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Dompe (consultant) (All relevant relationships have been mitigated)



The following:

- (1) amoxicillin/clavulanate potassium;
- (2) cephalexin;
- (3) azithromycin;
- (4) sulfamethoxazole/trimethoprim;
- (5) doxycycline; and
- (6) tetracycline;

The following antiglaucoma agents:

- (1) acetazolamide; and
- (2) methazolamide;

The following antiviral agents:

- (1) valacyclovir; and
- (2) acyclovir.

The Law

Review
Principles of Oral Medications and Use

LET ME HELP YOU OUT.....



- ◆Ancient symbol associated with healing
- ◆Contraction of Latin verb recipe: take thou or you take

Patient Care
Considerations

History Considerations

- Patient age
- Pediatric/Geriatric considerations
- Systemic Conditions
- Renal/Hepatic Disease
 - Cardiovascular Disease
 - Hypertension, congestive heart disease, arrhythmias
 - Pulmonary Disease
 - COPD, respiratory issues
 - Diabetes
- Current Medications → Drug Interactions
- Allergies

- Prescribing Considerations
- A=Allergies
 - B=Body weight
 - C=Current medications
 - D=Diseases
 - E=Each patient is unique

History Considerations Pregnancy

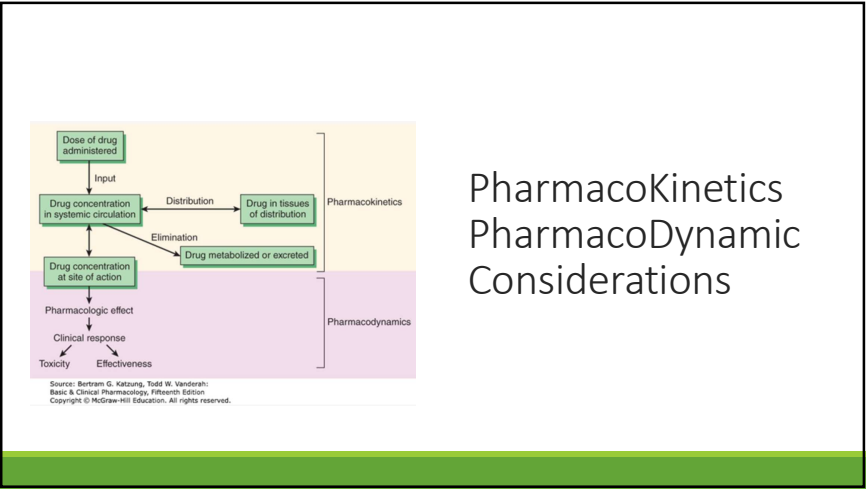
Pregnancy Categories (Prior 2015)

- Category A: no risk to fetus (Vitamin B6)
- Category B: no evidence of risk (Erythromycin, brimonidine)
- Category C: risk to fetus cannot be ruled out (latanoprost)
- Category D: risk to fetus, but benefit outweigh risk (tetracycline)
- Category X: definite fetal risk; avoid
- This category system over-simplification

Pregnancy (Updated)

Updated labeling includes 3 subsections:

- **Pregnancy**
 - Summary of risk
 - Data supporting summary
 - Prescribing and counseling info (clinical considerations)
- **Lactation**
 - Summary of risk
 - Data supporting summary
 - Prescribing and counseling info (clinical considerations)
- **Females and Males of Reproductive Potential**
 - Summary of risk
 - Data supporting summary
 - Prescribing and counseling info (clinical considerations)



Pharmacokinetics Pharmacodynamic Considerations

Pharmacokinetic Considerations

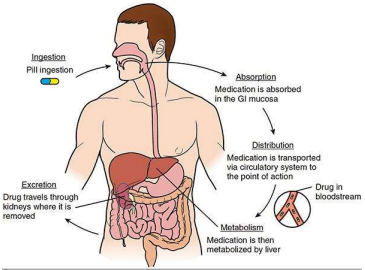
Drug considerations:

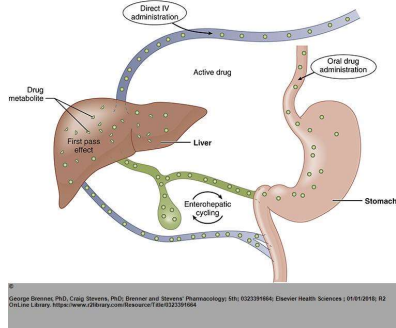
- Molecular size
- Ionization
- Lipid solubility
- Concentration gradient between plasma and target tissue
- Degree of protein binding
- Drug interactions other drugs
- How administered
- How metabolized
- Extended vs Immediate release

Pharmacokinetic Considerations

Pharmacokinetic Stages (ADME)

- A=Absorption
- D=Distribution
- M=Metabolism
- E=Excretion





The diagram illustrates the first pass effect where a drug administered orally is metabolized in the stomach and liver before reaching the systemic circulation. It also shows other routes like intravenous, sublingual, intramuscular, subcutaneous, inhalation, transdermal, and topical administration that bypass the first pass effect. Enterohepatic cycling is also depicted.

Drug Metabolism

First Pass effect

No first pass effect:

- Intravenous
- Sublingual
- Intramuscular
- Subcutaneous
- Inhalation
- Transdermal
- Topical=Ocular

Drug Metabolism

Liver major organ for metabolism

- **Cytochrome P450:** a family of isozyme responsible for biotransformation/metabolism of many drugs
- Cytochrome P450 enzymes also GI tract, kidneys, small intestine

Various factors that may affect drug metabolism

- Genetic (polymorphism)
- Diet and environment (grapefruit juice, alcohol, smoking, pesticides)
- Age (very young vs adults vs aging)
- Gut microflora
- Liver disease
- Drug interactions that induce or inhibit cytochrome P450

Grapefruit juice affects drugs by either:

1-Affecting metabolism:

By blocking enzyme's ability to metabolize drug resulting in increased drug in blood

OR

2-Affecting drug transporters:

By blocking transporter that moves drug to cells resulting in less drug entering the blood

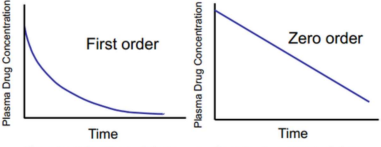
Drug Metabolism

Diet Effect on Drug Examples:

- Erythromycin, grapefruit juice inhibit CYPs
- Alcohol, cigarettes induce elevation of CYPs

Drug Interaction Examples:

- **Amoxicillin**, cephalexin, **sulfamethoxazole/trimethoprim** -> can induce bleeding in those taking warfarin (affect CYP and gut bacteria)
- Grapefruit juice or erythromycin increases risk of statin induced myopathy (due to inhibition of statin metabolism)
- **Azithromycin** generally safe with statins, but risk still present



The graphs show plasma drug concentration over time. The first-order graph shows an exponential decay, while the zero-order graph shows a linear decrease.

Drug Kinetics

First Order Kinetics

- Rate of movement is directly proportional to the concentration difference across the barrier
- Most ophthalmic topical drugs

Zero-order Kinetics

- Release of drug is constant over time
- Concentration of drug released (or eliminated) over time is independent of concentration in plasma or in body

Prodrugs

- Inactive derivative of drug converted to active form after tissue penetration
- Drug metabolite more active at receptor site than the parent form
- Advantage:
 - Better penetration
 - Less undesirable effects
- Examples
 - Codeine to morphine
 - Valacyclovir to acyclovir

PRESCRIPTION – CONSIDERATIONS

Weight Based Dosage Calculator

Input

Dosage 30 mg/kg

Weight 25.4 kg

Liquid Formulation (optional):

Med Amount 125 mg

Per Volume 5 mL

Results

Dose 782 mg

Liquid Dose 30.48 mL

Decimal Precision 2

Weight Based Divided Dose Calculator

Input

Dosage 30 mg/kg

Weight 25.4 kg

Liquid Formulation (optional):

Med Amount 125 mg

Per Volume 5 mL

Results

Dose 381 mg BID

Liquid Dose 15.24 mL BID

Decimal Precision 2

Preseptal Cellulitis (Children): Amoxicillin/clavulanate: 25-45mg/kg/day in 2 divided doses (q12h)
Available Susp: 125mg/31.25mg/5mL susp ;

-56 lb child = 25.4 kg>>>>Rx: 30 mg/kg/day divided q12h
Rx: 30.48 mL (total per day)/2(BID)=15.24mL BID (=1 tablespoon BID) of 125mg/31.25mg/5mL susp
(15.24mL~3.1 teaspoon=1 tablespoon)

Generics

As a copy of the brand-name drug FDA originally reviewed, a generic drug application submitted to FDA for approval must show that:

The generic drug is "pharmaceutically equivalent" to the brand.

The manufacturer is capable of making the drug correctly.

The manufacturer is capable of making the drug consistently.

The "active ingredient" is the same as that of the brand.

The right amount of the active ingredient gets to the place in the body where it has effect.

The "inactive" ingredients of the drug are safe.

The drug does not break down over time.

The container in which the drug will be shipped and sold is appropriate.

The label is the same as the brand-name drug's label.

Relevant patents or legal exclusivities are expired.

Waxman-Hatch Act of 1984 (Drug Price Competition and Patent Term Restoration Act). Generics must meet:

- Same active ingredient as brand
- Bioequivalency/availability
- Same pharmaceutical and therapeutic activity
- Meet FDA standards (stability, purity, strength, quality)
- Same labeling

<https://www.fda.gov/drugs/buying-using-medicine-safely/generic-drugs> (accessed 1-22-22)

[What Is the Approval Process for Generic Drugs? | FDA](#) (accessed 1-22-23)

Controlled Substance Schedule		
Schedule	Description	Drugs
I	Significant abuse&dependency potential Not commercially available (exception*)	Heroin, LSD, Mescaline Marijuana (medicinal use)*
II	Accepted for medical use High abuse & dependence potential Strict limitations Written Rx only No refills	Morphine, hydromorphone, codeine, oxycodone, methadone, amphetamine, barbiturates, cocaine Oxycodone+acetaminophen (Percocet) Oxycodone+aspirin (Percodan-brand d/c) Hydrocodone+acetaminophen
III	Significant but less abuse & dependency potential Refilled up to 5x q6mos May be verbal Rx	Limited narcotic in combination Codeine+acetaminophen (Tylenol #3=brand d/c) (Popular for ocular use) Hydrocodone+acetaminophen (Vicodin)
IV	Relatively low abuse potential May be verbal Rx Refilled up to 5x q6mos	Propoxyphene (Darvon) (no longer available) Propoxyphene+acetaminophen (Darvocet) (no longer available) Tramadol
V	Lower abuse potential (None common for ophthalmic use)	Cough suppressant: codeine/guaifenesin (Robitussin AC=brand d/c) Diarrhea: Diphenoxylate/atropine (Lomotil)

Patient Education

- ◆ Purpose
- ◆ Name of medication
- ◆ Directions for use
- ◆ Schedule for use
- ◆ Duration of treatment
- ◆ Side effects
- ◆ Drug interactions
- ◆ Storage
- ◆ Miscellaneous (refill, missed dose)
- ◆ Compliance issues



Anti-infective
and Bacterial
Overview

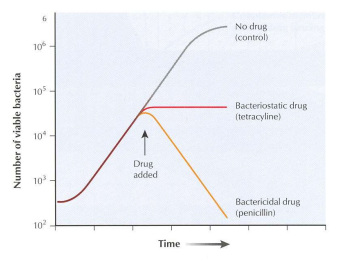
Figure 11-1 Morphology of a bacterial cell.

Anti-infective Overview

- Normal flora
- Considerations for infection
 - Barriers: skin and mucous membranes
 - Immune status
 - Organism
 - Viral, bacteria, fungi

Antibacterial Drugs

- Bactericidal: kills bacteria
 - Minimum bactericidal concentration (MBC): is the minimum concentration of drug which can kill 99.99% of the organism population
- Bacteriostatic: inhibit bacteria growth
 - Must work together with the immune system to remove the microorganisms from the body
 - Minimum inhibitory concentration (MIC): is the minimum concentration of drug which can inhibit the growth of the microorganism



Bactericidal Antibiotics	Bacteriostatic Antibiotics
Inhibit Cell Wall	Affect Intermediary Metabolism (Folic Acid)
Penicillins	Sulfonamides
Cephalosporins	Trimethoprim (may be cidal from synergy when combo drug)
Vancomycin	Pyrimethamine
Bacitracin	
Affect Cytoplasmic Membrane	
Polymyxin	
Gramicidin	
Affect Protein Synthesis	Affect Protein Synthesis
Aminoglycosides	Tetracyclines
	Macrolides
	Chloramphenicol (some cidal activity)
Affect DNA Synthesis	
Fluoroquinolones	

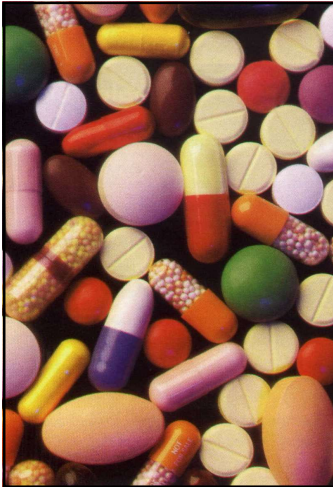
Note: Some antibiotics may have bactericidal and bacteriostatic activity dependent on dose or specific bacteria

Antibacterial Drugs

- Selective toxicity (bacteria vs human)
 - Bacteria: cell wall
 - Cell membrane
 - Similar
 - Ribosomes
 - Different size and composition
 - Biosynthetic pathways (intermediary metabolism)
 - Folic acid: bacterial cells synthesize
 - Enzyme DNA gyrase
 - An essential bacterial enzyme involved in DNA replication

Mechanisms of Resistance

- Bacterial production of enzymes that degrade/inactivate antibiotics
- Pump mechanisms or decreased permeability antibiotics
- Resistance genes
- Alteration of bacterial ribosomes
- Chromosomal mutation
- Cross resistance
- Misuse and overuse of antibiotics



Oral Antibacterial Drugs

- Clinical Indication Examples:
- Internal Hordeolum
 - Preseptal Cellulitis
 - Meibomianitis
 - Posterior Blepharitis
 - Ocular Rosacea
 - Dacryocystitis
 - Dacryoadenitis
 - Canaliculitis
 - Chlamydial Conjunctivitis
 - Orbital fractures
 - Inclusion conjunctivitis
 - Toxoplasmosis

Oral Antibiotic Considerations

- Use of probiotic
 - Some antibiotics such as amoxicillin-clavulanate may decrease effectiveness of lactobacillus
- Potential effect oral contraceptive
- Allergic reaction VS GI disturbance
 - Anaphylaxis (high risk history): shortness of breath/chest tightness or pain (DO NOT RECHALLENGE)
 - Mild to moderate allergy (moderate risk history): skin rash, urticaria, itchiness (consider rechallenge if >5yrs; skin testing)
 - Intolerance (low risk history): GI disturbance (food and drink may help) (direct challenge)
- Superinfection
 - Risk of overgrowth of other microbial organism with oral antibiotic
- Resistance consideration

Guidelines: Effective Antimicrobial Therapy

- Accurate diagnosis
- Microorganism sensitive to anti-infective
- Least toxic drug
- Adequate drug levels
- Optimum route of administration
- Appropriate dosage
- Appropriate treatment time
- Augment drug tx with physical procedures

Mechanisms of Antibiotic Action

- Inhibition of cell wall synthesis
 - Penicillins
 - Cephalosporins
 - Bacitracin
 - Vancomycin
- Increased bacterial cell membrane permeability
 - Polymyxin B
 - Gramicidin
- Inhibition of bacterial protein synthesis
 - Aminoglycosides
 - Macrolides
 - Tetracyclines
 - Chloramphenicol
- Inhibition of folic acid synthesis
 - Sulfonamides
 - Trimethoprim
- Damage to bacterial DNA
 - Fluoroquinolones

Antibacterial: Affecting Cell Wall Synthesis

Antibacterial: Affecting Cell Wall Synthesis

Penicillins

Figure 31.3
Bacterial cell wall of gram-positive bacteria. NAM = N-acetylmuramic acid; NAG = N-acetylglucosamine; PEP = cross-linking peptide.

Antibacterial: Affecting Cell Wall Synthesis

Penicillins

- Pharmacology:
 - Consist of:
 - Thiazolidine ring
 - β -lactam ring
 - Side chain
 - Bactericidal
 - Effective: Gram +, Gram -
 - Allergy:
 - Less true vs more likely adr to drug than previously thought
 - Less cross reactions with cephalosporins than previously thought

Figure 31.2
Structural features of β -lactam antibiotics.

Drugs: Affecting Cell Wall Synthesis
Penicillins:
Amoxicillin and Clavulanate (Augmentin)

- Penicillins with extended spectra of activity=**Amoxicillin/clavulanate**
 - Modification of basic penicillin structure
 - Amoxicillin alone - inactivated by penicillinase
 - Clavulanate:
 - B-lactamase inhibitor that protects penicillin component from inactivation by penicillinase or B-lactamase
 - Weak antimicrobial activity
 - Clinical uses: Hordeolum, Preseptal cellulitis, Dacryocystitis, Dacryoadenitis

Drugs: Affecting Cell Wall Synthesis
Penicillins:
Amoxicillin/Clavulanate (Augmentin)

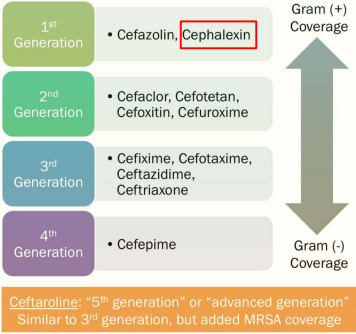
- Amoxicillin/Clavulanate (Augmentin)
 - May be used during pregnancy and breastfeeding
 - Adverse Reactions
 - GI disturbance (diarrhea, clostridium difficile, upset stomach)
 - Rash, urticaria
 - Steven-Johnson Syndrome
 - Hypersensitivity reaction
 - Superinfection
 - Drug interactions
 - Warfarin (Penicillins enhance effect resulting in increased risk of bleeding)
 - Potential effect on oral contraceptives

Antibacterial: Affecting Cell Wall Synthesis
Cephalosporins

Cephalosporins

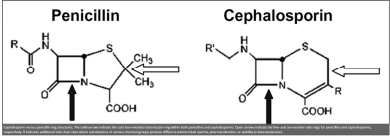
- Mechanism of action similar to Penicillins
- Spectrum: Gram(+), Gram(-)
- Classified as first, second, third, fourth generations drugs
 - 1st to 4th generation:
 - Greater gram(-) activity with subsequent generations
 - Less efficacy against gram positive with subsequent generations
 - Greater efficacy against resistant organisms with subsequent generations

CEPHALOSPORIN COMPARISONS



Antibacterial: Affecting Cell Wall Synthesis
Cephalosporins

- Pharmacology
 - B lactam ring
 - Similar penicillin
- Bactericidal
- Resistance
 - Drug inactivation by B lactamases
- Potential cross sensitivity Penicillin (lower than previously thought)
 - More likely see with 1st generation cephalosporins (e.g. Cephalexin=Keflex)
- May result in Vitamin K deficiency



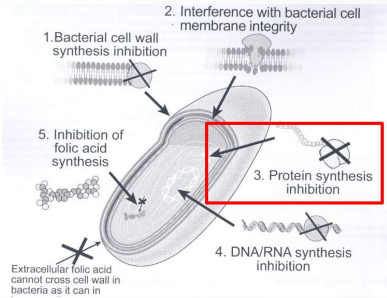
Drugs: Affecting Cell Wall Synthesis
Cephalosporins: Cephalexin
(Keflex=Brand d/c)

- First Generation: **Cephalexin (Keflex=brand d/c)**
 - May be used during pregnancy and breastfeeding
- Clinical use:
 - Preseptal cellulitis, Dacryocystitis, Dacryoadenitis, Orbital Fracture
- ADR:
 - Erythema multiforme, Steven-Johnson syndrome
 - GI (diarrhea, nausea, vomit)
 - Clostridium difficile
 - Cholestatic jaundice, increase liver enzymes
 - Hypersensitivity reactions
- Drug interactions:
 - Warfarin (risk increased bleeding)
 - Metformin (levels inc with cephalexin)

Antibacterial:
Affecting Protein Synthesis

Drugs Affecting Protein Synthesis

- Inhibition of bacterial protein synthesis
 - Aminoglycosides
 - Neomycin
 - Gentamicin
 - Tobramycin
 - Macrolides
 - Erythromycin
 - Azithromycin**
 - Clarithromycin
 - Tetracyclines
 - Tetracycline**
 - Doxycycline**
 - Minocycline
 - Chloramphenicol
 - Clindamycin



Antimicrobial Affecting Protein Synthesis
Tetracycline

Antimicrobials Affecting Protein Synthesis
Tetracycline Overview

- Pharmacology
 - Block protein synthesis
 - Bacteriostatic
 - Broad spectrum: G+/G-
 - Resistance (*S. aureus*)

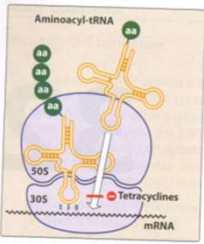


Figure 32.2
Tetracyclines binds to the 30S ribosomal subunit, thus preventing the binding of aminoacyl-tRNA to the ribosome. aa = amino acid.

Lippincott's Illustrated Reviews, Pharmacology.

Drugs Affecting Protein Synthesis
Tetracycline: Oral Overview

- Antibiotic activity
- Affect on free fatty acids- decreases bacterial lipase production
- Anti-inflammatory effect
- Anticollagenolytic activity
- Metalloproteinase-9 inhibitor

Antimicrobials Affecting Protein Synthesis
Tetracycline: Overview

Oral Use:

- Chlamydia
- Acne rosacea, meibomianitis
 - Free fatty acids
 - Irritating and inflammatory
 - Related to bacterial lipases (that is decreased by tetracycline)

Oral Use:

- Nontuberculous phlyctenular keratoconjunctivitis
- Noninfected corneal ulcers
 - Related to anticollagenolytic activity
- Recurrent corneal erosion

Antimicrobials Affecting Protein Synthesis
Tetracycline Oral Overview

- Absorption affected by:
 - Food (not doxycycline)
 - Iron containing tonics or antacids containing calcium, magnesium or aluminum
 - Sodium bicarbonate
- Restriction with use of:
 - antacids,
 - iron,
 - zinc
 - dairy products,
 - vitamin-mineral preparations

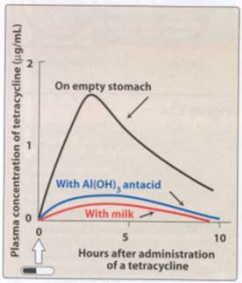


Figure 32.5
Effect of antacids and milk on the absorption of tetracyclines.

Lippincott's Illustrated Reviews, Pharmacology.



Antimicrobials Affecting Protein Synthesis
Tetracycline Oral Overview

Adverse Reactions

- Hypersensitivity reactions (Anaphylaxis, urticaria, rash, periorbital edema)
- Photosensitivity/toxic reactions
- GI irritation
- Epigastric distress (sore throat, glossitis)
- Dyspepsia/Esophageal irritation-avoid lying down for 1-2 hour

Adverse Reactions

- Changes during tooth development (discoloration, etc.)
- Depress bone growth
- Intracranial hypertension (pseudotumor cerebri)
- Blood dyscrasias
- Potentiate coumarin type anticoagulant effect (affect blood clotting)
- Vestibular toxicity (especially minocycline) (Lightheadedness, loss of balance, dizziness, nausea, tinnitus)



Antimicrobials Affecting Protein Synthesis
Tetracycline: Oral Overview

- Contraindications
 - Avoid during pregnancy (prior Pregnancy Category D)
 - May use short-term while breastfeeding-theoretical risk of permanent infant bone and teeth discoloration with prolonged use
 - Children under 8 years

Tetracyclines:
The Drugs

Drugs Affecting Protein Synthesis
Tetracycline : **Tetracycline**

- **Tetracycline** (Generic) Dosage Considerations:
 - Should be taken on empty stomach (no food or dairy products 1 hr before/2 hr after)
 - Use: rosacea, meibomianitis, resistant sebaceous blepharitis
 - Use weeks to months
 - Taper with improvement in rosacea, inflammatory
 - Posterior blepharitis – taper? no evidence supports since abnormal fatty acid vs inflammation

Drugs Affecting Protein Synthesis
Tetracycline:
Doxycycline

- **Doxycycline (Vibramycin)**
 - Use
 - Tetracycline of choice for:
 - Chlamydia infections
 - Acne rosacea
 - Meibomianitis
 - Ocular surface inflammatory disease
 - Depending on brand, may take with food
 - Note exception: ORACEA -Take on an empty stomach (1 hr before/2 hr after meal)
 - Take with full glass water (and food) to avoid GI upset
 - Avoid direct sunlight
 - Pregnancy: avoid (Category: D)

Antimicrobials Affecting Protein Synthesis
Macrolides

Drugs Affecting Protein Synthesis:
Macrolides

- The Drugs
- Erythromycin (Various)
 - **Azithromycin (Zithromax)**
 - Clarithromycin

Antimicrobials Affecting Protein Synthesis
Macrolides

- Pharmacology
 - Bind to 50S ribosomal subunit > inhibit bacterial protein synthesis
 - Low toxicity: do not bind to human ribosome
 - Bacteriostatic (some cidal activity in high doses)
 - Spectrum of activity can include:
 - Various: Gram positive, gram negative
- Clinical Use:
 - Chlamydial Infections
 - Sebaceous Gland Dysfunction
 - Ocular Rosacea
- Drug interactions: Dilantin, Digoxin, Warfarin, Cholesterol drugs

Drugs Affecting Protein Synthesis
Macrolides: **Azithromycin**

- Azithromycin (Zithromax)
 - Semisynthetic derivative of erythromycin
 - Use: chlamydia, gonococcal conjunctivitis, ocular rosacea
 - Pregnancy and lactation: may use
 - Side Effect:
 - GI upset,
 - Skin rash,
 - Cardiac (chest pain, palpitation, arrhythmias, QTc prolongation);
 - Dizziness
 - Risk of cardiac arrhythmias and sudden death
 - EKG monitoring
 - Drug interactions:
 - Statin drugs (increased potential risk of myopathy),
 - Warfarin (increase warfarin concentration)

Drugs Affecting Protein Synthesis
Macrolides: Azithromycin

- Azithromycin (Zithromax)**
 - Dosage:
 - Can take with/out food
 - Note: food helps to tolerate better
 - 1000mg single dose (chlamydia)
 - Extended half life > QD



azithromycin (generic) 1 g

CDC: 2021 Guideline Chlamydial Infections

Sexually Transmitted Infections Treatment Guidelines, 2021
CDC Center for Disease Control and Prevention

Sexually Transmitted Infections Treatment Guidelines, 2021 Home

Chlamydial Infections

Chlamydial Infection Among Adolescents and Adults

Recommended Regimens for Chlamydial Infection Among Adolescents and Adults
Doxycycline 100 mg orally 2 times/day for 7 days
Alternative Regimens
Azithromycin 1 g orally in a single dose OR Levofloxacin 500 mg orally once daily for 7 days

Recommended Regimen for Chlamydial Infection During Pregnancy
Azithromycin 1 g orally in a single dose
Alternative Regimen
Amoxicillin 500 mg orally 3 times/day for 7 days

- Azithromycin vs doxycycline for urogenital chlamydial infection had higher treatment failure among men for azithromycin.
- Doxycycline more efficacious for rectal infection for men and women
- Sex partners during 60 days preceding onset of symptoms or dx should be tested (or last contact if >60 days)
- Doxycycline delayed release 200 mg QD is as effective as doxycycline 100mg bid x 7days for urogenital C trachomatis, with lower GI ADR, but more costly

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Clinical Sciences

Oral azithromycin versus doxycycline in meibomian gland dysfunction: a randomised double-masked open-label clinical trial

Mohsen Bafraei Kachak, MD, PhD, FRCOphth, Victoria Kachak, MD, PhD, FRCOphth, Marziyeh Nouri, MD, PhD, FRCOphth

ABSTRACT

Background: To assess the efficacy and safety of oral azithromycin compared with doxycycline in the treatment of meibomian gland dysfunction (MGD). **Methods:** A randomised, double-masked, open-label, parallel-group trial comparing oral azithromycin (500 mg on day 1 and then 250 mg daily for 5 days) with oral doxycycline (200 mg daily for 1 month). **Results:** The azithromycin group showed significantly better improvement in MGD signs and symptoms compared with the doxycycline group. **Conclusion:** A 5-day course of oral azithromycin is recommended for its better effect on improving the signs, better overall clinical response and shorter duration of treatment.

Received either

- 5-day azithromycin(200mg/day) Or
- 1 month doxycycline (200 mg/day)

Conclusion:

5 day course of oral azithromycin is recommended for its better effect on improving the signs, better overall clinical response and shorter duration of treatment.

- 5 day treatment course may need to be repeated because MGD is chronic

Antibacterials Affecting Intermediary Metabolism (Folic Acid)

Drugs Affecting Intermediary Metabolism (Folic Acid)

- -Sulfonamides
- -Pyrimethamine
- -Trimethoprim

1. Bacterial cell wall synthesis inhibition

2. Interference with bacterial cell membrane integrity

3. Protein synthesis inhibition

4. DNA/RNA synthesis inhibition

5. Inhibition of folic acid synthesis

Extracellular folic acid cannot cross cell wall in bacteria as it can in human cells

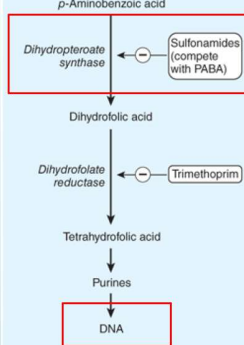
Antibacterials Affecting Intermediary Metabolism Sulfonamides

Antibacterial Affecting Intermediary Metabolism

Sulfonamides

Sulfonamides

- Broad spectrum
 - Gram positive and gram negative
- Also:
 - Chlamydia
 - Toxoplasma
 - Sulfadiazine/pyrimethamine or
 - **Sulfamethoxazole/trimethoprim (Bactrim)**
- Resistance to Staphylococcus, Pseudomonas a.



```

graph TD
    A[p-Aminobenzoic acid] --> B[Dihydrodipicolate synthase]
    B --> C[Dihydrodipicolic acid]
    C --> D[Dihydrodipicolate dehydrogenase]
    D --> E[Tetrahydrodipicolic acid]
    E --> F[Purines]
    F --> G[DNA]
    S[Sulfonamides (complete with PABA)] -.-> B
    T[Trimethoprim] -.-> D
    style B stroke:#f00,stroke-width:2px
    style D stroke:#f00,stroke-width:2px
    style G stroke:#f00,stroke-width:2px
            
```

The diagram illustrates the pyrimidine synthesis pathway. It begins with p-Aminobenzoic acid, which is converted to Dihydrodipicolic acid by the enzyme Dihydrodipicolate synthase. This step is inhibited by Sulfonamides (which compete with PABA). Dihydrodipicolic acid is then converted to Tetrahydrodipicolic acid by the enzyme Dihydrodipicolate dehydrogenase, a step inhibited by Trimethoprim. Tetrahydrodipicolic acid is further converted to Purines, which are eventually used to synthesize DNA. The enzymes Dihydrodipicolate synthase and Dihydrodipicolate dehydrogenase, along with the final product DNA, are highlighted with red boxes in the original image.

Source: Bertram G. Katzung, Anthony J. Trevor:
www.accesspharmacy.com
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Antibacterials Affecting Intermediary Metabolism Sulfonamides

- Pharmacology
 - Inhibit synthesis of folic acid (chemical required for synthesis of nucleic acid and protein)
 - Humans: absorb preformed folic acid
 - Bacteriostatic
- ADR:
 - Steven Johnson Syndrome,
 - blood dyscrasias,
 - hypersensitivity,
 - transient myopia
- Not used during pregnancy

Sulfa Drugs

Nc1ccc(cc1)C(=O)O

para-aminobenzoic acid
PABA

Nc1ccc(cc1)S(=O)(=O)N(R1)R2

Sulfonamide base structure

Sulfa Drug - Antimetabolite

Normal reaction:

pterdine + Nc1ccc(cc1)C(=O)O (para-aminobenzoic acid PABA) → pteridine + PABA + glutamic acid → folic acid

Antimetabolite reaction:

pterdine + Nc1ccc(cc1)S(=O)(=O)N(R1)R2 (Sulfonamide base structure) → pteridine + 1st enzyme "fooled" + glutamic acid → folic acid (2nd enzyme inhibited)

Sulfonamide base structure

© Osipov, c. 2003

Class	Drugs
Antimetabolites	Sulfacetamide Sulfadiazine Sulfamerazine Sulfamethoxazole Sulfanilic acid Sulfapyridine Sulfathiazole Sulfisoxazole Sulfonamide
Nonmetabolites	Ampicillin + Dihydroxy Trimethoprim Fosfomycin + Trimethoprim
Carbonic anhydrase inhibitors	Acetazolamide Bumetanide Dorzolamide Methazolamide
CXCR2 inhibitors	Gefixotin Erdofitin Valkoditin
Loop diuretics	Bumetanide Furosemide Zemvelite
Sulfing bases	Acetabenzamide Chloroxyquinidine Gleipoxide Ciglitide Cyflutide Tolazamide Tolazamide
Diazotic diazonics	Sulfonamidechloride Benzothiazide Chlorothiazide Chlorothiazide Cyclothiazide Hydroxymethylthiazide Hydroxymethylthiazide Methylthiazide Polythiazide Quinethazone
Typhoid	Alosetron Diclofenac Doxonitran Nasoproline Risperone Sustained Zincoglutamate
Miscellaneous	Chloroquine Inorganic Methylene Phenyl Thioether Zincobutene

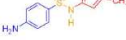
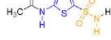
* Contains an Nc-sulfonamide group.

Sulfonamide medications include:

- sulfonamide antimicrobials,
- sulfonamide nonantimicrobials, and
- nonsulfonamide sulfur-containing compounds

Structural elements required for potent antimicrobial activity and associated with typical sulfa allergy*:

- 1-Sulfonamide moiety (NH₂-SO₂) in orange,
- 2-*Aryl-amine (-Ar-NH₂) at N4 in blue
- 3-*Nitrogen ring at N4 in red

ANTIMICROBIAL SULFONAMIDES (HIGH RISK OF CROSS-REACTIVITY)	NONANTIMICROBIAL SULFONAMIDES (LOW RISK OF CROSS-REACTIVITY)	NONSULFONAMIDE SULFUR-CONTAINING (NO CROSS-REACTIVITY)
 Sulfamethoxazole	 Acetazolamide	 Inorganic sulfate



A sulfonamide



An antimicrobial sulfonamide



PABA

Sulfonamide Allergies

Sulfonamide Allergies: Pharmacy Sept 2019

```
graph TD
    A[Patient with self-reported history of allergy prescribed a sulfonamide medication] --> B[Conduct thorough patient interview and medication history to determine if true sulfonamide allergy]
    B -- NO --> C[Sulfonamide intolerance or incorrect allergy listing]
    B -- YES --> D[True sulfonamide allergy]
    D --> E[Sulfonamide nonantimicrobial agent prescribed]
    D --> F[Sulfonamide antimicrobial agent prescribed]
    E --> G[Low risk of cross-allergenicity*]
    F --> H[High risk of cross-allergenicity]
```

Figure 5. Decision making in patients with sulfonamide antimicrobial allergies. Chart adapted from Ref. [40]. * Patient with true sulfonamide allergy may be at risk for multiple drug allergy syndrome despite low risk of cross-reactivity.

- Sulfonamide allergy: 3-8%
 - Rash=most common
 - Stevens-Johnson Syndrome=less common, more serious
- Cross reactivity to allergies to sulfonamide antimicrobials with nonantimicrobial sulfonamide meds
 - Substitutions at N1 and N4 are the primary determinants of drug allergy instead of common sulfonamide moiety (SO2-NH2)
- Sulfonamide antimicrobial agents do not appear to have cross-reactivity with nonantimicrobial sulfonamide agents
- While risk of cross reactivity is low, patients with sulfonamide allergies may have increased risk of multiple drug allergies (vs a cross reactivity)
- Maculopapular eruptions – can rechallenge, more severe reactions consider alternative treatment

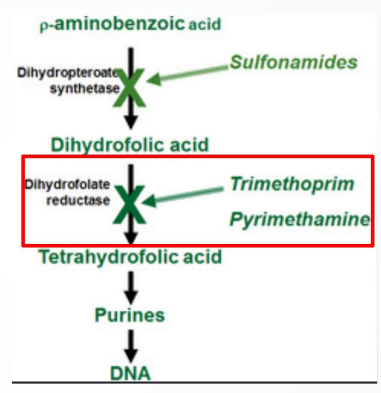
Drugs Affecting Intermediary Metabolism

Pyrimethamine and Trimethoprim

Antibacterials Affecting Intermediary Metabolism

Trimethoprim

- Pharmacology
 - Inhibit folic acid synthesis
 - Block a sequential step in pathway
- Trimethoprim: effective MRSA**
- Bacteriostatic
- ADR: GI, hypersensitivity



Sulfamethoxazole/trimethoprim (Bactrim)

- Use: toxoplasmosis, orbital fracture, preseptal cellulitis
- Treatment option in MRSA
- Adverse effects
 - Dermatologic: photosensitivity, erythema multiforme, Steven-Johnson syndrome
 - Cardiac: arrhythmias, hyperkalemia
 - GI disturbances: nausea/vomit/diarrhea, pancreatitis
 - Hematologic: aplastic anemia, thrombocytopenia
- Drug interactions
 - Warfarin (increased bleeding)
 - Multiple

sulfamethoxazole/trimethoprim
generic

Pregnancy/Lactation ⓘ

Pregnancy
Clinical Summary
sulfamethoxazole: weigh risk/benefit during pregnancy, esp. in 3rd trimester; risk of kernicterus near-term based on human data
trimethoprim: weigh risk/benefit during pregnancy, esp. in 1st trimester; possible risk of spontaneous abortion based on limited human data; possible risk of congenital neural tube and cardiovascular defects based on conflicting human data and drug's mechanism of action

Lactation
Clinical Summary
sulfamethoxazole: avoid use while breastfeeding infant w/ G6PD deficiency; otherwise weigh risk/benefit while breastfeeding; possible risk of poor infant feeding based on limited human data; theoretical risk of hyperbilirubinemia in high-risk infants based on drug's mechanism of action; no human data available to assess effects on milk production
trimethoprim: may use while breastfeeding; no known risk of infant harm based on limited human data; no human data available to assess effects on milk production

Antibacterials Affecting Bacterial DNA Synthesis

Fluoroquinolones

Systemic Fluoroquinolones

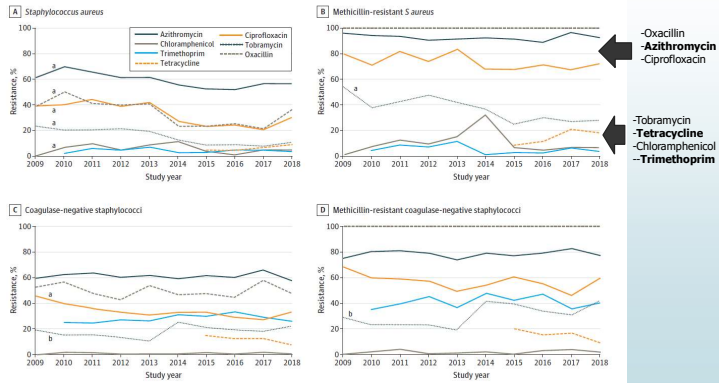
Drugs Affecting Bacterial DNA Synthesis
Fluoroquinolones

- Fluoroquinolones (systemic drugs):
 - Adverse reactions:
 - Common:
 - Gastrointestinal tract (nausea and diarrhea)
 - CNS (HA and dizziness)
 - Uncommon
 - Increased risk of tendon rupture
 - Prolongation of QT interval
 - Arthropathy
 - Idiosyncratic reactions (hepatitis)
 - May be related to chemical moiety of the molecular structure of the FQ

Antibacterial
Considerations

Trends in Antibiotic Resistance Among Ocular Microorganisms in the United States From 2009 to 2018

Figure 4. Antibiotic Resistance Among Isolates Over Time



Clinical Oral Treatment Considerations

- Internal hordeolum
 - Amoxicillin/clavulanate (Augmentin)
 - Cephalexin (Keflex)
- Preseptal
 - Amoxicillin/clavulanate (Augmentin)
 - Sulfamethoxazole/trimethoprim (Bactrim)
 - Cefaclor (Ceclor), Levofloxacin (Levaquin), Moxifloxacin (Avelox)
- Dacryocystitis
 - Amoxicillin/clavulanate (Augmentin)
- Dacryoadenitis
 - Amoxicillin/clavulanate (Augmentin)
 - Cephalexin (Keflex)
- Canaliculitis
 - Cephalexin (Keflex)
- Orbital fracture
 - Amoxicillin/clavulanate (Augmentin)
 - Sulfamethoxazole/trimethoprim (Bactrim)
 - Cephalexin (Keflex)
- Inclusion conjunctivitis
 - Azithromycin
- Posterior blepharitis
 - Doxycycline
- Recurrent corneal erosion
 - Doxycycline
- Toxoplasmosis
 - Sulfamethoxazole/trimethoprim (Bactrim)
- Hyperacute bacterial conjunctivitis (nongonococcal)
 - Cephalexin (Keflex)

Main Reference: Dr. Brian Hall Antibacterial Drug Lecture (2023-NYState Orals Course)



The Law

37 (iii) the following antiviral agents used for herpes zoster ophthalmi-
38 cus; provided an optometrist shall use or prescribe in maximum, one
39 seven-day prescription; provided, however, if a patient is diagnosed
40 with herpes zoster ophthalmicus and has not already been examined by a
41 primary care physician or other appropriate physician for such viral
42 condition, an optometrist shall refer the patient to a licensed primary
43 care physician, licensed physician specializing in diseases of the eye,
44 or other appropriate physician within three days of such diagnosis:
45 (1) valacyclovir; and
46 (2) acyclovir.

HZO:
(1) 7day rx
(2) if not seen
physician=refer
within 3 days

The following antiviral agents:
(1) valacyclovir; and
(2) acyclovir.



Virus: Overview

- Virus:
 - Obligate parasites - cannot multiply outside the living cells
 - Lack cell wall and cell membrane
 - Consists of proteins and nucleic acids

Herpes Overview

- Simplex vs Varicella/Zoster
 - The infection (vaccination)
 - Reactivation
 - Risks
 - Manifestations
 - Both may affect corneal sensitivity (neurotrophic keratitis)
 - Dendrite vs pseudo dendrite (no central ulceration, no end bulbs, minimal stain)
 - Dilate! (r/o retinal involvement)

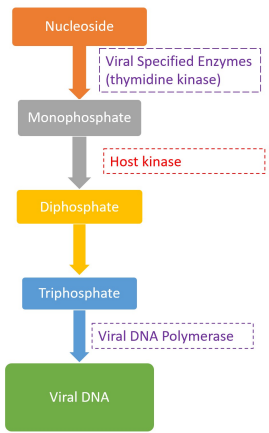
Herpes Zoster Ophthalmicus

- Herpes Zoster Ophthalmicus
 - Pre-eruption/Acute Eruption/Resolution
 - Hutchinson sign (not always present)
 - Antiviral: within 72 hours
 - Treatment considerations:
 - Cutaneous lesions (moist compresses, topical antibiotic)
 - Epithelial lesions (lubricant, antibiotic ung)
 - Stroma, endothelial keratitis, uveitis (topical steroid, cycloplegic)
 - Neurotrophic ulcer (artificial tears, bandage CL, amniotic membrane, autologous serum, cenegermin, tarsorrhaphy, PK)
 - Post herpetic neuralgia
 - Pain treatment may include: capsaicin, gabapentin (Neurontin), pregabalin (Lyrica), tricyclic antidepressants (amitriptyline), narcotic analgesic (oxycodone)
 - SHINGRIX vaccine

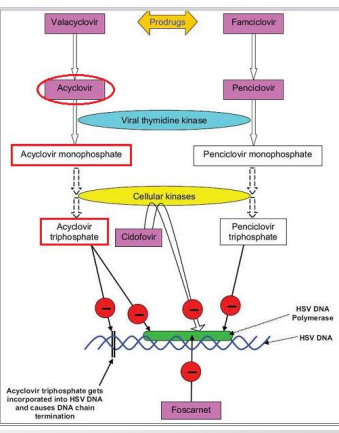
Herpes Simplex Overview

- Primary vs Reactivation Ocular
 - Treatment considerations
 - Blepharoconjunctivitis (topical or oral antivirals)
 - Cornea
 - Epithelial: oral or topical antiviral, debridement
 - Stromal: steroid and antiviral cover (topical or oral)
 - Endothelitis (disciform keratitis): topical steroid and oral antiviral (poor penetration topical antiviral)
 - Uveitis (topical steroid and oral antiviral cover)
 - Consider immune status of patient (may do both oral and topical antiviral in immunocompromised)

Viral Life Cycle (DNA/Herpes)



Anti-Herpes Simplex Viral Drugs: Principal Mechanisms of Action¹



AntiVirals (Herpes)

Oral Antiviral Agents

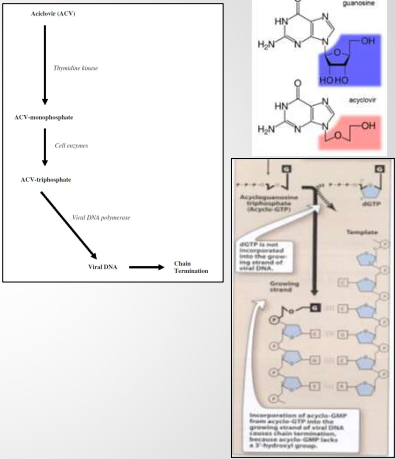
Acyclovir (Zovirax)
Valacyclovir (Valtrex)
Famciclovir (Famvir=brand d/c)

- Use:
 - Herpes Zoster
 - Herpes Simplex
 - Bell's Palsy
 - Acute Retinal Necrosis



Antiviral Drugs Acyclovir

- Pharmacology
 - Guanosine analog that is selectively phosphorylated by HSV and HZV thymidine kinase
 - Inhibits viral replication by acting as a substrate for DNA polymerase
 - This results in chain termination and elongation of the viral DNA chain
- Only partially absorbed by human GI tract.
 - The bioavailability at therapeutic doses is limited at 20%
 - Therefore needs to be administered in high doses and at higher frequency



Antiviral Drugs Acyclovir

- Adverse Reactions
 - Safe
 - Nausea, vomit, diarrhea
 - HA
 - Skin rash
 - BUN or creatinine elevated
 - Dizziness
 - Photosensitivity
- Caution in renal impairment and dehydration
- Maintain hydration
- ACV resistance: 1% prevalence, but immunocompromised ~5%

acyclovir
generic

Pregnancy/Lactation ⓘ

Pregnancy

Clinical Summary

may use during pregnancy; no known risk of teratogenicity based on human data

Lactation

Clinical Summary

may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production

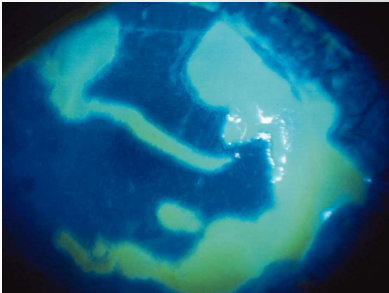
Acyclovir Treatment in Herpes Zoster

- Should be started within 72 hours of skin lesions, maximum efficacy 48 hours
- 800 mg 5 x/ daily for 7 days for HZO



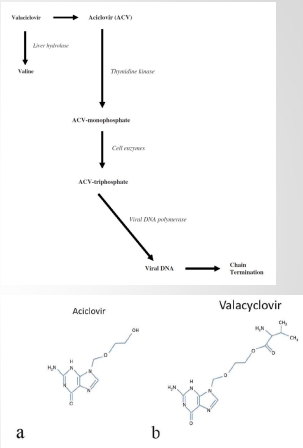
Acyclovir Treatment Summary

- HSV keratitis (off label)
 - 400 mg 5x/day
 - Prophylactic: 400 mg BID
- Herpes zoster ophthalmicus (off label)
 - 800 mg 5x/day x 7 days
- Bell palsy (new onset) (off-label)
 - 400 mg 5x/day for 10 days in combination with corticosteroids (not alone)
 - Begin within 3 days of symptom onset



Antiviral Drugs
Valacyclovir (Valtrex)

- Pharmacology
 - Prodrug of acyclovir
 - Metabolized to acyclovir
 - Higher bioavailability than acyclovir by 3-5 fold compared to oral ACV
 - Higher plasma ACV concentrations than oral ACV, comparable to IV ACV
 - Unlike ACV bioavailability of 10-20% because of low absorption, valacyclovir's (ACV) bioavailability >50%
 - This results in e.g. VAL BID vs ACV 5x/day



Antiviral Drugs
Valacyclovir (Valtrex)

- Caution: renal disease and dehydration
- ADR:
 - Nausea, vomit, diarrhea
 - HA
 - Skin rash
 - Liver enzymes elevated
 - Dizziness
 - Photosensitivity
- Pregnancy and Lactation: may use

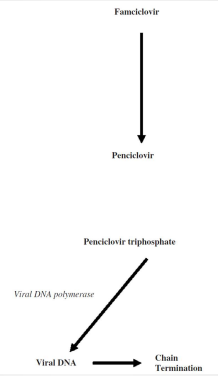


Antiviral Drugs Valacyclovir (Valtrex)

- Dosage:
 - HS keratitis: 500 mg TID
 - HZ: 1000mg TIDs (within 72 hours, max efficacy w/in 48 hours)
 - HS prophylactic: 500mg QD
- Bell Palsy (new onset) (off label)
 - Adjunctive with corticosteroid
 - 500 mg TID x 7 days (within 72 hours of onset)

Antiviral Drug: Famciclovir

- Pharmacology
 - Prodrug of penciclovir
 - Selectively inhibits herpes DNA synthesis
 - Interferes with action of viral DNA polymerase
 - Rapidly absorbed and converted
 - Bioavailability 77% vs ACV 20%
 - Longer half life compared to ACV = less frequent dosages
 - Caution: Renal Impairment
 - ADR: Nausea, vomit, diarrhea, HA,



```
graph TD;
    A[Famciclovir] --> B[Penciclovir];
    B --> C[Penciclovir triphosphate];
    C --> D[Viral DNA polymerase];
    D --> E[Viral DNA];
    E --> F[Chain Termination];
```

famciclovir generic
Pregnancy/Lactation ⓘ
Pregnancy Clinical Summary weigh risk/benefit during pregnancy; inadequate human data available; no known risk of fetal harm based on animal data at 1.4-10.8x systemic exposure and 1.1-6x MPOD
Lactation Clinical Summary weigh risk/benefit while breastfeeding; no human data available to assess risk of infant harm or effects on milk production

Oral AntiViral Treatment Summary

- Acyclovir
 - HSV keratitis: 400mg 5x/day
 - Prophylactic: 400 mg BID
 - HZ: 800 mg 5x/day X 7 days
- Valacyclovir (Valtrex)
 - Prodrug of acyclovir
 - HS Keratitis: 500 mg TID x 7 days
 - Prophylactic: 500mg QD
 - HZ: 1000mg TID x 7 days
- Famciclovir (Famvir=brand d/c)
 - Prodrug of penciclovir
 - HS Keratitis: 250 mg TID x 7 days
 - Prophylactic consider: 250mg BID
 - HZ: 500 mg TID x 7 days

Caution in those with renal impairment
Those at risk of renal disease: check BUN and creatinine before high dose

Note for all HZ:

- Start within 72 hours of skin lesions,
- Max effect w/in 48 hours

Herpes Simplex Studies

- HSV epithelial keratitis
 - Oral ACV may be effective tx
- HSV epithelial keratitis:
 - No benefit to add oral ACV to trifluridine to prevent development of herpes stromal keratitis or iritis
- HSV stromal keratitis:
 - No benefit to add oral ACV with topical steroids and trifluridine
- HSV iridocyclitis
 - Add oral ACV with topical steroid and trifluridine, may be beneficial
- HSV recurrent eye disease
 - Prophylactic oral ACV decreases
 - Long term oral ACV effective in decreasing recurrence

Herpes Zoster Studies

- HZO
 - Oral ACV (800mg 5x) best within 72 hours of rash onset
- Post herpetic neuralgia (HZO)
 - Contradictory evidence oral ACV decreases
 - Oral valacyclovir may be more effective in decreases

Neurotrophic Keratitis

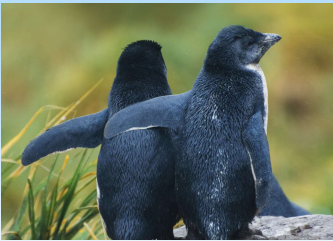
- Decreased corneal sensitivity and poor healing
- Herpes most common cause
- Treatment considerations
 - Lubrication (preservative free)
 - Antibiotic prophylaxis
 - Bandage CL
 - Scleral lens
 - Amniotic Membrane
 - Autologous serum
 - Patching
 - Cenegegermin (Oxervate)
 - Tarsorrhaphy

Anti-Fungal

Fungal Keratitis

- Risk Factors may include:
 - Trauma with vegetative matter (e.g. branches)
 - CL wear
 - CL solutions
 - Chronic ocular surface disease
- Dx: cultures and smears
- Treatment examples: natamycin (ophthalmic); fluconazole, itraconazole, voriconazole

Glaucoma Medications



30 (ii) the following antiglaucoma agents used for the management of
31 acute increases in intraocular pressure; provided, however, an optome-
32 trist may use or prescribe a maximum of one twenty-four hour
33 prescription and shall immediately refer the patient to a licensed
34 physician specializing in diseases of the eye:
35 (1) acetazolamide; and
36 (2) methazolamide; and

GI:
1-24hr rx
2-Refer
immediately

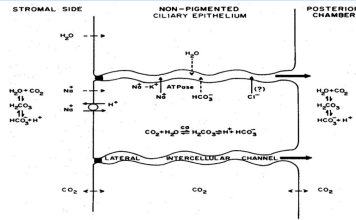
CARBONIC ANHYDRASE INHIBITORS

Carbonic Anhydrase Inhibitors
Mechanism

- Bicarbonate production in ciliary epithelium plays role in aqueous formation
- CAIs inhibit enzyme carbonic anhydrase
 - ◆ Decrease bicarbonate formation
 - ◆ Alters intracellular pH and ATPase activity
 - ◆ Sodium and water affected
 - ◆ NET result: decrease aqueous formation

Carbonic Anhydrase Inhibitors
Mechanism

- $\text{CO}_2 + \text{H}_2\text{O} + \text{Carbonic Anhydrase} \rightarrow \text{(I)}$
 $\text{H}_2\text{CO}_3 \text{ (Carbonic Acid)} \rightarrow \text{(II)} \text{H}^+ + \text{HCO}_3^- \text{ (Bicarbonate)}$
 - ◆ Reaction I:
 - ◆ Carbonic anhydrase catalyzes
 - ◆ Hydration of carbon dioxide to carbonic acid (H_2CO_3)
 - ◆ Reaction II:
 - ◆ Dehydration of carbonic acid to bicarbonate (HCO_3^-)
 - ◆ Ionic dissociation, no enzyme



Carbonic Anhydrase Inhibitors

- Systemic
 - ◆ Acetazolamide (Diamox=brand d/c)
 - ◆ Methazolamide (Neptazane=brand d/c)
- Topical
 - ◆ Dorzolamide (Trusopt)
 - ◆ Brinzolamide (Azopt)
 - ◆ Cosopt
 - ◆ Simbrinza

Carbonic Anhydrase Inhibitors: Systemic

Carbonic Anhydrase Inhibitors
Systemic: **Acetazolamide**

- Use
 - ◆ Glaucoma (open angle, angle closure, secondary)
 - ◆ Pseudotumor cerebri, altitudinal sickness, seizure disorder
- Decrease aqueous production: 27%
- Decrease IOP: 20-30%
- 95% bound to plasma proteins
- Sulfa based drug

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- Acetazolamide
 - ◆ Tab: 125 , 250 mg
 - ◆ Onset: 1-1.5 hr
 - ◆ Duration: 8-12 hours
 - ◆ ER: 500 mg
 - ◆ Onset: 2hr
 - ◆ Duration: 18-24 hours
 - ◆ 500 mg vial (injection)
 - ◆ Onset: 2-10 min
 - ◆ OAG: 125-250mg BID-QID or 500mg ER BID
 - ◆ ACG: 125-250 mg Q4H (start 500 mg)



Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- **Contraindications and Cautions:**
 - ◆ Hypersensitivity to sulfonamides
 - ◆ Hypokalemia
 - ◆ Adrenal insufficiency
 - ◆ Impaired renal function
 - ◆ Liver disease
 - ◆ Severe COPD
 - ◆ Sickle cell (and hyphema)
 - ◆ Elderly
 - ◆ Diabetes (may increase blood glucose)
- Safe pregnancy

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- Side effects:
 - ◆ Intolerable effects: 30-80% (max doses)
 - ◆ 26% tolerate (tablets) > 6 weeks
 - ◆ 58% tolerate timed release

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- **Common Side Effects:**
 - ◆ Numbness/tingling/paresthesias (up to 20%): extremities, perioral
 - ◆ Metallic taste/taste changes
 - ◆ Fatigue, malaise
 - ◆ Transient myopia
 - ◆ Ciliary body edema producing forward displacement of lens-iris diaphragm
 - ◆ GI irritation:
 - ◆ Abdominal cramps, nausea, diarrhea
 - ◆ Helps: Food, Sustained release, Sodium bicarbonate

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- Side Effects
 - ◆ Metabolic acidosis (results from bicarbonate loss)
 - ◆ Hypokalemia
 - ◆ Kidney stones
 - ◆ Blood dyscrasias
 - ◆ Dermatitis
 - ◆ Depression
 - ◆ Reduced libido
 - ◆ Stevens-Johnson syndrome

Carbonic Anhydrase Inhibitors
Systemic: Methazolamide

- Clinical Uses
 - ◆ Consider as 1st CAI for systemic glaucoma treatment
- Better tolerated than acetazolamide
 - ◆ Similar, less ADR than acetazolamide
- 55% binds to plasma proteins (vs 90-95% acetazolamide)
- IOP effect slightly less than acetazolamide
- Onset: 2-4 hours; Duration: 10-18 hours
- Half life 14 hours (vs acetazolamide 5 hours)
- Cautions similar to acetazolamide

HYPEROSMOTICS:
SYSTEMIC

Hyperosmotics: Systemic

- | | |
|---------------|--|
| ■ Oral: | ■ Indications: |
| ◆ Glycerin* | ◆ Acute angle closure glaucoma |
| ◆ Isosorbide* | ◆ Intraocular surgery |
| ■ Intravenous | ■ Mechanism: |
| ◆ Mannitol | ◆ ^ serum osmolality |
| ◆ Urea ** | ◆ Result: fluid movement from eye to hyperosmotic plasma via retinal and uveal blood vessels |

*Not available?

**Not available ocular use

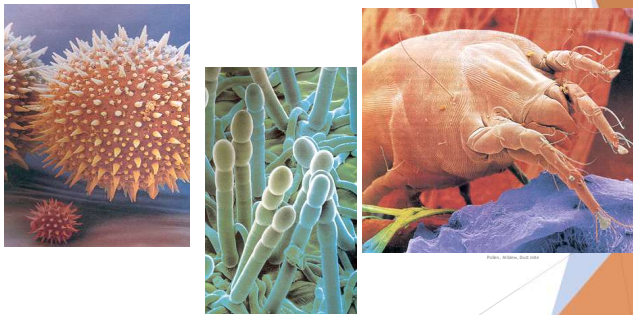
Hyperosmotics: Systemic-Orals

- Glycerin (Osmoglyn) (?available?)
 - ◆ Onset: 10-30 min
 - ◆ Lime flavored
 - ◆ Serve chilled = Decreases nausea and vomit
 - ◆ Caution/contraindication: Diabetics
- Isosorbide (Ismotic) (?available?)
 - ◆ Onset: 30-60 min
 - ◆ Vanilla mint flavored
 - ◆ Serve chilled
 - ◆ Can use in diabetics

Angle Closure Treatment

- Topical treatment
 - ◆ Beta Blocker (e.g. timolol),
 - ◆ Alpha 2 agonist (e.g. brimonidine or apraclonidine),
 - ◆ CAI (e.g. dorzolamide),
 - ◆ Cholinergic agonist (note pilocarpine does not work when IOP >60)
 - ◆ 3 rounds separated by 15 minutes
- Repeat topical if needed 1 hour
- Oral acetazolamide:
 - ◆ 2x 250 mg (NOT extended release)
 - ◆ Not in sulfonamide induced angle closure or sickle cell
- Oral isosorbide over ice
- Indentation gonioscopy
- Topical hyperosmotic to reduce corneal edema
 - ◆ Steroid-may help reduce corneal edema

Antiallergy:
Antihistamines

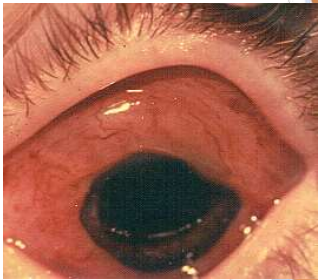


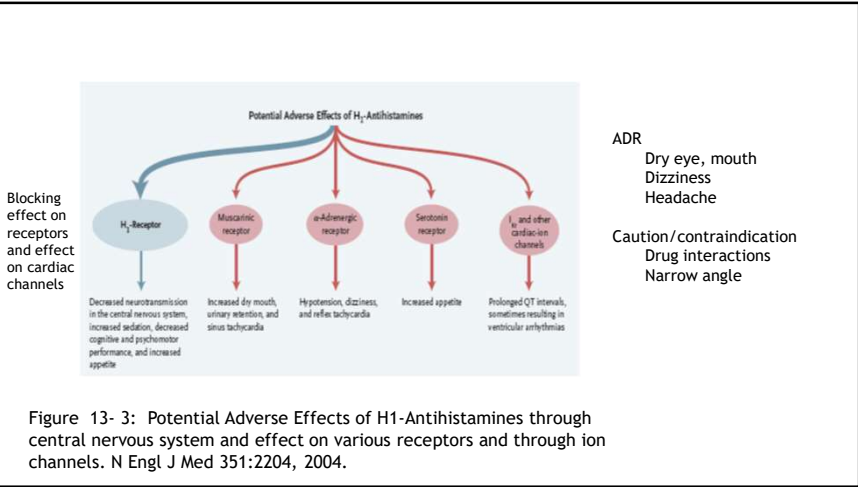
Allergies

- ▶ Type 1 and Type IV Hypersensitivity
- ▶ Treatment considerations:
 - ▶ Avoid offending agent
 - ▶ Lubricants
 - ▶ Antihistamines (topical or oral)
 - ▶ Mast cell stabilizers/combo with antihistamine
 - ▶ Topical or oral steroid
 - ▶ Allergist, dermatologist as needed

Antihistamines: Oral

- ▶ General uses
 - ▶ Allergy (sinusitis, rhinitis)
 - ▶ Moderate to severe lid edema (angioedema), chemosis
 - ▶ Lid myokymia
 - ▶ Drug to structures not reached by topicals
 - ▶ Sedation (vs Not)
 - ▶ Anticholinergic effect





2nd Generation Antihistamines: Non-Sedating Oral

- ▶ Considerations:
 - ▶ Cetirizine (Zyrtec) = potential for drowsiness
 - ▶ Loratadine (Claritin) = potential for torsades de pointes when used with amiodarone
- ▶ Food and Drug Interactions:
 - ▶ Absorption delayed with food:
 - ▶ cetirizine and loratadine
 - ▶ Absorption and concentration decreased with grapefruit, orange/apple juice, antacids:
 - ▶ fexofenadine
 - ▶ Increase concentration with erythromycin or ketoconazole:
 - ▶ fexofenadine

Inflammation and Pain Management



Pain Management

Pain Mechanism

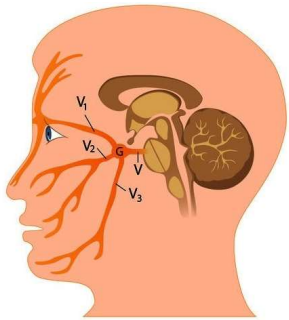
History

Clinical Presentation

Level of Pain

The Drugs

- Narcotic vs Non Narcotic
- WHO Analgesic Ladder
 - Mild pain (acetaminophen, NSAIDs)
 - Moderate pain (mild opioid)
 - Severe pain (strong opioid)
- Consider alternating acetaminophen and ibuprofen (for pain and fever)



Inflammation Management

- NSAIDs
- Steroids
- Immunosuppressants
- Biologics
- Disease modifying anti-rheumatic drugs (DMARDs)

FIGURE 12.6 Pathways of synthesis of prostaglandins and leukotrienes. (Adapted from Jampol LM. Pharmacologic therapy of aphakic cystoid macular edema. Ophthalmology 1982;89:894.)

Steroids

Anti-inflammatory effects:

- Nonspecific
- Does not correct disorder

Control inflammatory process and its effects:

- ❖ Inhibits cell mediated immune responses
- ❖ Inhibit degranulation of mast cells, basophils, neutrophils
- ❖ Reduces circulating eosinophils and monocytes

Affects infection control and tissue repair:

- ❖ By attenuation of bactericidal activity of macrophages and monocytes
- ❖ By affecting tissue regeneration and repair

Steroids (Systemic)

Ocular use:

Severe allergic reaction; scleritis; dermatitis; periocular poison ivy/oak; recalcitrant anterior uveitis/scleritis; herpes zoster, giant cell arteritis; insect bites

Hx considerations:

Diabetic, HT, pregnant, immunocompromised, TB, peptic ulcer

Treatment concepts:

Alternate day therapy: utilizes circadian rhythm of natural steroid secretion

Taper: allows for the adrenal glands to resume their normal functions

Medrol Dose pack (methyl prednisone) – pack with self tapering dose over 6 days

Contraindications/Cautions:

Untreated infection/diabetes/pregnancy/stomach ulcers/osteoporosis/recent heart attack/heart failure/liver dysfunction

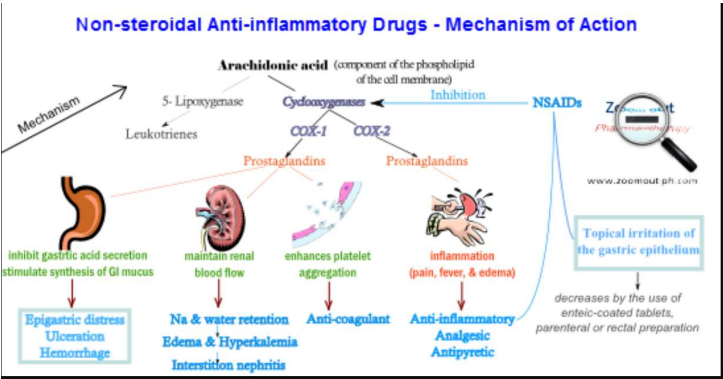
ADR:

Increased appetite and weight gain; HT, increase blood sugar, slowed wound healing, osteoporosis, thinning of skin, stomach ulcer, mood swings, adrenal crisis

TABLE 2: Side effects of corticosteroids.

Cardiovascular	Sodium and fluid retention, hypertension
Gastroenterological	Pancreatitis with high dose steroids, peptic ulcer
Neurologic	Psychosis, altered mood states, headaches, pseudotumor
Opthalmic	Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos
Musculoskeletal	Osteoporosis, vertebral and femoral fractures, aseptic necrosis of femoral head. Myopathy, muscle weakness
Endocrine	Diabetes mellitus/glucose intolerance, Cushingoid facies, hyperlipidemia, growth retardation, menstrual irregularities, suppression of pituitary-adrenal axis
Skin	Acne, increased bruising, impaired wound healing
Infectious	Increased risk of infections, including fungal

A comprehensive review of immunosuppression used for liver transplantation. J Transplant doi:10.1155/2009/701464



Nonopioid (NonNarcotic) Analgesics

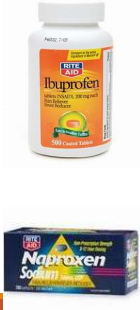
Salicylates

- Relatively safe and non-addicting
- Are a subclass of NSAIDs
- E.g. Aspirin
- Ceiling effect: dosage beyond which no further analgesia occurs
- I.e.. Increasing doses have progressively smaller incremental effect

Nonopioid (NonNarcotic) Analgesics

Nonsalicylate NSAIDs

- Mechanism: Inhibit cyclooxygenase
- Metabolized by liver and eliminated through kidney
- Superior to aspirin in analgesic efficacy, with ADR
- Side Effects:
 - GI effects
 - Inhibit platelet function
- Contraindications
 - Peptic ulcer, renal insufficiency
- Propionic acid derivatives: ibuprofen and naproxen



NSAIDs

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include: • heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	Other side effects include: • stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness
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<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d6b3822b-8f14-4137-8d53-24863f4c605e&type=display> (accessed 6-3-23)

Nonopioid (NonNarcotic) Analgesics

Nonsalicylate NSAIDs

Ibuprofen

- Lower GI complications (bleeding) compared to other NSAIDs when ≤ 1200 mg/day
- However odds double when ≥ 1800 mg/day
- Analgesic vs Anti-inflammatory ceiling of ibuprofen:
 - Analgesic ceiling: 1200/day
 - Anti-inflammatory ceiling dose: 2400-3200 mg/day
- Maximum dose: 3200mg/day (arthritis); 2400mg/day (pain)
- Ibuprofen 400mg QID=acetaminophen 300mg/codeine 30 mg (formerly Tylenol 3)



Nonopioid (NonNarcotic) Analgesics

Acetaminophen

- Little or no inflammatory effect
- Does not:
 - inhibit platelet aggregation, affect prothrombin time, produce GI irritation
- Dosage: 325-1000mg Q4-6H
- Max: 1g/4h and 4g/day
- Side effects:
 - Liver toxicity
- Contraindications
 - Chronic alcoholism

Opioid (Narcotic) Analgesics

Side Effects

- CNS
 - Drowsiness, dizziness, euphoria
- Eye
 - Blurred vision, diplopia
- GI
 - Nausea, vomit, constipation
- Respiratory
 - Respiratory depression, shortness of breath, cough suppressant
- Cardiovascular
 - Palpitations

Naloxone: opioid receptor antagonist=reverses effects of opioid drugs

Opioid Analgesics: Codeine



Codeine

- Prodrug
- Metabolized by cytochrome P-450 to active compound = morphine
- When administered to patient carrying CYP2D6 gene duplication, ~50% more morphine is produced
- Ceiling effect (further increase in dosage has no additional effect)
- Schedule II or Schedule III
- 30mg+acetaminophen(300mg) (Tylenol 3-brand d/c) (ocular use)

