehydration
  - Cross sensitivity with sulfa (except ethacrynic acid)

Potassium Sparing Diuretics

- Drugs: Spironolactone, Triamterene, Amiloride
- MOA:
  - Blocks aldosterone (Spironolactone)
  - Directly inhibits K+ channels (Triamterene, Amiloride)
- Disadvantages
  - Take up to 6 weeks to lower BP when used alone
  - Hyperkalemia, gynecomastia
  - Caution with ACE-I, renal insufficiency

Beta Blockers

- Drugs: Metoprolol, Labetolol, Atenolol, Propanolol
- MOA: Decrease heart rate, contractility and renin output
- Advantages
  - Many uses (arrythmias, migraines, tremor, anxiety)
  - Cardioselectivity
- Disadvantages
  - Bradycardia, fatigue, AV block, dizziness
  - Taper rather than D/C abruptly
  - They can mask hypoglycemic symptoms

Alpha-Beta Blockers

- Drugs: Labetolol, Carvedilol
- MOA: Main effects at beta receptor

    - Alpha block adds to vasodilatory actions
- Advantages
    - Labetolol useful in hypertensive crisis
    - Doesn't increase lipids
- Disadvantage
    - Not more effective for HTN

ACE inhibitors
- Drugs: Enalapril, Lisinopril, Quinapril
- MOA
    - Inhibits the conversion of angiotensin I to angiotensin II
    - Blocks degradation of bradykinin
- Advantages
    - Renal protection in susceptible patients
    - Prevents remodeling in post MI and HF patients
- Disadvantages
    - Cough, hyperkalemia, angioedema, metallic taste
    - Increase serum creatinine (<30% or 1 mg/dL OK)
    - Pregnancy category X

Angiotension Receptor Blockers
- Drugs: Losartan, Valsartan, Olmesartan
- MOA: Directly blocks ATI receptor that mediates effects of angiotensin II
- Advantages
    - Same efficacy as ACEIs
    - No bradykinin effects
    - Can use in patient unable to tolerate ACEI
    - Works well in combo with other diuretics
    - Fewer side effects than ACEI
    - Can use in diabetes mellitus, nephropathy, HF patients
- Disadvantages
    - Pregnancy category X
    - Hyperkalemia
    - Orthostatic hypotension

Calcium Channel Blockers
- Drugs: Nondihydropyridines (Diltiazem, Verapamil), Dihydropyridines (Nifedipine, Amlodipine)
- MOA:
    - Block voltage-sensitive calcium channels
    - Relaxation of cardiac and smooth muscles -> vasodilation
    - Negative inotropic effects (nondihydropyridines)
- Advantages
    - Good for use in angina (long-acting dihydropyridines)
    - Alternative for diabetes patients
    - Raynaud's syndrome
- Disadvantages
    - Headache
    - Hypotension
    - AV block
    - Gingival hyperplasia
    - Flushing/dizziness

Alpha-1 Receptor Blockers
- Drugs: Prazosin, Terazosin, Doxazosin
- MOA: Inhibit catecholamine uptake in smooth muscle cells ->vasodilation

- Advantages
  - HTN with concomitant benign prostatic hyperplasia
- Disadvantages
  - Not a first line agent. Used as adjunctive therapy
  - 1st dose syncope, vivid dreams, postural hypotension
- Counseling Tips
  - Take first dose in MD office if possible
  - Take at bedtime if experiencing side effects
  - Observe for changes in urine output if taking it for BPH as well as hypertension

Centrally Acting Agents
- Drugs
  - Clonidine (2nd or 3rd line) – available as patch
  - Methyldopa (used for hypertension during pregnancy)
- MOA
  - Stimulates alpha-2 receptors in the brain
  - Reduces sympathetic outflow
  - Increases vagal tone
- Advantages
  - Good for special populations
- Disadvantages
  - Chronic use could lead to Na+ and H20 retention
  - Rebound hypertension if withdrawn too fast (taper)
  - Sedation, dry mouth, hepatitis (check LFTs)

Direct Vasodilators
- Drugs: Hydralazine, Minoxidil
- MOA: Direct arteriolar smooth muscle relaxation
- Used as adjunct therapy
- Last line of agents when nothing works
- Hydralazine (side effects)
  - Usually combined with isosorbide
  - May cause Lupus-like syndrome (more common in women) – use <200mg/day
  - Drug fever, peripheral neuropathy, hepatitis, headache
- Minoxidil
  - Causes hair growth (Rogaine) – use with loop-diuretic
  - More potent, may cause fluid overload
  - **patient must be on beta blocker when taking minoxidil to prevent reflex tachycardia

ISCHEMIC HEART DISEASE
Adapted from Barb Arnold, PharmD and Angela Worral, PharmD

Guidelines
- ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina
- American College of Cardiology: www.chestnet.org
- American Heart Association: www.americanheart.org

Definition of Ischemic Heart Disease
- Heart problems caused by narrowed heart arteries
- Narrowed arteries lead to lack of blood flow and oxygen to the heart muscle
- An imbalance between myocardial oxygen supply and demand
- Many disorders within ischemic heart disease
    - Acute Coronary Syndrome (ACS)
        - Unstable Angina
        - Acute Myocardial Infarction (AMI)
            - ST-segment elevation MI (STEMI)
            - Non-ST segment elevation (NSTEMI)
    - Angina
        - Stable, chronic, exertional
        - Unstable
        - Variant/Prinzmetal (coronary artery vasospasm)

Determinants of O2 supply:	Determinants of O2 demand:
▪ Arterial O2 content ▪ Coronary blood flow (fixed) **Can't alter with drugs well	▪ Heart rate ▪ Inotropy ▪ Afterload ▪ Preload **Respond to drugs

Angina
- Clinical syndrome characterized by:
    - Discomfort in chest, jaw, shoulder, back or arm
        - Frequently referred to as "discomfort"
        - Almost never sharp or shooting
    - Typical duration is minutes
- May be associated with the following symptoms:
    - SOB
    - N/V
    - Weakness
    - Dizziness
    - Anxiety
    - Numbness in upper extremities
    - Diaphoresis
- Causes of Angina
    - Damaged endothelium
        - Results in decreased nitric oxide (NO) release leading to unopposed sympathetic innervation → increased vasoconstriction
    - Atherosclerosis – The most common cause
        - Plaques begin as fatty streaks → Macrophages ingest oxidized LDL particle becoming foam cells → the plaque develops a fibrous cap → and finally develops a lipid core.

- Precipitating factors for Angina
  - Any situation that increases myocardial oxygen demand (exertion, tachycardia, arrhythmias, cold weather, eating heavy meal, high stress)

Stable Angina
- Predictable, consistent
- Typically aggravated by a certain amount of stress
- Relieved by:
  - Rest
  - Nitroglycerin, usually within 30 sec. to several minutes

Unstable Angina
- Angina at rest and usually lasts > 20 min.
- Severe, new onset angina
- Increasing angina: increased frequency, duration, and lower stress threshold

******Unstable Angina predicts a much higher short-term risk of an acute coronary event!

Variant/Prinzmetal Angina
- Caused by focal spasm of rather normal coronary arteries
- May occur at rest or be triggered by exertion, and exertion may be variable
- Characterized by ST elevation

Clinical Assessment of Angina
- Characterize the pain:
  - Quality, location, duration
  - Factors that promote and relieve
- Classify the pain
  - *Typical* angina
    - Substernal chest discomfort with a characteristic quality and duration
    - Provoked by stress
    - Relieved by NTG or rest
  - *Atypical* angina
    - Meets 2 of above criteria
  - *Noncardiac* chest pain
    - Meets less then 2 of the typical criteria
- Risk Factors for CAD
  - Modifiable: smoking, hypertension, hyperlipidemia, diabetes
  - Non-modifiable: age, gender (male), genetics, past history of peripheral or cerebrovascular disease

Non-cardiac Conditions That Exacerbate Angina

Increase O2 demand:	Decrease O2 supply
▪ hyperthermia ▪ hyperthyroid ▪ sympathomimetic toxicity ▪ hypertension ▪ anxiety ▪ arteriovenous fistulae	▪ anemia ▪ hypoxemia (COPD, asthma, pneumonia, etc.) ▪ sickle cell dz

Therapy
- Aspirin: 75-325mg daily

    - TXA2 production inhibition via **irreversible** COX blockade
    - Use clopidogrel if aspirin is contraindicated
- Smoking Cessation
- Diet, exercise and weight reduction
- Lipid control
    - Statins, fibrates, niacin
    - Primary goal LDL < 100 mg/dL
- Blood Pressure control
    - Primary goal < 140/90, <130/80 if diabetic
- Beta Blockers:
    - **Do NOT** use in variant angina
    - All beta blockers appear to be equivalent in angina
    - Start at low doses and titrate to HR of 55-60 bmp, watch for bradycardia (<50 bpm)
    - Absolute Contraindications
        - Severe bradycardia
        - High degree of AV blockade
        - Sick sinus syndrome
        - Severe, unstable LV failure
    - Relative Contraindications
        - Asthma and bronchospasm
        - Severe depression
        - Peripheral Vascular Disorder (due to the unopposed alpha receptors → vasoconstriction)
    - Adverse Effects
        - Fatigue, insomnia, nightmares, worsening claudication (PVD)
- Calcium Channel Blockers
    - Verapamil and Diltiazem decrease heart rate and myocardial contractility
    - Dihydropyridines (amlodipine, felodipine, nifedipine) – vasoselective, little inotropic effect. Useful in variant angina
    - Longer acting CCBs are preferred to short acting which have increase cardiac risk
    - Contraindications
        - Overt decompensated HF
        - Bradycardia, sinus node dysfunction, AV nodal blockade
    - Adverse Effects
        - **Constipation**
        - Edema (DHPs)
        - Headache (DHPs)
        - Flushing
        - Dizziness
        - Hypotension
- ACE inhibitor consideration
    - **Use in all patients with stable IHD**
    - Perindopril (Aceon®) – Only ACE inhibitor approved for angina
- Nitrates
    - Sublingual Nitroglycerin
        - All patients with angina
        - 1 SL tablet every 5 minutes times 3 prn chest pain, then call 911
        - store away from heat, moisture and light
    - Long acting nitrates

- Decrease myocardial oxygen demand and improve perfusion
- Have antithrombotic and antiplatelet effects
- Can be used in variant angina
- Improve exercise tolerance and effectiveness of BBs and CCBs in angina and ischemia
- Contraindications
    - Severe aortic valve stenosis
    - Do not give within 24 hours of sildenafil, vardenafil; 48 hrs of tadalafil
- Adverse effects
    - Tolerance to antianginal, hemodynamic, and antiplatelet effects.
        - 8-12 hour nitrate fee period daily
    - Headache
    - Hypotension, syncope, presyncope

MENTALLY ILL AND CHEMICALLY AFFECTED (MICA)
Adapted from Angelo Ballasiotes, PharmD

Definitions

- MICA patient: A person having BOTH a substance abuse or dependence problem AND a diagnosable, significant, psychiatric problem (example- major depression, schizophrenia, bipolar disorder, anxiety disorder).
- Drug abuse: using a mood-altering substance to intoxication in an intermittent or repetitive way
- Drug addiction or dependence: compulsive use of a psychoactive substance despite adverse consequences and is the focus of the user's life
- Physical dependence: chronic use of a drug that results in physiologic adaptation and results in withdrawal reaction upon discontinuation
- Tolerance: progressive decrease in drug effectiveness through physiological adaptation

Commonly abused substances: alcohol, nicotine, marijuana, stimulants, opiates, and hallucinogens.

Treatment options for MICA:

**Treat both addiction and mental disorders simultaneously

1) Psychotherapy
2) AA or other support groups
3) Group therapy
4) Pharmacotherapy

Common mental illnesses of MICA patients

- Schizophrenia:
  - Drugs of abuse producing schizophrenic symptoms: Cocaine, steroids, amphetamines, LSD, marijuana, ecstasy, steroids, and alcohol withdrawal.
  - Treatment: typical or atypical antipsychotics
- Bipolar Disorders (mania and/or depression):
  - Acute phase treatment
    - Anxiolytic and antipsychotic (nonspecific) agents are used to control symptoms.
    - Mood stabilizers (lithium, valproate, cabamazepine, lamotrigine)
  - Maintenance phase treatment
    - Mood stabilizers are primarily used, due to high recurrent nature of bipolar.
    - Can use antipsychotic (Zyprexa) for monotherapy.
- Major Depressive Disorder:

Adjunct Therapies for Substance Abuse

- Disulfiram (Antabuse®)
  - Use – alcoholism. Patient MUST have abstained from alcohol 12 hours prior to administering and must wait 1-2 weeks to eliminate from body.
  - Dose – initial dose is 500mg PO for 1st 1-2 weeks. Maintenance – 250mg daily.
  - Adverse effects – fatigue, dermatitis, impotence, mental changes, LIVER DISEASE. Extreme cases –

respiratory depression, MI, cardiovascular collapse, death.

- Naltrexone (ReVia®)
  - Use – cravings of alcohol and heroin.
  - Dose – Patient has to be opiate free for 7-10 days prior to administration. 50mg daily, 100mg every other day, or 150mg every 3rd day.
  - Adverse effects – headache, N/V, insomnia, joint pain, abdominal cramping, OPIATE withdrawal.
- Acamprosate (Campral®)
  - Use – maintenance therapy for alcohol cravings. Initiated immediately after alcohol detox and recommended therapy is for 1 year.
  - Dose – 666 mg TID
  - Adverse effects – N/V/D, abdominal pain, vasodilation, hypertension, peripheral edema, syncope.

MULTIPLE SCLEROSIS
Adapted from Brian Gates, PharmD

Resources
- National Multiple Sclerosis Society: www.nmss.org
- Multiple Sclerosis Association of America: www.msaa.com

Characteristics
- Inflammatory CNS disease of the myelin sheath around nerves. Flare-ups caused by myelin damage, but can be repaired by body. Permanent disability caused by nerve damage.
- Normal physiology
  - Oligodendrocytes produce, nourish, and sometimes repair myelin (remyelination).
  - Astrocytes are supporting cells in the CNS that may be able to produce and nourish myelin.
- MS pathophysiology: oligos decrease or disappear. Astrocytes increase in number and size, forming thick dense plaques

Symptoms
- Visual disorders
- Slurred speech
- Swallowing disorders
- Numbness
- Dizziness/vertigo
- Bladder, bowel and sexual dysfunction
- Spasticity, weakness, tremor
- Chronic aching pain
- Mild cognitive difficulties
- Impaired mobility
- Extreme fatigue
- Depression
- Migraine

Diagnosis
- Pt. must have 2 neurological events lasting at least 24 hours that were separated by at least 1 month with CNS damage present. Without other explanations.
- Diagnostic tools: CSF fluid, MRI, CT scan, evoked potentials
- Lhermitte's sign: tingling down spine/limbs when neck flexed

Etiology
- Primarily autoimmune dz, genetic predisposition, smoking, viral cause (?), bacterial cause (?), vitamin D deficiency (?)

Clinical Courses
- Benign: Abrupt onset, few exacerbations, no permanent disability, 20% of patients
- Relapsing/Remitting: Abrupt onset, exacerbations can last 1-3 months, 40% develop into secondary, 20-30% of patients
- Secondary Progressive: initial remissions, progressive disability, 40-70% of patients, many start with relapsing/remitting then develop secondary progressive
- Primary progressive: Slow onset, few attacks, disability that worsens over time with unfavorable prognosis, 10-20% of pts

- Progressive/Relapsing: Least common form, progressive decline in dz., will have relapse from which may or may not have recovery

**Attacks less frequent with time and recovery is faster after attack with all types of MS

Complications

- Spasticity: severe constant muscle contractions, originates in CNS.
  - Baclofen (Lioresal®) max 80mg po qd
  - Tizanadine (Zanaflex®) start 4mg tid, max 36mg/day. Watch for orthostatic hypotension and monitor LFTs.
  - Clonazepam (Klonopin®) 0.5-1mg bid, Diazepam (Valium®) 0.5-1mg bid.
  - Dantrolene (Dantrium®): 25mg po qd, max 100mg bid-qid. Watch for hepatotoxicity.
- Depression – treatment can exacerbate
- Neuropathy:
  - Gabapentin (Neurontin®): 100mg tid or 300mg hs.
  - TCAs: Nortriptyline, desipramine preferred in elderly
  - Lidoderm patches
  - Capsaicin
  - Carbamazepine: 100-200mg bid. Useful for trigeminal neuralgia.
- Constipation
  - Diet, various agents
  - Avoid regular enemas
- Urinary incontinence
  - Tolterodine may have fewer SE
  - Concern that anticholinergics will worsen constipation
- Falls
- Fatigue
  - Stimulants, antidepressants helpful
  - Sometimes amantadine helps
- Optic neuritis (lesions on optic nerve)
  - IV steroids then oral steroid taper
- Sexual dysfunction—PDE inhibitors
- Heat intolerance
  - MS Society gives out cooling vests

Treatment

- Preventing or reducing attack severity, slows disease progression—spares neurons
- Treatment of Acute Exacerbations:
  - Corticosteroids: decrease immune response and decrease swelling.
    - Mild exacerbations: Prednisone 60-80mg x 3-5 days with taper
    - Severe exacerbations: Methylprednisolone 500-1000mg daily, decrease with improvement
- Maintenance Therapy
  - Relapsing-remitting MS: Interferon beta-1b, glatiramer acetate, mitoxantrone
  - Secondary progressive MS: Interferon beta-1b, glatiramer acetate, mitoxantrone

MS Drugs

Agent	Dose	MOA	Adverse

			Effects
Interferon beta-1b (Betaseron®, Berlex®)	8 million IU SQ QOD	Suppress T cells, augment suppressor cells, ↓ IFNγ secretion	Injection site rxn, flu-like sx, depression
Interferon beta-1a (Avonex®)	30mcg IM once weekly—most convenient	Natural sequence, glycosylated	Fewer local rxn than Betaseron, less depression
High dose Interferon beta-1a (Rebif®)	22 or 44mcg SQ 3 times per week	Same as Avonex®	Greater SE, maybe more effective than Avonex®
Glatiramer acetate (Copaxone®)	20mg SQ QD	Suppress T-cells;↓ binding class II MHC receptors "suicide drug"	Best tolerated. Mild SE with pain, pruritis at injection site; AMI symptoms: mild chest tightness, flushing, and dyspnea
Mitoxantrone (Novantrone®)	12mg/m^2 short IV infusion Q 3 months. Max lifetime dose is 140mg/m^2	Potent anti-immune agent; also used for some cancers	Immune suppressant, cardiotoxicity with cumulative doses

PERIPHERAL ARTERIAL DISEASE
Adapted from Steve Setter, PharmD, CGP, CDE, DVM

Peripheral Arterial Disease
- Definition: disorder that limits blood flow to the lower limbs—caused by atherosclerosis
- PAD is a marker for CAD; affects ~20% of elderly
- Primary risk factor for atherosclerosis is smoking

Chronic Critical Limb Ischemia
- Worst form of PAD; no blood flow, and tissue dies
- Ischemic rest pain, ulceration, gangrene—often can't walk
- Usually requires amputation—many die after surgery

Intermittent Claudication
- Exertional aching, pain, cramping, tightness, fatigue
- Occurs in muscle groups, not joints
- Reproducible one day to next resolves completely in 2-3 min
- Occurs again at same distance once activity resumed
- Many patients unable to walk more than ½ to 4 blocks

Diagnosis of PAD
- Vascular history
- Physical examination (assess pulses)
- **Ankle- Brachial index measurement (ABI)**
- Noninvasive vascular laboratory
- Ateriography

***ABI is 95% sensitive and 99% specific for PAD**

Intermittent Claudication Care Plan
- Risk factor reduction:
  - Smoking cessation
  - Lipid management
  - Hypertension management
  - Diabetes management
- Treatment:
  - Exercise rehabilitation—must exercise for drugs to work
  - Pharmacologic intervention

Antiplatelet Therapies for PAD
- ASA: 81 mg-225 mg daily
- Ticlodipine (Ticlid®): 250 mg BID
- Clopidogrel (Plavix®): 75 mg daily

Current Drug Therapies for Claudication
- Pentoxifylline (Trental®): 400 mg TID with meals (BID dosing for elders)
  - SE: dizziness, headache, N/V, stomach pain
- Cilostazol (Pletal®) 50 mg or 100 mg BID on empty stomach

**Reduction of symptoms in patients with intermittent claudication, as indicated by an increased walking distance
  - MOA – inhibition of phosphodiesterase III (increase in cAMP) resulting in:
    - antiplatelet activity
    - antithrombotic activity
    - produces vasodilation
    - mildly increases heart rate
    - increases blood flow
    - increases HDL-C

        - Decreases triglycerides
        - In vitro inhibition of vascular smooth muscle cells
    - Excretion renal (74%), hepatic (20%)
    - Metabolized by CYP 3A4—use half dose if patient on CYP3A4 inhibitor
    - Initial benefit achieved over 2-12 weeks
    - Benefit declines after 1 month of discontinuation
    - *Cilostazol should be used for the life of the patient*
    - SE: headache, diarrhea, palpitations, dizziness, edema
    - Take APAP for HA and loperamide for diarrhea
    - Contraindications: CHF of any severity

PARKINSON'S DISEASE
Adapted from Steve Setter, PharmD, CGP, DVM

Resources
- National Parkinson Foundation: www.parkinson.org
- Worldwide Education and Awareness of Movement Disorders Website: www.wemove.org

Background
- Pathophysiology: Parkinson's is a disease defined by its striatal dopamine deficiency.
- Diagnosis must include two of the following: tremor at rest, rigidity, bradykinesia, and postural instability and absence of secondary cause. Other signs include masked face, soft speech, swallowing difficulties, microphagia, flexed posture, shuffling gait, and freezing.
- Drug-induced causes of Parkinson's
  - Antipsychotics (haloperidol, chlorpromazine, thioridizine, perphenzine, risperidone, olanzapine)
  - Antiemetics (metoclopramide, and prochlorperazine)
  - Dopamine depletors (methyldopa, reserpine, tetrabenazine)
  - Triavil (amitriptyline and perphenazine)

  **Treatment is to stop the offending medication and the symptoms are usually reversible.

Treatment
- Treatment is symptomatic only.
- As the disease progresses, the therapeutic window narrows
- There are regular and predictable declines in response 2-4 hours after the levodopa dose.
- There are also sudden and unpredictable "off periods" unrelated to dosing schedules that are very difficult to manage.
- May get muscle freezing, which increases fall/fracture risk
- General SE associated with all dopamine meds: nausea, dizziness, somnolence, fatigue, constipation, vivid dreams and nightmares, confusion, and hallucinations.
- Treatment strategies are to replace dopamine (levodopa and dopamine agonists) , enhance dopamine (COMT inhibitors and Amantadine) or block Ach (anticholinergics) and are as follows:

Meds to Treat Parkinson's Diesease			
Medication	Starting Dose	Side Effects	Indication
Levodopa			
Carbidopa / levodopa (Sinemet®)	25/100 bid-tid	low BP, nausea, confusion, dyskinesia	First line or add to DA
Carbidopa / levodopa CR (Sinemet CR®)	50/200 bid		
Stalevo® 50mg	-	dyskinesia, nausea, ab. pain,	Levodopa wearing off
Stalevo® 100mg	-		

Stalevo® 150mg	-	constipation, dizziness, fatigue, hallucinations	
Dopamine Agonists (DA)			
bromocriptine (Parlodel®)	2.5mg tid	low BP, nausea, edema, discolored skin blotches, confusion	First line or add to levodopa
pergolide (Permax®)	0.05 -0.25 mg tid		
pramipexole (Mirapex®)	0.125 mg tid	above + sleep attacks, sedation, hallucinations	
ropinirole (Requip®)	0.25 mg tid	nausea, low BP, sleep attacks, sedation	
Apomorphine (Apokyn®)			Hypomobility or off episodes in advanced PD
Catecholamine-o-methyltransferase (COMT) Inhibitors			
entacapone (Comtan®)	200 mg with each dose levodopa	blood in urine, diarrhea, low BP, nausea, confusion, dyskinesia tolcapone: liver faliure	Second line wearing off
tolcapone (Tasma®r)	100 mg tid		Third line, motor fluctuations
Amantadine			
(Symmetrel®)	100 mg bid-tid	low BP, nausea, edema, discolored skin blotches, confusion	Second line, motor fluctuations
MAO-type B Inhibitor			
Selegiline (Carbex® | Eldepryl®)	5 mg BID with breakfast and lunch	Insomnia, hallucinations, nausea, anxiety, dyskinesias (Do not take with Meperidine)	In combo with levodopa
Anticholinergics			
Trihexy-phenidyl (Artane®)	1 mg tid - qid	Dry mouth, sedation, confusion, constipation, urinary retention	Adjunctive treatment for mild motor problems
Benztropine (Cogentin®)	0.5 – 1 mg HS		
Biperiden (Akineton®)	2 mg tid - qid		

PITUITARY DISORDERS
Adapted from Ken Cathcart, DO

Acromegaly
- Excessive growth hormone production
- 98% are from growth hormone secreting pituitary adenoma
- Presentation
  - Coarsening of facial features
  - Increased hand volume
  - Increased shoe size
  - Enlarged tongue
  - Osteoarthritis
  - Glucose intolerance
  - Heart/kidney enlargement
  - Lose ~10 years of life
- Treatment
  - Surgery = current standard, but will change in 5 years
  - Dopamine agonists
    - Bromocriptine, pergolide, cabergoline, lisuride, quinagolide—only help ~1/2 of patients
    - Octreotide
      - Suppresses GH and IGF-1
      - 100 mcg IM/SQ q8hrs—increase by 50 mcg q1-2 weeks
    - Pegvisomant
      - Decoy—binds GH receptor but no signaling

Growth Hormone Deficiency
- Can be congenital or acquired after trauma/radiation
- Presentation
  - Short
  - Centrally obese
  - Prominent forehead
  - Immature face
  - Diabetes
  - Osteoporosis
  - Depression
- Treatment
  - Growth hormone 0.15-0.3 mg/kg/wk
    - SE: injection site pain, arthralgias, intracranial hypertension, expense
  - GHRH 0.03 mg/kg/d SQ
    - No serious SE, but not as effective as GH

Hyperprolactinemia
- Causes: tumors, stress, dopamine antagonists (antipsychotics), SSRIs, metoclopramide, hormones
  - Any drugs that work in CNS can cause
- Presentation: sexual dysfunction, lactation, amenorrhea
- Treatment
  - Removal of drug cause
  - Irradiation
  - Dopamine agonists
    - Bromocriptine 1.25 BID up to 20 mg BID
    - Pergolide off-label
    - Cabergoline 0.5 mg once weekly initially

PSYCHOSIS/SCHIZOPHRENIA
Adapted from Brandy Singer, RPh

Resources
- VA recommendations for atypical antipsychotics: www.vapbm.org
- Audio/video for schizophrenia: www.schizophrenia.com
- Virtual Hallucination: www.npr.org/programs/atc/features/2002/aug/schizophrenia/
- National Alliance for the Mentally Ill: www.nami.org

Psychosis/Schizophrenia
- Definition: psychosis is a syndrome (set of symptoms) in which a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others is impaired
- Diagnosis: disturbance for >6 mo with >1 mo of delusions, hallucinations, disorganized speech, grossly disorganized catatonic behavior, or negative symptoms
- Initiation: Long-term alteration in neuronal function due to variety of environmental factors. Limbic system of the brain is affected. Possible initiation factors: prenatal alteration of temporal lobe due to hypoxia, exposure to stress, abuse of pyschomotor stimulants (cocaine, amphetamine).

Postive Symptoms: ("excess" of normal functions)
- Delusions: misinterpretation of perception or experiences (persecutory, referential, somatic, religious, grandiose)
- Hallucinations: auditory, visual, olfactory, gustatory, tactile
- Disorganzied speech: exaggerations in language, "word salad"
- Disorganized behavior (inappropriate laughing/tears)
- Catatonic behavior
- Depersonalization
- Derealization
- Agitation
- Paranoia

Negative Symptoms: ("reduction" in normal functions)
- Affective flattening (bland emotions) – Apathy
- Alogia (speechlessness caused by mental confusion)
- Avolition (lacking energy, spontaneity, motivation, or initiative)
- Anhedonia (lack of pleasure)
- Attention impairment

**often come out after positive symptoms are treated

Cognitive Symptoms: (can overlap with negative)
- Impaired attention/ vigilance
- Impaired memory
- Impaired verbal fluency
- Impaired abstract thinking
- Impaired visual processing
- Neologisms (meaningless words)
- Odd use of language (incoherent, loose association)

Aggressive Symptoms: (can overlap with positive)
- Hostile (verbally or physically abusive)

- Impulsive (suicide, sexually acting out, self-injurious behavior, arson, property damage)

Depressive/Anxious Symptoms
- Depressed / anxious mood
- Guilt, tension, irritability, worry

Neurochemistry of Schizophrenia
- Mesolimbic Pathway (positive symptoms)
  - Increased DA leads to positive symptoms
  - DA-2 blockade relieves positive symptoms (anti-psychotics block)
  - 5HT2a blockade doesn't increase DA significantly (good if trying to block positive symptoms)
- Mesocortical Pathway (negative symptoms and cognition)
  - DA-2 blockade worsens neg. sx and cognition (typicals)
  - DA-2 stim. improves neg. sx and cognition (atypicals)
  - 5HT2a blockade increases DA (improves neg. sx)
- Nigrostriatal Pathway (involuntary movements)
  - DA-2 Blockade leads to EPS
  - Stimulation of DA-2 causes hyperkinetic movements
  - 5HT2a blockade increases DA
- Tuberinfundibular Pathway (prolactin secretion)
  - ↑DA inhibits prolactin
  - DA-2 blockade leads to hyperprolactinemia
  - 5HT2a blockade doesn't increase DA significantly (still get hyperprolactinemia with atypicals)

Receptor Blocking Activity of Antipsychotics

Drug	DA	5HT	α	H1	M1
Halo-peridol	D2>>> D1	Low	Mod	Low	Low
Cloz-apine	D2=D1, D4 (D2 40-60%)	5HT2, others (highest of atypicals)	Strong α1 and α2	Strong	Strong
Risper-idone	D2 (75-80%), D4, low D1	Balanced D2, 5HT blocker	Strong α1 and α2	Mild	Weak
Olanz-apine	D2=D1 & D4	Mod 5HT2	Mild-mod α1	Mod-strong	Strong
Quetia-pine	D2 (mod) > D1 (low)	Mod 5HT2	Mod α1 and α2	Mod	Minimal
Zipras-idone	5HT2 > D2 (11:1); 5 HT1 Agonist; blocks reuptake of NE/5HT		Mod α1, mild α2	Mod	Mild
Aripip-razole	D2 partial agonist; D3	5HT1A partial agonist; 2A antag.	Mod α1	Mod	None?

Side Effects of Receptor Blockade

- Alpha blockade = dizziness, postural hypotension, drowsiness, reflex tachycardia, sexual dysfunction.
- Muscarinic (M1) blockade – anticholinergic side effects (dry mouth =xerostomia, urinary retention, constipation, dilated pupils=mydriasis, tachycardia, confusion, memory problems)
- Histamine (H1) blockade = drowsiness, weight gain
- DA-2 blockade worsens negative symptoms, cognition, EPS, hyperprolactinemia

Atypical vs. Typical Symptom Relief

	Atypicals	Typicals
Positive sx	Helps☺	Helps☺
Negative sx	Helps☺	Hurts
Cognitive sx	Helps☺	Hurts
Aggressive sx	Helps☺	Helps☺
Depressive / Anxiety sx	Helps☺	?

Comparison of adverse effects:

1. Weight gain- H1 & 5HT2 blocking
Clozaril® > Zyprexa® > Seroquel® = Risperdal® >Geodon® = Abilify®
2. Orthostatic Hypotension – α1 blockade
Clozaril® > Seroquel® = Risperdal® > Zyprexa® > Geodon® = Abilify®
3. Anticholinergic Side Effects – Muscarinic blockade
Clozaril® > Zyprexa® > Seroquel® = Risperdal® = Geodon® = Abilify®
4. Serum Prolactin levels elevated
Risperdal® > Zyprexa® > Geodon® > Seroquel® = Clozaril® = Abilify®
5. Sedation
Clozaril® > Zyprexa® = Seroquel® > Risperdal® = Abilify® > Geodon®
6. Constipation
Clozaril® > all other atypicals
7. EPS
Risperdal® > Zyprexa® > Geodon® > Seroquel® = Abilify® = Clozaril®

Antipsychotic Drug Therapies

Drug	Dose	Main SE	Tidbit
Clozapine (Clozaril®)	12.5 – 900 mg divided BID	Agranulocytosis, weight gain, hypotension, sedation, anticholinergic, seizures, constipation	▪ Effective for refractory cases, negative symptoms ▪ Weekly WBC x 6 mo then q2 wks
Risperidone (Risperdal®)	2 – 8 mg divided BID	EPS, prolactin elevation, hypotension	▪ Doses >6 mg/day no more effective ▪ Long-acting injection
Olanzapine (Zyprexa®)	5 – 40 mg HS	Weight gain, diabetes, lipids	Expensive
Quetiapine (Seroquel®)	50 – 1200 mg/d divided BID	Sedation, weight gain, anticholinergic, hypotension, QT prolongation	▪ No prolactin elevation ▪ Hold if BP < 90/60 mmHg

Ziprasidone (Geodon®)	40 – 320 mg/d divided BID	EPS, sedation, hypotension	▪ Weight neutral ▪ Increase dose quickly to avoid agitation ▪ Take with food for absorption
Aripiprazole (Abilify®)	15 – 30 mg QD	Mildest SE profile	Difficult to predict response

**all are equally effective—choose drug with best SE profile

SEIZURE DISORDERS
Adapted from Brandy Singer, RPh

Definitions
- Seizure: excessive discharge of neurons; spontaneous abnormalities of brain electrical activity.
- Convulsion: violent, involuntary contractions of voluntary muscles.
- Epilepsy: a recurrent paroxysmal disorder of cerebral function marked by sudden, brief attacks of altered consciousness, motor activity, or sensory phenomena
- Status Epilepticus: seizure that is prolonged or repeated at short intervals to produce unvarying or enduring epileptic condition
- Febrile Seizure: seizure with fever—most common in peds

Seizure Etiology

Etiology	Example
Mechanical	Head trauma, stroke, tumor
Metabolic	Hypoglycemia, hyponatremia
Toxins	CNS infection, high fever
Genetic/Idiopathic	
Drug Withdrawal	CNS depressants
Other	Hyperventilation, sleep deprivation, hormonal changes
Drugs	CNS stimulants (cocaine), phenothiazines, TCAs, anti-infective accumulation (beta-lactams, imipenem, acyclovir, ganciclovir, quinolones), theophylline, anticonvulsant "intoxication" (paradoxical), pertussis immunization (febrile seizure risk)

International Classification of Epileptic Seizures (ICES)
- Partial: Involves only one portion of brain at onset.
  - Simple: without LOC
  - Complex: with LOC
  - Secondary generalized: starts local, then spreads to generalized
- Generalized: Diffuse, affects both cerebral hemispheres
  - Absence: Altered consciousness, staring, loss of postural tone. Lasts 10-30 seconds. Usually young pts.
  - Myoclonic: Involuntary jerking of facial, limb, trunk muscles. Brief.
  - Tonic-clonic: Sudden loss of consciousness, falls to ground, rigid, respiration interrupted, legs extend, back arches, grunting. 1 minute. (tonic) Rapid bilateral muscle jerking, flaccidity, hyperventilation, incontinence, tongue biting, tachycardia, salivation. (clonic)

When to Treat with Drugs
- One seizure with one or more risk factors (family history, partial seizures, etc)
- Two or more seizures

**Goal is to be free of adverse effects—decreasing seizure frequency doesn't impact quality of life like adverse effects

Guidelines with Drug Therapy

- Shoot for monotherapy
- Start at 1/4 - 1/3 of the maintenance dose
- Adjust slowly for response/tolerability
- Mood disorders and cognitive function also impacted by epilepsy, not just a seizure disorder
- Treatment is usually life-long
- May try gradual withdrawal (over 6-36 wks) if seizure free for >2-4 yrs
- Must avoid driving for >4 mo after starting withdrawal
- Check drug levels if poor seizure control, drug interaction, toxicity

Adverse Effects

- Common: fatigue, concentration problems, tremor
- Pregnancy/Contraception
  - Drugs can lower effectiveness of BCPs (esp. low-dose estrogen and older anti-epileptic drugs)
  - Planned pregnancies: use monotherapy 6 mo before conception
  - AEDs interfere with folate metabolism—must give 0.4 – 5 mg/day folic acid and multivitamin to prevent neural tube defects
  - Risk of malformation increases with number of AEDs
- Osteopenia/osteoporosis
  - AEDs reduce bone mineral density
  - Recommend calcium and vitamin D supplement
    - 1200-1500 mg and 600 IU per day
  - Consider bisphosphonates, calcitonin, HRT
- Metabolic Side Effects
  - Weight gain (can be >20%)
  - Sexual Dysfunction
  - Menstrual cycle abnormalities (shorter or longer cycle length, mid-cycle bleeding)
  - Ovulatory dysfunction (trouble conceiving or history of early-term miscarriage)
  - Polycystic ovarian syndrome
    - Hirsutism, obesity, acne, insulin resistance
    - Increased androgens and LH/FSH ratio
- Rash
  - All AEDs have rash potential
  - Gabapentin, levetiracetam, and Depakote® have least potential for rash
  - Usually see erythematous maculopapular or morbilliform lesions on trunk, face, or upper arms
  - Warning signs: temp >40°C, exfoliation, facial edema, skin pain/necrosis, mucosal lesions, asthmatic symptoms, lymph node enlargement, palpable purpura

Drugs of Choice Based on International League Against Epilepsy: ICES scheme

Antiepileptic Drug Choices based on Seizure Types[a]				
Primary Generalized Tonic-Clonic	Secondarily Generalized Tonic-Clonic	Simple or Complex Partial	Absence	Myoclonic Atonic/Akinetic
Most Effective----------Acceptable Toxicity				
Valproate Phenytoin Carbamazepine (may worsen some types) (Lamotrigine)[b] (Topiramate)[b] (Tigavine)[b] (Gabapentin)[b] (Levetiracetam)[b] (Zonisamide)[b] (Oxcarbazepine)[b]	Carbamazepine Phenytoin Valproate (Lamotrigine)[b] (Topiramate)[b] (Tigavine)[b] (Gabapentin)[b] (Levetiracetam)[b] (Zonisamide)[b] (Oxcarbazepine)[b]	Carbamazepine Phenytoin Valproate Lamotrigine (Topiramate)[b] (Tiagabine)[b] Gabapentin)[b] (Levetiracetam)[b] (Zonisamide)[b] (Oxcarbazepine)[b]	Ethosuxamide Valproate Lamotrigine[b] Topiramate[b]	Valproate Clonazepam (Lamotrigine)[b] (Topiramate)[b] (Tiagabine)[b]
Effective----------Often have unacceptable toxicity				
Phenobarbital Primidone (Felbamate)[c]	Phenobarbital Primidone (Felbamate)[c]	Clorazepate Phenobarbital Primidone (Felbamate)[c]	Clonazepam Trimethadione	(Felbamate)[c]
Of Little Value				
Ethosuxamide	Ethosuxamide	Ethosuxamide	Carbamazepine	

Trimethadione	Trimethadione	Trimethadione	Phenytoin Phenobarbital Primidone	

[a] Drugs are listed in general order of preference within each category. Recommendations by various authorities may differ, especially regarding the relative place of valproate and the role of phenytoin as a first-line AED. Many authorities now discourage the use of Phenobarbital and primidone.
[b] The places of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, zonisamide, & levetiracetam are yet to be determined. They are placed on this table only to indicate the types of seizures for which they appear to be effective. Much more clinical experience is needed before their roles as possible primary AEDs are clarified.
[c] More experience is needed before felbamate's role as a primary AED is clarified. Felbamate has been associated with aplastic anemia and hepatic failure; until a possible causative role is clarified, felbamate cannot be recommended for treatment of epilepsy unless all other, potentially less toxic treatment options have been exhausted
Chart adapted from Rex Lott, PharmD.

Traditional Antiepileptic Medications

Drug	Effective level	Clinical Uses	Mechanism	Side Effects
Phenytoin (Dilantin®)	10-20 mcg/ml (free level 1-3 mcg/ml)	Partial and tonic-clonic AVOID in absence (worsens)	Prolongs closing of inactivating gate of Na^+ channels of excitatory NT receptors in the CNS	Ataxia, vertigo, diplopia, nystagmus. Tissue overgrowth (gingival hyperplasia). Hirsutism, acne, altered vitamin D metab., altered folate metab., weak hepatic inducer, fetal malformation
Fosphenytoin (Cerebyx®)		Given IV and IM	See above. Dosed as "phenytoin equivalents"	Incompatibilities with other IV. Cardiac depression. Pain w/ IM, erratic absorption

Carbamazepine (Tegretol®)	4-12mcg/ml	Partial and tonic-clonic. AVOID in absence, myoclonic	Prolongs closing of inactivating gate of Na^+ of excitatory NT receptors in CNS	Sedation, ataxia, blurred vision, serious hematological toxicity (aplastic anemia, agranulocytosis), hyponatremia, autoinducer
Phenobarbital (Luminal®) Primidone (Mysoline®)	10-40mcg/ml	Partial and tonic-clonic. 1st line in neonatal seizures. DISCOURAGE use in absence	Facilitates the inhibitory action of GABA, increases the duration of Cl^- channel opening at GABA-A receptors	Sedation, abnormal vitamin D metab, decreased folate level, irritability and hyperactivity in children, respiratory depression possible, induces ALS-synthetase. Risk of dependence, withdrawal, overdose, interacts with alcohol and MAOI, autoinducer
Ethosuximide (Zarontin®)	50-100 mcg/ml	Absence	Inhibits low-threshold T-type Ca^{++} currents in thalamic neurons	Nausea, anorexia, mood changes, headaches
Clonazepam (Klonopin®)	0-1mcg/ml	Absence and myoclonic	Facilitates the inhibitory actions of GABA	Sedation, lethargy (50%), dependence and withdrawal
Diazepam (Valium®)	600mcg/ml	Status epilepticus	Increases the frequency of opening of Cl^- channel of GABA-A receptor	Behavioral disturbances in children, interaction with alcohol, interaction with valproic acid
Chlorazepate (Tranzene®)		Partial myoclonic, absence		
Valproic Acid (Depakene®) Divalproex Na	50-100mcg/ml	Partial, tonic-clonic, and absence	Prolongs the inactivation of Na^+ channels of excitatory NT receptors	Nausea, alopecia, hepatitis, weight gain, mild elevation AST, ALT, LDH. Potent inhibitor. Interacts with aspirin

(Depakote®)			in CNS. Inhibits low-threshold T-type Ca^{++} currents in thalamic neurons. ↑ the amt. of GABA in CNS. ↑ GAD activity. ↓GABA-T and succinic semialdehyde dehydrogenase activity	(bleeding), alcohol, other CNS depressants
Trimethadione	20mcg/ml	Absence	Inhibits low-threshold T-type Ca^{++} currents in thalamic neurons	Sedation, hemeralopia, hepatitis, nephrosis, mild neutropenia (20%), aplastic anemia, SE are serious and limiting
Bromide	10-20mcg/ml	Epilepsy in porphyrias	Not known	Skin rash. Sedation. Behavior changes

Newer Antiepileptic Drugs

Drug	Clinical Uses	Mechanism	Side effects
Felbamate (Felbatrol®)	Partial seizures, Lennox-Gastaut syndrome	Possible blockade of NMDA receptor	Nausea, anorexia, wt. loss, fatigue, drowsiness, anxiety, HA, severe hepatitis (1/10000), aplastic anemia (1/3000)
Gabapentin (Neurontin®)	Adjunct drug for partial and generalized tonic-clonic seizures	Increases the release of GABA	Somnolence, dizziness, ataxia, HA, weight gain
Lamotrigine	Partial seizures	Prolongs closing of inactivating gate	Dizziness, HA, diplopia, somnolence, skin

		of Na^+ channel	rash
Levetiracetam (Keppra®)	Adjunct drug for partial seizures with or without secondary generalization	Not known	Minimal drowsiness, anxiety, amnesia
Oxcarbazepine (Trileptal®)	Partial seizures with or without generalization	Blockage of voltage sensitive Na^+ channels. Like carbamazepine but is metabolized to 10-hydroxy derivative	CNS SE, hematological abnormalities and effects on drug metabolizing enzymes are less than carbamazepine
Tiagabine (Gabatril®)	Adjunct for partial seizures	Inhibition of GABA uptake	Nervousness, dizziness, tremor, depression, weight loss, kidney stones
Topiramate (Topamax®)	Partial and generalize tonic-clonic seizures	Prolongs closing of inactivating gate of Na^+ channel, potentiates the GABA effect and block AMPA receptors	Somnolence, fatigue, dizziness, paresthesia, confusion
Vigabatrin (Sabril®) not in US	Partial seizures	Irreversible inhibitor of GABA aminotransferase (GABA-T)	Drowsiness, dizziness, wt. gain, psychosis
Zonisamide (Zonegran®)	Partial and generalized tonic-clonic seizures	Inactivation of Na^+ and Ca^{++} channels	Drowsiness, cognitive impairment, kidney stones, rash

STROKE
Adapted from Heather Gamache, PharmD

Recognizing Stroke
- Sudden numbness/weakness of face, arm, leg, especially on one side of the body
- Sudden confusion, trouble speaking/understanding
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance/coordination
- Sudden, severe headache with no known cause

Risk Factors: Non-modifiable
- Age: >55 years old
- Gender:
  - Morbidity: men > women
  - Mortality: women > men
- Race/Ethnicity: African Americans, Hispanic, Native American, some Asian populations
- Heredity; Close FMH of stroke/TIA, CAD, DM, or other vascular disease may increase hereditary risk

Risk Factors: Modifiable
- Hypertension is the number one cause of stroke
- Cardiac disease: A fib, stenosis, calcification or enlargement of valves
- Diabetes
- Cigarette smoking
- Illicit drug use
- Life style factors

Conditions that Mimic Stroke
- Hypoglycemia
- Seizures
- Brain tumor
- Encephalopathy
- Migraine

Ischemic Stroke
- ~85% of strokes
- Caused when an artery to the brain is blocked which stops or decreases blood flow
  - Thrombotic stroke: diseased or damaged cerebral arteries become blocked by the formation of a blood clot within the brain
  - Embolic stroke: cerebral arteries become blocked by a clot within the artery, but the clot was formed somewhere other than in the brain
- Treatment:
  - Aspirin 325 mg if > 3 hrs, but <48 hrs since onset
  - Clot-buster: FDA approved – Tissue Plasminogen Activator – t-PA (Activase®) or alteplase requires <u>3 hour time window</u>
- t-PA Protocol Guideline:
  - Patient Eligibility
    - >18 yo
    - Clinical diagnosis of ischemic stroke
    - Measurable neurologic deficit
    - Rule out seizure or migraine event

        - 3 hr time frame from symptom onset to treatment
    - Contraindications/Warnings
        - Intracranial hemorrhage
        - Minor or resolving symptoms
        - Platelets < 100,000/mm^3
        - Heparin within 48 hrs
        - Current warfarin use
        - INR > 1.6
        - Surgery, trauma, active bleeding
        - Blood glucose <50 or >400 mg/dL
    - Alteplase Dosing
        - 0.9 mg/kg (NTE 90 mg)
        - Give 10% of total dose as IV bolus over 1 minute
        - Give other 90% as infusion over 60 min
        - Dilute to 1 mg/ml in D5W or NS
        - Do not give aspirin, heparin, warfarin, or other antiplatelet agents within firs 24 hrs after symptom onset
        - SE: bleeding, hypotension, fever, N/V
    - Monitoring
        - Monitor BP q 15 min
        - BP should be <185/110 mmHg before giving t-PA
            - Nitroglycerin paste or labetalol 10-20 mg to lower blood pressure
        - BP should be <180/105 mmHg during treatment
        - Suspect hemorrhage if
            - Acute neurologic deterioration
            - New headache
            - Acute hypertension
            - N/V
        - If hemorrhage, D/C t-PA, get immediate CT
            - Type and cross match:
                - 6-8 units cryoprecipitate with factor VIII
                - 6-8 units platelets
            - Consult neurosurgeon

Secondary Prevention – American College of Chest Physicians:

- First line agents following acute stroke:
    - Aspirin 81-325 mg daily
    - Clopidogrel (Plavix®) 75 mg daily
    - Extended release dipyridamole plus aspirin (ERDP + ASA)—about as effective as aspirin
- Stroke with A fib:
    - Warfarin (INR goal = 2.5)
- DVT Prevention—heparin or enoxaparin
- ACE-Inhibitor/ARB, diuretic—JNCVII recommendation
- Statin—NCEP recommendation
- Non-Pharmacologic:
    - Carotid Endarterectomy
    - Carotid Stenting

Hemorrhagic Stroke

- ~15% of strokes
- Caused by burst or leaking blood vessels in the brain
- Intracerebral hemorrhagic stroke: a blood vessel within the brain ruptures, forming a hematoma

- Subarachnoid hemorrhagic stroke: a blood vessel just outside the brain ruptures
- Treatment:
    - Surgical Intervention or endovascular Procedures, e.g., “coils”
- Manage:
    - Blood pressure
    - Raised intracranial pressure
        - Steroids – swelling
            - Dexamethasone 10 mg IV stat then 4 mg IV q 6 hrs until response
        - Anticonvulsant – seizures
            - Phenytoin 15-25 mg/kg IV load then 5-6 mg/kg/day IV q 8 hrs

THYROID DISORDERS
Adapted from Ken Cathcart, DO

Hyperthyroidism
S/S: over 150 symptoms, but most common are weakness and fatigue

Two mechanisms based on RAIU:
1. Hyperthyroidism with high RAIU:
    - Grave's disease, toxic adenoma or multinodular goiter
    - Treatment: thionamides (1st line for Grave's), surgery, radioablation
2. Hyperthyroidism with low RAIU:
    - Subacute thyroiditis: DeQuervain's thyroiditis (viral), chemical toxicity (amiodarone), and radioactive thyroiditis.
    - Treatment: high-dose beta blocker (e.g. 100 mg atenolol BID-TID), NSAID, ASA and prednisone

Thyroid Storm:
- Life threatening, characterized by fever >103 ^{o}F, tachycardia, tachypnea, dehydration, delirium, and coma
- *Treatments:* suppression of thyroid hormone, antiadrenergics, corticosteroids, and treatment of cause
    - Iopinoic acid ~5g stops conversion of T_4 to T_3 and useful for thyroid storm

Management of Hyperthyroidism
- Thionamides [Propylthiouracil (PTU), and methimazole]:
    - MOA: likely immunosuppression
    - PTU:
        - Dose: 300-450mg q8h, maintenance: 100-150 mg/day divided q8-12h
        - Renal adjustment: CrCl=10-50% gives 70% of the dose, CrCl = <10% gives 50% of the dose
        - SE: rash, leukopenia→agranulocytosis, arthralgia, GI, and hepatitis
        - DO NOT cross placenta
    - Methimazole:
        - Dose: 15mg/day for mild disease (dz), 30-40mg/day for moderately severe dz, 60mg/day for severe dz
        - Maintenance: 5-15mg/day divided TID with meals
        - SE: rash, arthralgia, hepatitis, GI, and CNS
        - Precaution: agranulocytosis
- Surgery: no longer done because high risk
- Radioiodine:
    - Most popular treatment: oral radioactive iodine-131 then revaluate in 6-8 weeks
    - Caution: women child bearing age

Hypothyroidism:
1. Primary Cause: Hashimoto's, iodine deficiency (Cretinism)
2. Secondary Cause: pituitary failure—TSH deficiency
3. Tertiary Cause: hypothalamus—TRH deficiency
4. Iatrogenic hypothyroidism following radiation or surgery

Treatment
- Thyroid replacement:

no need for T_3

- Levothyroxine: Oral dose-1.7mcg/kg/day, average dose 100mcg/day.
- Elderly w/o cardiac dz: 25-50mcg/day and 12.5-25mcg for cardiac dz.
- Administration: empty stomach

Drug Interactions

Increase TBG	*Decrease TBG*	*Decrease Bioavailability of levothyroxine*	*Increase Clearance of levothyroxine*
Estrogen	Androgen	Aluminum hydroxide	Carbamazepine
Fluorouracil	Glucocorticoid	Sucralfate	Phenobarbital
Heroin	Anabolic steroid	Ferrous Sulfate	Phenytoin
Methadone	Nicotinic acid (CR)	Cholestyramine	Rifampin
Mitotane		Colestipol	
Tamoxifen		Calcium Carbonate	

TOURETTE'S SYNDROME
Adapted from Clarke St. Dennis, PhD, BCPP

Characteristics
- Movement disorder characterized by motor and phonic tics, which must be present for at least one year for diagnosis
  - Motor Tics
    - Eye blinking, head jerking, grimacing, shrugging
  - Phonic Tics
    - Throat clearing, grunting, snorting, barking, hooting, repetitive words/parts of words

    **excessive swearing or gesturing is rare
- Cause = imbalance of dopamine, serotonin, and NE leads to decreased function of brain's inhibitory mechanisms
- Symptoms usually start in childhood (usually by 14 yo), stabilize in twenties, and resolve with older age
- Symptom severity varies with patient

Epidemiology
- Strong genetic link—family members often have chronic tics, Tourette's, or OCD
- Other co-morbid disorders: ADHD (~60%), OCD (~50%)
- Affects 0.05% of population—2-4x more common in boys

Treatment
- General Principles
  - Tourette's patients are often sensitive to medications—start with low doses and increase at weekly intervals
  - Initial effect often plateaus after several weeks
  - Always taper off drugs to avoid withdrawal
  - If tics disappear for several weeks, decrease dose or taper off completely
- Antipsychotics
  - Most effective
  - Often avoided in children because EPS concern with long-term use
  - FDA-approved typical antipsychotics
    - Pimozide (Orap®)
      - Probably better than haloperidol
      - Maximum daily dose = 20 mg/day
    - Haloperidol (Haldol®)
      - Start 0.25-0.5 mg/d HS and increase slowly
      - Usual maintenance dose 5-10 mg/day
      - May reduce tics within 2-3 days of starting
  - Atypical antipsychotics: fewer EPS SE, increased cognition, anxiolytic activity, mood stabilization, and equal to typical antipsychotics for agitation/aggression
    - Risperidone (Risperdal®)
      - Average daily dose = 2.7 mg
    - Olanzapine (Zyprexa®)
- Alpha-2 Agonists
  - Clonidine (Catapres®)
    - Test dose with 0.025 – 0.05 mg in morning
    - Usual maintenance 0.15 – 0.25 mg/day in 3-4 divided doses (max dose 0.5 mg/day)
    - SE: sedation, hypotension, death when combined with Ritalin®

        - Often see attention/behavioral benefit with no reduction in tics
    - Guanfacine (Tenex®)
- Nicotine (gum or patch)—minor decrease in tic frequency
- High-dose SSRI if concomitant OCD
    - SSRIs cause restlessness and disinhibition in 20-40% of patients, though—D/C if patient becomes manic
- If concomitant ADHD
    - Stimulants may worsen tics, but not confirmed in trials
    - If tics worsen, consider antidepressant

TYPE 1 DIABETES MELLITUS
Adapted from Steve Setter, PharmD, CGP, CDE, DVM

Resources
- Using Insulin by John Walsh, PA, CDE
- Diabetes Health Website: www.diabeteshealth.com

Pathophysiology
- Cause - beta cell destruction with lack of insulin (absolute insulin deficiency).
- Requires treatment with exogenous insulin
- Usually first diagnosed after DKA episode

Type 1 vs. Type 2 Diabetes

	Type 1 Diabetes	Type 2 Diabetes
Percent of Diabetic Patients	5 – 10%	~90%
Typical Age of Onset	< 30 yo	> 40 yo
Pathogenesis	Autoimmune	▪ Insulin resistance ▪ β-cell dysfunction ▪ Increased glucose output by liver
Obesity	Uncommon	Common
Treatment	Insulin	▪ Lifestyle ▪ Pharmacotherapy including insulin
Diabetic Ketoacidosis	Common	Rare

Diabetes Targets by ADA and AACE

	American Diabetes Association	American Association of Clinical Endocrinologists
Target HbA1c	< 7%	< 6.5%
Target Fasting Glucose	< 90-130 mg/dL	< 110 mg/dL
Peak PPG	< 180 mg/dL	< 140 mg/dL
When to screen	> 45 yo	> 30 yo

Symptoms of Hyperglycemia
- Weak
- Stomach pains
- Loss of appetite
- Poor sleep
- Fatigue

Insulin Therapy = cornerstone of treatment
- Decreases blood sugar by increasing storage in liver and muscle, decreasing output by liver; also promotes triglyceride storage by adipose tissue
- Type 1 diabetics make no insulin and need supplement
- Must "think like a pancreas"—basal/bolus model

Basal/Bolus Model
- Normal Physiology
  - Pancreas produces ~1-1.5 units insulin/hr with bolus of 1 unit/10 gm carbs during meals

    - Basal insulin suppresses glucose between meals and overnight
    - Bolus controls post-prandial glucose
    - ~Half of daily insulin requirement is basal, other half divided between meals
- Best insulin therapy models normal physiology "think like a pancreas"
- Use rapid or short-acting insulin for bolus
    - Rapid is best, because easier to time with meals and adjust for postprandial control
    - Rapid has less incidence of hypoglycemia
- Use long-acting insulin for basal
    - Glargine best, because no peak, and once-daily dosing

Tight Glycemic Control

- Benefits: delayed onset and progression of retinopathy, neuropathy, nephropathy
- When to Avoid Tight Control:
    - Elderly patients (esp. if living alone)
    - Those taking long-acting insulins
    - Frequent hypoglycemic episodes

Complications of Insulin Therapy

- Hypoglycemia is most common
    - Mild Hypoglycemia (55-70 mg/dL)
        - Shakiness, palpitations, tachycardia, irritability, nervousness, pallor
    - Moderate hypoglycemia (40-55mg/dL)
        - Blurred vision, night sweats, extreme fatigue, mood changes, confusion, slowed reaction time
    - Severe hypoglycemia (<40mg/dL)
        - Coma, unconciousness, convulsions, seizures
    - Treatment for hypoglycemia
        - 15 gm carbohydrate
            - Glucose tablets, 1 cup soda pop, skim milk, 5-6 lifesavers
            - Symptoms should resolve in 10-20 minutes.
        - If unconscious, give 1 mg glucagon SC or IM.
            - Symptoms should resolve in 15 minutes.
        - Person should take oral liquids containing sugar when they regain their consciousness.
        - If patient is hospitalized, give 50 ml of D50W.
- Lipoatrophy
    - Breakdown of adipose tissue around injection site.
    - Characterized by depression in skin.
    - Mainly a problem with bovine and porcine insulins
- Lipohyperthrophy
    - Subcutaneous tissue accumulates at injection site
    - Caused by repeated insulin injections at the same site—rotate sites

Mixing Insulins

- Patients Who Benefit Most from Premixed Insulins
    - Persons with stable diabetes
    - Elderly patients
    - Visually impaired patients or indiviuals who have trouble mixing insulin.
    - Patients who are on 2 injections per day

- Insulins that May be Mixed in Same Syringe
  - Regular and NPH (most common), Lente, or Ultralente
  - Lispro and NPH (use immediately)
  - Semilente and Ultralente
- Insulins that should not be mixed:
  - NPH with any of the lentes
  - Lantus should not be mixed with any of the other insulins

Dawn Phenomenon
- Pre-breakfast hyperglycemia from early morning (4-8AM) release of growth hormone, catecholamine, cortisol
- Treat by increasing bedtime insulin dose

Samoygi effect:
- Rebound hyperglycemia in morning from nocturnal hypoglycemia
- Identify by taking early morning blood glucose (1-5AM).
- Evening/bedtime insulin regimen should be tapered.
- Consumption of evening snacks should be evaluated.

Available Insulins

Types	Onset	Peak	Duration	Examples
Rapid-acting	15-30 min	1-2 hr	3-4 hr	Insulin lispro (Humalog®) Insulin aspart (Novolog®) Insulin glulicine (Apidra®)
Short-acting	0.5-1 hr	2-4 hr	6-8 hr	Regular Insulins
Intermediate-acting	1-4 hr	6-10 hr	10-16 hr	NPH Lente
Long-acting	4-6 hr	18 hr	24-36 hr	Ultralente Insulin detemir (Levemir®)
Ultra long-acting	1-3 hr	4-6 hr	24 hr	Insulin glargine (Lantus®)
NPH/Regular	Same as each insulin individually			70/30, 50/50
Lispro/NPL				75/25
Aspart/NPH				70/30

Pramlintide (Symlin)
- Physiology: amylin is a neuropeptide that is secreted by pancreatic beta cells. It works together with insulin to regulate postprandial glucose levels. Amylin is absent in type 1 diabetes and decreased in type 2 diabetes.
- Pramlintide is an amylin analog used as an adjunct therapy in patients with Type 1 diabetes who use mealtime insulin and who have failed to achieve glucose control despite optimal insulin therapy. The same also applies to Type 2 diabetes patients with or without a concurrent sulfonylurea agent and/or metformin.
- **3 different mechanisms** by which pramlintide works:

    - Slows gastric emptying without altering the overall absorption of nutrients
    - Suppresses postprandial glucagon secretion
    - Decreases appetite centrally
- Dosing regimen for Pramlintide for Type 1 DM:
    - Initial dose 15 mcg SC immediately before meals. Titrate by 15 mcg increments once no significant nausea for 3 days. Target dose: 60 mcg SC before meals. Reduce prandial insulin by 50% when initiating pramlintide treatment.
- SE: N/V, HA, anorexia, dizziness, fatigue, hypoglycemia
- Contraindications: gastroparesis, HbA1c > 9.0%, poor compliance with insulin regimen, hypoglycemic unawareness.