

New York State
Oral Pharmaceuticals Course

Pharmacology Principles For Clinical Application of
Oral Drugs (Part 3)

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Anti-Infectives

Antibiotics

Anti-infective and
Bacterial Overview

Anti-infective Overview

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

Normal Microbial Flora

- Can vary between individuals
- Can become pathogenic in the right circumstances, such as
 - Debilitating disease
 - Immunosuppression
- Helps to prevent the colonization of pathogenic species
 - Substances may be produced that inhibit the growth of other species

Normal Ocular Flora

- Bacteria typically recovered from 80 to 90% of normal eyes include:
 - Coagulase-negative staphylococci
 - Propionibacterium acnes
 - Corynebacterium species
- Staph aureus, Strep pneumoniae & H. flu are pathogens occasionally recovered from non-infected eyes

Bacteria

- Bacteria: single celled microorganisms
 - Subdivided by shape and gram stain
- Gram Positive
 - Staphylococcus (aureus, epidermidis)
 - Streptococcus (pneumonia, pyogenes, faecalis)
- Gram Negative
 - Rods: Haemophilus influenzae, Pseudomonas aeruginosa, Serratia marcescens
 - Cocci: Neisseria gonorrhoeae
- Unique structural morphology includes
 - Chlamydia (trachoma, inclusion conjunctivitis)
 - Mimic viruses
 - Treponema palladium (syphilis)

Anti-infective Overview

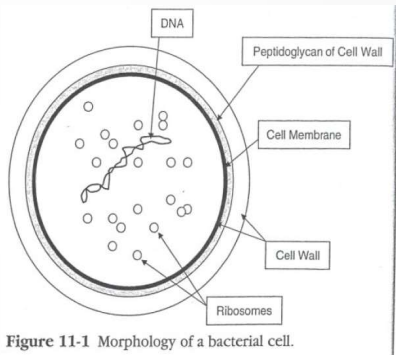
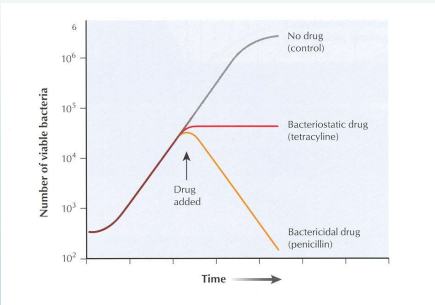


Figure 11-1 Morphology of a bacterial cell.

Antibacterial Drugs

- Bactericidal: kills bacteria
- Bacteriostatic: inhibit bacteria growth



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
 - May do this for example by interfering with bacterial protein production or bacterial cellular metabolism
 - 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

Note: not always a precise distinction between static and cidal antibiotics

- High concentrations of some bacteriostatic agents are also bactericidal
 - For example: macrolides can be bactericidal in high doses
- Certain antibiotics may be cidal to certain pathogens and static to others

Bactericidal Antibiotics	Bacteriostatic Antibiotics
<i>Inhibit Cell Wall</i>	<i>Affect Intermediary Metabolism (Folic Acid)</i>
Penicillins	Sulfonamides
Cephalosporins	Trimethoprim (may be cidal from synergy when combo drug)
Vancomycin	Pyrimethamine
Bacitracin	
<i>Affect Cytoplasmic Membrane</i>	
Polymyxin	
Gramicidin	
<i>Affect Protein Synthesis</i>	<i>Affect Protein Synthesis</i>
Aminoglycosides	Tetracyclines
	Macrolides
	Chloramphenicol (some cidal activity)
<i>Affect DNA Synthesis</i>	
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
 - Antibacterial drug: Inhibit synthesis of cell wall
 - Cell membrane
 - Similar
 - Ribosomes
 - Different size and composition
 - Inhibit bacterial protein synthesis

All Cells have:

- 1. Genetic Material
- 2. Cytoplasm
- 3. Ribosomes
- 4. Cell Membrane
- 5. Cytoskeleton

Prokaryotes

- 1. No nucleus
 - DNA in cytoplasm
- 2. No MB organelles
 - still have ribosomes to make proteins

Eukaryotes

- Nucleus
 - DNA is in nucleus, more compacted
- MB organelles
 - ribosomes for protein synthesis

Prokaryotic Ribosome

Bacteria

70S

50S subunit

30S subunit

5S RNA

23S RNA

16S RNA

Eukaryotic Ribosome

Animals/Plants/Fungi

80S

60S subunit

40S subunit

5S RNA

5.8S

28S RNA

18S RNA

Antibacterial Drugs

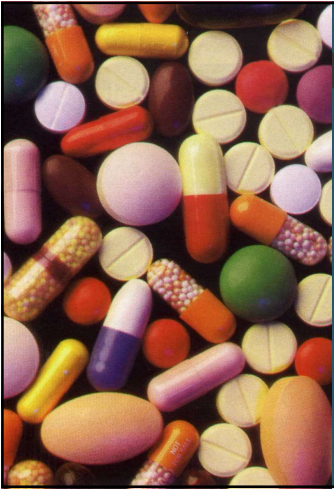
- Selective toxicity (bacteria vs human)
 - Biosynthetic pathways (intermediary metabolism)
 - Folic acid: bacterial cells synthesize
 - Enzyme DNA gyrase
 - An essential bacterial enzyme involved in DNA replication

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

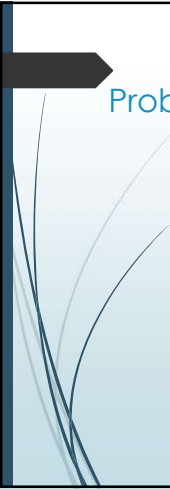
Mechanisms of Resistance

- Cross resistance
- Misuse and overuse of antibiotics
 - During the systemic use of antibiotics
 - Inappropriate use
 - Patient non-compliance
 - With the use of antibiotics in animal feed



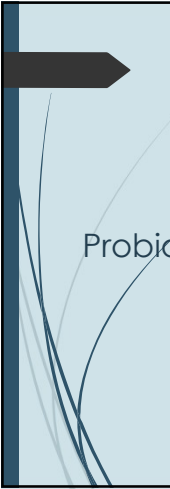
Oral Antibacterial Drugs

- Clinical Indications
 - Meibomianitis
 - Internal Hordeolum
 - Ocular Rosacea
 - Dacryocystitis
 - Preseptal Cellulitis
 - Chlamydial Conjunctivitis
 - Prophylaxis (orbital fractures, sinusitis)



Probiotics

- Probiotics are live nonpathogenic microorganisms administered to improve microbial balance, particularly in the GI tract
 - Defined: live microorganism thought to confer health benefits
- Broadly describes various strains of bacteria and yeast
 - Consist of yeast or lactic acid bacteria
- They are regulated as a dietary supplement and food
- Used for a variety of conditions including up to 30% on antibiotics experiencing antibiotic associated diarrhea
- Food examples: yogurt, sauerkraut, kimchi
- Timing: when to take (do not take with antibiotic ie space at least 2 hours before/after antibiotic doses)
- Generally safe, with flatulence and bloating most frequent side effect
- Used cautiously with patients taking immunosuppressants (e.g. tacrolimus, chemotherapy, proton inhibitors) or who are immunocompromised—can cause infection



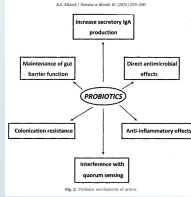
Probiotics

- Things to look for:
 - Colony Forming Units (CFU) – (range can vary 10 million to 1 billion to 50 billion CFUs)
 - Strain Diversity – e.g. 8-12 separate strains
 - Strains – e.g. Lactobacillus acidophilus
 - Prebiotics – fiber based to nourish good bacteria
 - Enteric coated – survives stomach acid
 - Manufacture/expiration date – decreased effectivity with time
- Use Examples:
 - Diarrheal illness
 - Antibiotic-associated diarrhea
 - Inflammatory bowel disease
 - Irritable bowel syndrome
 - Allergic disease (atopic dermatitis, allergic asthma, allergic rhinitis, food allergies)
 - Atherosclerosis



Probiotics

- Effects through:
 - Lowering intestinal pH (suppress growth of pathogenic bacteria, reestablishing gut flora balance)
 - Enhance mucin from gut epithelial cells (serve as antibacterial barrier prevent binding of pathogens)
 - Promote secretory IgA (that binds to pathogens)
 - Interfere with quorum sensing (a mechanism by which bacteria enhance their virulence)
 - Exert anti-inflammatory effect in gut
 - Decreasing colonization (by competitively blocking their adhesion to the epithelium)
 - Decreasing invasion by pathogenic organisms (production of various substances that are toxic to pathogenic microorganism)
 - Modifying host immune response
 - May activate opioid and cannabinoid receptors in gut (ameliorate visceral pain)

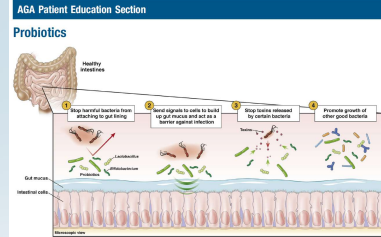


AGA Abstract / Review Article 10 (2015) 100-108
Fig. 3. Probable mechanism of action.

Clinical Gastroenterology and Hepatology 2019;17:xxx

AGA Patient Education Section

Probiotics



Oral Contraceptive and Antibiotics

- Failure rate associated with OCs are typically 1-3% *
- Various hypothesis:
 - Decreased enterohepatic circulation, increased liver degradation, contraceptive displacement from receptor site
 - Antibiotic-induced diarrhea
 - Increased liver p450 enzyme induction
- However - Inconsistencies in study findings over time if OC failure with oral antibiotics

*Oral contraceptive failure rates and oral antibiotics. JAMAcadDermatol 1997;36:705-10

BMJ Evidence-Based Medicine; 2020-111363

- Non-enzyme inducing antibacterial drugs e.g.: cephalexin, ciprofloxacin, erythromycin, trimethoprim
- Enzyme-inducing drug e.g.: carbamazepine, topiramate, rifampicin
- Risk of unintended pregnancies:
 - Enzyme-inducing drugs: 13 fold increase
 - Antibacterial drugs: 7 fold increase
- Many groups (WHO, US Center for Disease Control and Prevention) do not advise any additional precautions
- This article however based on the uncertainties advised precautions

Analysis of reports of unintended pregnancies associated with the combined use of non-enzyme-inducing antibiotics and hormonal contraceptives

Jeffrey K Aronson, Robin E Ferner

Abstract
Background: Enzyme-inducing antibiotics can inhibit the efficacy of hormonal contraceptives. However, the effect of non-enzyme-inducing antibiotics on the efficacy of hormonal contraceptives is unclear. We conducted a systematic review of the literature to assess the effect of non-enzyme-inducing antibiotics on the efficacy of hormonal contraceptives.

Key message box

What is already known about this subject?

- Anecdotal reports have suggested that the use of non-enzyme-inducing antibacterial drugs may reduce the efficacy of hormonal contraceptives, leading to contraceptive failure.
- Formal studies have either suggested that there is no interaction of this kind but without conclusive evidence or have shown no evidence of an interaction.
- Most previously negative or inconclusive studies have been too small to rule out an interaction in a small subset of women, and other criticisms of previous studies have the question of an interaction open.

Box 1 Your medicine and the pill

- Your doctor has prescribed an antibiotic medicine to treat your infection.
- If you are taking the pill or using some other type of hormonal contraceptive, the antibiotic may make it less effective.
- This means that you may get pregnant if you have sex, even though you are taking a contraceptive.
- If you are keen not to get pregnant, it is best to avoid sex or to take extra precautions, such as using a condom, while you are taking the antibiotics and for 7 days after completing the course.

Anti-infective Overview

- Drug considerations
 - Selective toxicity
 - Spectrum of activity
 - Species which drug shows intrinsic activity
 - Narrow vs broad
 - Resistance

Guidelines: Effective Antimicrobial Therapy

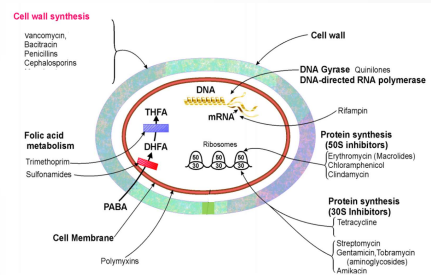
- Accurate diagnosis
- Microorganism sensitive to anti-infective
- Least toxic drug
- Adequate drug levels
- Optimum route of administration
- Appropriate dosage
- Appropriate treatment time
- Augment drug tx with physical procedures

Antimicrobial Failure

- Inaccurate diagnosis
- Resistance
- Inadequate drug dosage
- Noncompliance
- Inadequate supplemental physical procedures
- Inadequate immune system response

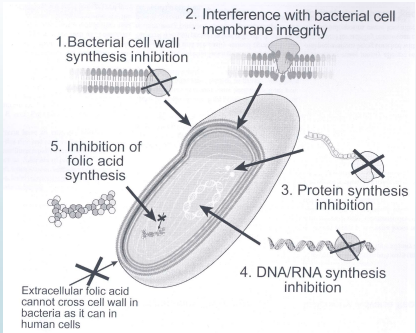
Mechanisms of Antibiotic Action

- 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

- Inhibition of cell wall synthesis
 - Penicillins
 - Amoxicillin and clavulanate (Augmentin)
 - Dicloxacillin
 - Cephalosporins
 - Cephalexin (Keflex=brand d/c)
 - Cefaclor (Ceclor=brand d/c US)
 - Bacitracin
 - Vancomycin



Antibacterial:
Affecting Cell Wall
Synthesis
Penicillins

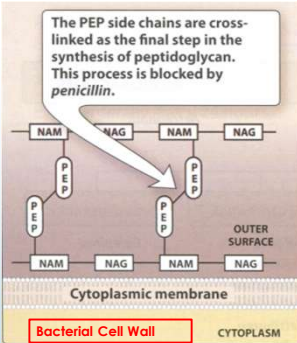


Figure 31.3
Bacterial cell wall of gram-positive bacteria. NAM = N-acetylmuramic acid; NAG = N-acetylglucosamine; PEP = cross-linking peptide.

Lippincott's Illustrated Reviews, Pharmacology.

Antibacterial: Affecting Cell Wall Synthesis
Penicillins

- Pharmacology:
 - Contain common nucleus composed of:
 - Thiazolidine ring
 - β -lactam ring
 - Necessary for biological activity
 - Side chain
 - Determines antibacterial spectrum
 - Susceptibility to bacterial degradative enzymes (β -lactamase enzymes)
 - Pharmacokinetic properties
- Bactericidal
- Effective: Gram +, Gram -

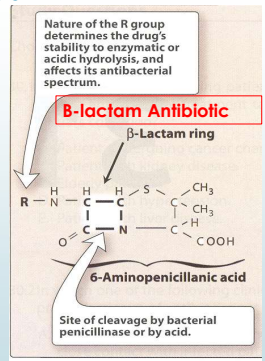


Figure 31.2
Structural features of β -lactam antibiotics.

Lippincott's Illustrated Reviews, Pharmacology.

Antibacterial: Affecting Cell Wall Synthesis
Penicillins: Use

- Penicillins Use:
 - Hordeolum
 - Preseptal cellulitis
 - Dacryocystitis
 - Dacryoadenitis

Antibacterial: Affecting Cell Wall Synthesis
Penicillins

- Adverse Reactions
 - Hypersensitivity response
 - GI irritation: Nausea, vomit, diarrhea
 - Superinfection

Allergic to Penicillin? You May Not Be

Nineteen out of 20 people who have been told they are allergic to penicillin are not truly allergic to the drug.



By Roni Caryn Rabin

Jan. 22, 2019

Millions of Americans who believe they are allergic to penicillin are not actually allergic. But they are steered away from using some of the safest

JAMA, 2019 Jan 15;321(2):188-199. doi: 10.1001/jama.2018.19283

Evaluation and Management of Penicillin Allergy: A Review.

Shenoy ES^{1,2,3}, Macy E⁴, Rowe T⁴, Blumenthal KG^{4,5,7}.

Abstract

IMPORTANCE:

β-Lactam antibiotics are among the safest and most effective antibiotics. Many patients report allergies to these drugs that limit their use, resulting in the use of broad-spectrum antibiotics that increase the risk for antimicrobial resistance and adverse events.

OBSERVATIONS:

Approximately 10% of the US population has reported allergies to the β-lactam agent penicillin, with higher rates reported by older and hospitalized patients. Although many patients report that they are allergic to penicillin, clinically significant IgE-mediated or T lymphocyte-mediated penicillin hypersensitivity is uncommon (<5%). Currently, the rate of IgE-mediated penicillin allergies is decreasing, potentially due to a decreased use of parenteral penicillins, and because severe anaphylactic reactions to oral amoxicillin are rare. IgE-mediated penicillin allergy wanes over time, with 80% of patients becoming tolerant after a decade. Cross-reactivity between penicillin and cephalosporin drugs occurs in about 2% of cases, less than the 8% reported previously. Some patients have a medical history that suggests they are at a low risk for developing an allergic reaction to penicillin. Low-risk histories include patients having isolated nonallergic symptoms, such as gastrointestinal symptoms, or patients solely with a family history of a penicillin allergy, symptoms of pruritus without rash, or remote (>10 years) unknown reactions.

- ~10% report allergy to penicillin (higher in older and hospitalized patients)
- However, hypersensitivity uncommon (<5%)
- Cross-react penicillin and cephalosporin ~2% (vs 8% previously reported)

JAMA, 2019 Jan 15;321(2):188-199. doi: 10.1001/jama.2018.19283

Evaluation and Management of Penicillin Allergy: A Review.

- Low risk history
 - Nonallergic symptoms (e.g. GI symptoms)
 - Direct amoxicillin challenge
- Moderate risk history
 - Urticaria or other pruritic rashes
 - Penicillin skin testing
- High risk history
 - Anaphylaxis, + penicillin skin testing, recurrent penicillin reactions, or hypersensitivities to multiple β-lactam antibiotics

CONCLUSIONS AND RELEVANCE:

Many patients report they are allergic to penicillin but few have clinically significant reactions. Evaluation of penicillin allergy before deciding not to use penicillin or other β-lactam antibiotics is an important tool for antimicrobial stewardship.

Antibacterial: Affecting Cell Wall Synthesis

Penicillins: Classification

- Penicillin Classification:
 1. Penicillins effective Gram +
 - Penicillin G (IV, IM), Penicillin V (PO)
 2. Penicillins resistant to penicillinase
 - Dicloxacillin: PO
 3. Penicillins with extended spectra of activity, with improved activity against Gram -
 - Amoxicillin, Amoxicillin and clavulanate (Augmentin): PO
 4. Penicillin with antipseudomonal activity

- Inhibition of cell wall synthesis
 - Penicillins
 - Amoxicillin and clavulanate (Augmentin)
 - Dicloxacillin

- Penicillins with extended spectra of activity (Amoxicillin/clavulanate)
 - Modification of basic penicillin structure
 - Inactivated by penicillinase
 - Clavulanate:
 - B-lactamase inhibitor that protects penicillin component from inactivation by penicillinase or B-lactamase
 - Weak antimicrobial activity
 - Amoxicillin and clavulanate (Augmentin)

- Amoxicillin/Clavulanate (Augmentin)
 - May be used during pregnancy and breastfeeding
 - Clinical uses:
 - Hordeolum
 - Preseptal cellulitis
 - Dacryocystitis
 - Dacryoadenitis

Treatment Example:

Preseptal cellulitis:

Adult: Amoxicillin/clavulanate 875/125 mg q12h
(with or without meal, better with food to lessen stomach upset)

Children: Amoxicillin/clavulanate: 25-45mg/kg/day in 2 divided doses (q12h)

Augmentin amoxicillin/clavulanate Adult Dosing Ⓢ Dosage forms: TAB: 250 mg/125 mg, 500 mg/125 mg, 875 mg/125 mg; SLURP: 125 mg/31.25 mg per 5 mL, 250 mg/62.5 mg per 5 mL. Infections, bacterial [500-mg/125-mg-475-mg PO q12h] At: 250 mg/125 mg-500 mg/125 mg PO q8h; info: give w/ food or milk		Augmentin amoxicillin/clavulanate Peds Dosing Ⓢ Dosage forms: TAB: 250 mg/125 mg, 500 mg/125 mg, 875 mg/125 mg; SLURP: 125 mg/31.25 mg per 5 mL, 250 mg/62.5 mg per 5 mL. Dosage Forms Discontinued in US [schedule tab, 200 mg/28.5 mg PO q8h] 400 mg/57 mg per 5 mL, susp not av; brand; see generic
	amoxicillin/clavulanate generic Pregnancy/Lactation Ⓢ Pregnancy <i>Clinical Summary</i> may use during pregnancy; possible risk of teratogenicity based on conflicting human data; no known risk of fetal harm observed at animal data at 2-9x MHD Lactation <i>Clinical Summary</i> may use while breastfeeding; no known risk of infant harm, though possible risk of infant diarrhea, rash, otitisitis, thrush, and candidiasis based on limited human data, no human data available to assess effects on milk production	amoxicillin/clavulanate generic Peds Dosing Ⓢ Dosage forms: TAB: 125 mg/31.25 mg, 500 mg/125 mg, 875 mg/125 mg; ER TAB: 1000 mg/62.5 mg; CHWABLE: 200 mg/28.5 mg, 400 mg/57 mg; SLURP: 125 mg/31.25 mg per 5 mL, 250 mg/62.5 mg per 5 mL, 500 mg/125 mg per 5 mL, 800 mg/100 mg per 5 mL, 400 mg/57 mg per 5 mL, 500 mg/62.5 mg per 5 mL, 500 mg/62.5 mg per 5 mL. Infections, bacterial PO max, +40 kg Dose: 10 mg/kg/day PO divided q12h; info: give 125 mg/31.25 mg, susp; dose based on amoxicillin component; give w/ food or milk D 5 mo and older, <40 kg Dose: 25-40 mg/kg/day PO divided q12h, up to 200 mg/28.5 mg or 400 mg/57 mg tabs; At: 20-40 mg/kg/day PO divided q8h, up to 100/13.1 mg or 200 mg/28.5 mg tabs; info: dose based on amoxicillin component; give w/ food or milk D 5 mo and older, >40 kg see Adult Dosing
amoxicillin/clavulanate generic Adult Dosing Ⓢ Dosage forms: TAB: 250 mg/125 mg, 500 mg/125 mg, 875 mg/125 mg; ER TAB: 1000 mg/62.5 mg; CHWABLE: 200 mg/28.5 mg, 400 mg/57 mg; SLURP: 125 mg/31.25 mg per 5 mL, 250 mg/62.5 mg per 5 mL, 500 mg/125 mg per 5 mL, 800 mg/100 mg per 5 mL, 400 mg/57 mg per 5 mL, 500 mg/62.5 mg per 5 mL, 500 mg/62.5 mg per 5 mL. Infections, bacterial [500-mg/125-mg-475-mg PO q12h] At: 250 mg/125 mg-500 mg/125 mg PO q8h; info: give w/ food or milk	Enocrates	

Drugs: Affecting Cell Wall Synthesis
Penicillins: Dicloxacillin

- Penicillins resistant to penicillinase: Dicloxacillin
 - A penicillinase resistant penicillin that is NOT inactivated by bacterial penicillinase enzyme (that would otherwise destroy the beta-lactam ring of the antibiotic)
 - May be used during pregnancy and breastfeeding
 - Clinical uses:
 - Internal Hordeolum
 - Preseptal cellulitis
 - Treatment Example:
Internal Hordeolum
Dicloxacillin: 250mg q6h (1-2wks)
(empty stomach)(1 hr before, 2 hr after meals)

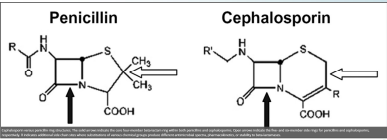
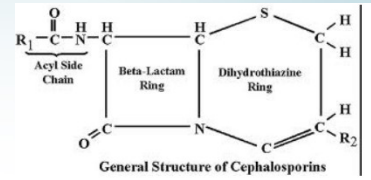
Antibacterial: Affecting Cell Wall Synthesis
Cephalosporins

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

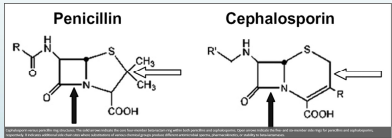
Antibacterial: Affecting Cell Wall Synthesis
Cephalosporins

- Pharmacology
 - B lactam ring
 - Similar penicillin/similar mechanism
 - Addition of different side chains modify and create 1,2,3 generations
- Broad spectrum
- Bactericidal
- Resistance
 - Drug inactivation by B lactamases



Antibacterial: Affecting Cell Wall Synthesis
Cephalosporins

- Adverse reactions
 - Hypersensitivity reactions
 - Cross sensitivity
 - 20% penicillin allergy with cross sensitivity was historic thinking, but probably much less – approximately 1%
 - More likely see with 1st generation cephalosporins
 - Vitamin K deficiency
 - Nausea, vomit, diarrhea



Antibacterial: Affecting Cell Wall Synthesis
Cephalosporins

- Clinical Conditions:
- Preseptal cellulitis
 - Dacryocystitis
 - Dacryoadenitis
 - Orbital fracture
 - Other (fortified use)



Drugs: Affecting Cell Wall Synthesis
Cephalosporins: Cephalexin

- First Generation: Cephalexin (Keflex=brand d/c US)
 - May be used during pregnancy and breastfeeding
 - Clinical use:
 - Preseptal cellulitis
 - Dacryocystitis
 - Dacryoadenitis

Treatment Example:

- Dacryoadenitis:
 - Cephalexin 250-500 mg QID (or q6h)
 - With or without meals
- Preseptal
 - Cephalexin 500 mg TID or 875 mg BID
 - With or without meals

Drugs: Affecting Cell Wall Synthesis
Cephalosporins: Cefazolin

- First Generation: Cefazolin
 - Dosage form: injection
 - May be used during pregnancy and breastfeeding
 - Fortified:
 - Sterile water and 500 mg of cefazolin dry powder to form 10 mL of solution = strength of 50 mg/mL
 - Treatment Example:
 - Bacterial keratitis: fortified cefazolin (50 mg/mL)

Antibacterial: Affecting Cell Wall Synthesis

Vancomycin

Drugs: Affecting Cell Wall Synthesis

Vancomycin

- Pharmacology
 - Highly active gram positive
- Bactericidal
- Dosage considerations
 - Solution for injection, capsule, dry powder (for fortified)
- Use during pregnancy:
 - Drugs.com: use only if clearly needed
 - Epocrates: Inj-avoid 1st and 2nd trimesters; weigh risk/benefit 3rd trimester
 - Epocrates: Other formulations: may use during pregnancy and breastfeeding
- Highly toxic
 - Anaphylaxis, vasculitis, nephrotoxicity, ototoxicity, neutropenia, others

Drugs: Affecting Cell Wall Synthesis

Vancomycin

- Use:
 - Bacterial endophthalmitis
 - Methicillin/penicillin resistant infections
 - Bacterial keratitis – vision threatening
 - Ruptured globe
 - Orbital cellulitis

Treatment example:
Bacterial keratitis (resistant/vision threatening): fortified vancomycin (25 mg/mL) q1h

Ototoxicity and Drug Therapy

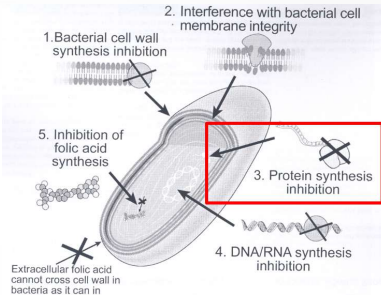
- Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus.
- Hearing loss can be temporary but is usually irreversible with most agents.
- Generally, antibiotic-induced ototoxicity is bilaterally symmetrical, but it can be asymmetrical.
- The usual time of onset is often unpredictable, and marked hearing loss can occur even after a single dose.
- Additionally, hearing loss may not manifest until several weeks or months after completion of antibiotic or antineoplastic therapy.

Medscape

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:
 - Gram positive and negative
 - Chlamydia
- Resistance (*S. aureus*)
- Short, intermediate, long acting

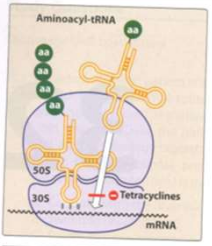


Figure 32.2
Tetracyclines binds to the 30S ribosomal subunit, thus preventing the binding of aminoacyl-tRNA to the ribosome. aa = amino acid.

Lippincott's Illustrated Reviews. Pharmacology.

Drugs Affecting Protein Synthesis
Tetracycline: Oral Overview

- Oral Overview:
- Antibiotic activity
 - Affect on free fatty acids- decreases bacterial lipase production
 - Anti-inflammatory effect
 - Anticollagenolytic activity

Antimicrobials Affecting Protein Synthesis
Tetracycline: Overview

- Oral Use:
 - Chlamydia (inclusion conjunctivitis or trachoma)
 - Acne rosacea, meibomianitis
 - Free fatty acids
 - Released from sebum by bacterial lipases
 - Irritating and inflammatory
 - Tetracycline: decrease lipase production
 - Nontuberculous phlyctenular keratoconjunctivitis
 - Noninfected corneal ulcers
 - Related to anticollagenolytic activity of systemic tetracycline

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

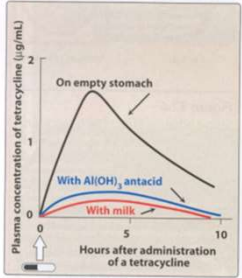


Figure 32.5
Effect of antacids and milk on the absorption of tetracyclines.

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
 - With food improve, but affect drug's absorption (not doxycycline)
 - Epigastric distress (sore throat, glossitis)



Drugs and Photosensitivity Reactions

- Drug induced photosensitivity may be result from:
 - Phototoxic reaction: damage to tissues is direct
 - Photoallergic reaction: damage to tissues is immunologically mediated
 - Usually reaction results from UV-A and UV-B
- May result from various drugs for example:
 - Phenothiazines, amiodarone, NSAIDs, antimicrobials
 - e.g. tetracyclines, NSAIDs, sulfonamides (UV-A primarily)

Antimicrobials Affecting Protein Synthesis
Tetracycline: Oral Overview

- Adverse Reactions
 - **Changes during tooth development**
 - Discoloration, dysgenesis, staining, caries



Antimicrobials Affecting Protein Synthesis
Tetracycline: Oral Overview

- Adverse Reactions
 - **Depress bone growth**
 - Drug attracted to embryonic and growing bone tissue > form tetracycline-calcium complex > temporarily depressing bone growth
 - **Intracranial hypertension (pseudotumor cerebri)**
 - Mechanism: may be decrease cerebrospinal fluid absorption, at arachnoid villi

Increased Incidence of Pseudotumor Cerebri Syndrome Among Users of Tetracycline Antibiotics
Samuel F. Passi, MD, Ryan Butcher, MS, MBA, Daniel R. Orme, MD, Judith E.A. Warner, MD, Gregory J. Stoddard, MBA, MPH, Allison V. Crum, MD, Ramkiran Gouripeddi, MBBS, MS, Brian H. Kirk, MD, Kathleen B. Digre, MD, Bradley J. Katz, MD, PhD
Journal of Neuro-Ophthalmology 2022;42:323-327

Tetracyclines and Pseudotumor

- **Purpose:** determine use of tetracycline class antibiotic association with increased risk of developing pseudotumor cerebri syndrome
- **Results:**
 - 12-50 yo: incidence of tetracycline induced PTC 63.9 per 100,000 person-years
 - vs incidence of idiopathic intracranial hypertension (IIH) < 1 per 1000,000 person-years
- **Conclusion:**
 - Causative link not firmly established, study suggests PTC among tetracycline users significantly higher than incidence of IIH in general population

Antimicrobials Affecting Protein Synthesis
Tetracycline: Oral Overview

- Adverse Reactions
 - Blood dyscrasias
 - Potentiate coumarin type anticoagulant effect (affect blood clotting)
 - Vestibular toxicity (minocycline)
 - Lightheadedness, loss of balance, dizziness, nausea, tinnitus

Figure 32.6
Some adverse effects of tetracycline.

Pharmacology Lippincott's Illustrated Reviews 4th Ed 2009

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

Tetracycline Pregnancy Warnings

Tetracycline has been assigned to pregnancy category D by the FDA. Animal studies have revealed evidence of embryotoxicity and teratogenicity, including toxic effects on skeletal formation. There are no controlled data in human pregnancy; however, congenital defects and maternal hepatotoxicity have been reported. When used during tooth development (second half of pregnancy) tetracyclines may cause permanent yellow-gray-brown discoloration of the teeth and enamel hypoplasia. The use of tetracycline during pregnancy is generally not recommended, especially during the last half of pregnancy.

Drugs.com 1-29-23

Tetracycline Breastfeeding Warnings

Tetracycline is excreted into human milk in small amounts. Theoretical risks of dental staining and inhibition of bone growth exist, although are unlikely. In one study, tetracycline levels were undetectable in nursing infants. Tetracycline is considered compatible with breast-feeding by the American Academy of Pediatrics. However, the manufacturer recommends that because of the risk of serious potential adverse reactions in nursing infants, a decision should be made whether to continue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

Tetracycline

tetracycline
generic

Pregnancy/Lactation ⓘ

Pregnancy
Clinical Summary
avoid use during pregnancy; inadequate human data available, though possible risk of spontaneous abortion; risk of fetal permanent bone/teeth discoloration and enamel hypoplasia based on human data w/ tetracycline class; possible risk of embryo-fetal toxicity based on conflicting animal data w/ tetracycline class

Lactation
Clinical Summary
avoid breastfeeding if >3wk tx duration, otherwise may use short-term while breastfeeding; no known risk of infant harm w/ short-term use based on limited human data and drug properties; theoretical risk of permanent infant bone and teeth discoloration w/ prolonged use based on drug's mechanism of action; no human data available to assess effects on milk production

Epocrates 1-29-23

tetracycline
generic

Contraindications / Cautions ⓘ

- hypersensitivity to drug or ingredient
- pregnancy
- pts <8 yo
- avoid: breastfeeding (>3wk tx duration)
- caution: renal impairment
- caution: hepatic impairment
- caution: SLE
- caution: abx-associated colitis hx, recent
- caution: botulism

doxycycline
generic

Pregnancy/Lactation ⓘ

Pregnancy
Clinical Summary
may use during pregnancy for anthrax infection; weigh risk/benefit during pregnancy for malaria tx; otherwise, avoid use during pregnancy; inadequate human data available, though possible risk of spontaneous abortion; risk of fetal permanent bone/teeth discoloration and enamel hypoplasia based on human data w/ tetracycline class; possible risk of embryo-fetal toxicity based on conflicting animal data w/ tetracycline class

Lactation
Clinical Summary
Lyme Dz: avoid breastfeeding during tx and x5 days after D/C; no known risk of infant harm w/ short-term use based on limited human data and drug properties; theoretical risk of permanent infant bone and teeth discoloration w/ prolonged use based on drug's mechanism of action; no human data available to assess effects on milk production
All Other Indications: avoid breastfeeding if >3wk tx duration, otherwise may use short-term while breastfeeding; no known risk of infant harm w/ short-term use based on limited human data and drug properties; theoretical risk of permanent infant bone and teeth discoloration w/ prolonged use based on drug's mechanism of action; no human data available to assess effects on milk production

doxycycline
generic

Contraindications / Cautions ⓘ

- hypersensitivity to drug or ingredient
- pregnancy (except anthrax infection or malaria tx use)
- pts <8 yo
- avoid: breastfeeding during tx and x5 days after D/C (Lyme dz use)
- avoid: breastfeeding (>3wk tx duration except in Lyme dz use)
- caution: overweight female pts of childbearing age
- caution: female pts of childbearing age w/ intracranial HTN hx
- caution: abx-associated colitis hx, recent
- caution: botulism

doxycycline

Epocrates 1-29-23

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Tetracyclines: The Drugs

Drugs Affecting Protein Synthesis Tetracycline : Tetracycline

- Tetracycline (Generic)
 - Use:
 - Chlamydia
 - Acne Rosacea
 - Meibomianitis
 - Resistant sebaceous blepharitis
- Doxycycline
 - Tetracycline of choice for:
 - Chlamydia
 - Acne rosacea
 - Meibomianitis
 - Ocular surface inflammatory disease

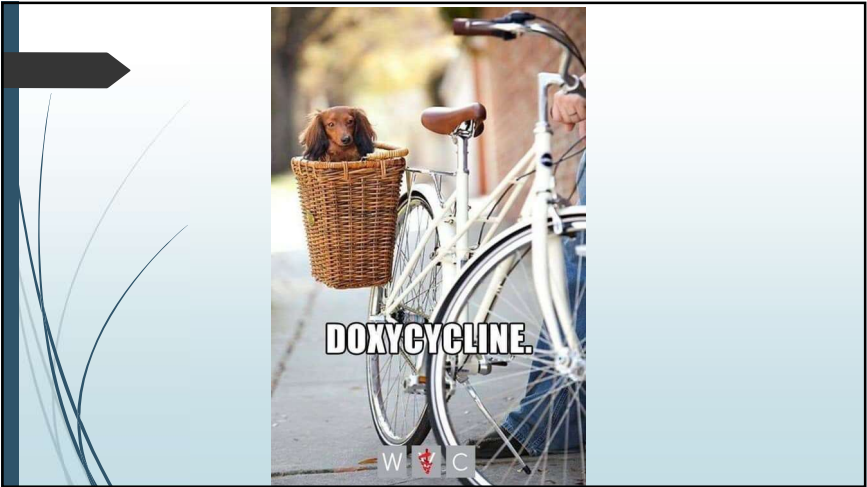
Drugs Affecting Protein Synthesis Tetracycline : Tetracycline

- Tetracycline (Generic) Dosage:
 - Spectrum: Gram(+), Gram(-); Chlamydia
 - Accumulate in Sebaceous Glands
 - Avoid pregnancy and lactation (prior Pregnancy category D)
 - Resistance can be a problem

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)
 - 250 mg & 500 mg capsules
 - Adults and children > 8 years old:
 - Use: rosacea, meibomianitis, resistant sebaceous blepharitis
 - Use weeks to months, taper with improvement
- Treatment Example:
 - Meibomian Gland Dysfunction:
 - tetracycline 250 mg qid x 3-4 wks





Drugs Affecting Protein Synthesis
Tetracycline:
Doxycycline

- Doxycycline (Vibramycin)
 - Use
 - Tetracycline of choice for:
 - Chlamydia infections (inclusion conjunctivitis, trachoma, etc.)
 - Acne rosacea
 - Meibomianitis
 - Ocular surface inflammatory disease
 - May have anti-inflammatory properties by suppressing interleukin activity
 - Various cap, tab, susp, inj
 - Depending on brand, may take with food
 - Note: ORACEA -Take on an empty stomach (1 hr before/2 hr after meal)
 - Pregnancy: avoid and Lactation: avoid if >3 wk tx (Category: D)

doxycycline
generic

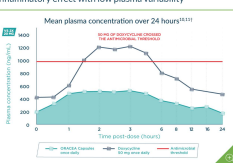
Adult Dosing ^①

Dosage forms: CAP: 50 mg, 75 mg, 100 mg, 150 mg; DR CAP (75% IR/25% DR): 40 mg; TAB: 20 mg, 50 mg, 75 mg, 100 mg, 150 mg; DR TAB: 50 mg, 75 mg, 100 mg, 150 mg, 200 mg; SUSP: 25 mg per 5 mL; INJ: various

Drugs Affecting Protein Synthesis
Tetracycline: Doxycycline



ORACEA® 40 mg Capsules provide sustained anti-inflammatory effect with low plasma variability^{①②③}



Time post-dose (hours)	ORACEA 40 mg capsules (mean)	Doxycycline 40 mg capsules (mean)	Doxycycline 40 mg capsules (range)
0	~1000	~1000	~1000
1	~1000	~1000	~1000
2	~1000	~1000	~1000
4	~1000	~1000	~1000
6	~1000	~1000	~1000
8	~1000	~1000	~1000
10	~1000	~1000	~1000
12	~1000	~1000	~1000
14	~1000	~1000	~1000
16	~1000	~1000	~1000
18	~1000	~1000	~1000
20	~1000	~1000	~1000
22	~1000	~1000	~1000
24	~1000	~1000	~1000

Ocular Rosacea:

- Doxycycline: 100 mg bid x 2 wks (then taper)

OR

- Doxycycline (ORACEA)
 - 40 mg capsule (30mg immediate release and 10 mg delayed release doxycycline)
 - 40 mg qAM (empty stomach)

OR

- Erythromycin: 250 mg qid or Azithromycin 500 mg/day for 3 cycles with 7-day intervals

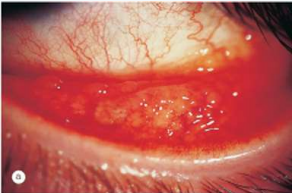
Antimicrobials Affecting Protein Synthesis
Macrolides

Antimicrobials Affecting Protein Synthesis Macrolides

- Pharmacology
 - Bind to 50S ribosomal subunit > inhibit bacterial protein synthesis
 - Low toxicity: do not bind to human ribosome
 - Bacteriostatic
 - Spectrum of activity can include:
 - Various: Gram positive, gram negative
 - Streptococci, Staphylococci, Chlamydia, Neisseria, Hemophilus influenzae*

Antimicrobials Affecting Protein Synthesis Macrolides

- Clinical Use:
 - Chlamydial Infections
 - Sebaceous Gland Dysfunction



Chlamydia

Drugs Affecting Protein Synthesis: Macrolides

The Drugs

- Erythromycin (Various)
- Azithromycin (Zithromax)
- Clarithromycin

Drugs Affecting Protein Synthesis Macrolides: Erythromycin

- Erythromycin
 - Prototype macrolide, obtained from *Streptomyces erythreus*
 - Active against gram +, gram -, chlamydia
 - Oral and topical
 - Use:
 - Lid infection
 - Prophylaxis ophthalmia neonatorum
 - Gonococcal conjunctivitis
 - Chlamydial infection
 - Safer for pregnant women, nursing mothers, children < 8 years
 - Prior Designation: Pregnancy Category B



Gonococcal keratoconjunctivitis

Drugs Affecting Protein Synthesis
Macrolides: Erythromycin

- Erythromycin Oral
 - Forms:
 - Erythromycin base – destroyed by stomach acid and administered with enteric coating
 - Food interferes with absorption=take on empty stomach
 - If enteric coating and stomach upset may take with food
 - Erythromycin stearates – fairly acid-resistant and better absorbed
 - Take empty stomach
 - Erythromycin ethylsuccinate
 - ADR: GI disturbances
 - Pregnancy:
 - Weigh risk/benefit (use only if clearly needed)
 - possible risk of fetal harm based on conflicting human data;
 - no known risk of fetal harm based on animal data at 1-3x max recommended human dose
 - Historically: Pregnancy Category B

Drugs Affecting Protein Synthesis
Macrolides: Erythromycin

- Erythromycin Oral
- Treatment Example:
 - Meibomitis:
 - Erythromycin 200 mg BID
 - With or without food

erythromycin ophthalmic
generic

Pregnancy/Lactation ⓘ

Pregnancy
Clinical Summary
may use during pregnancy; no human data available, though risk of fetal harm not expected based on expected limited systemic absorption

Lactation
Clinical Summary
may use while breastfeeding; no human data available, though risk of infant harm and adverse effects on milk production not expected based on limited maternal systemic absorption

erythromycin base
generic

Pregnancy/Lactation ⓘ

Pregnancy
Clinical Summary
weigh risk/benefit during pregnancy; possible risk of fetal harm based on conflicting human data; no known risk of fetal harm based on animal data at 1-3x MRHD

Lactation MRHD=maximum recommended human dose
Clinical Summary
may use while breastfeeding; possible risk of infantile hypertrophic pyloric stenosis and diarrhea based on limited human data; no human data available to assess effects on milk production

Drugs Affecting Protein Synthesis
Macrolides: Azithromycin

- Azithromycin (Zithromax)
 - Semisynthetic derivative of erythromycin
 - Use: chlamydia, gonococcal conjunctivitis, ocular rosacea
 - Pregnancy:
 - May use during pregnancy;
 - Prior pregnancy Category B
 - Drugs.com: lactation-distributed in milk; use with caution
 - Side Effect: GI upset, skin rash
 - May take with or without food

azithromycin
generic

Pregnancy/Lactation ⓘ

Pregnancy
Clinical Summary
may use during pregnancy; possible risk of spontaneous abortion based on conflicting human data; no known risk of fetal harm for PO route based on animal data at 1.6x and 3.2x recommended human dose

Lactation
Clinical Summary
may use while breastfeeding; possible risk of infant diarrhea, vomiting, and rash based on limited human data; possible risk of infantile hypertrophic pyloric stenosis based on conflicting human data; no human data available to assess effects on milk production

azithromycin
generic

Adult Dosing ⓘ

Dosage forms: TAB: 250 mg, 500 mg, 600 mg; PWDR: 1 g per pkt; SUSP: 100 mg per 5 mL, 200 mg per 5 mL; INJ: various

Drugs Affecting Protein Synthesis
Macrolides: Azithromycin

Azithromycin (Zithromax)

- Dosage:
 - Can take with/out food
 - Note: food helps to tolerate better
 - Exception: Azithromycin Zmax extended-release suspension/liquid should be taken 1 hour before or 2 hours after a meal
- 1000mg single dose (chlamydia)
- Extended half life > QD

azithromycin
generic

Adult Dosing ¹
Dosage forms: TAB: 250 mg, 500 mg, 600 mg; PHDR: 1 g per pkt; SUSP: 100 mg per 5 mL, 200 mg per 5 mL; INJ: various



Azithromycin Drug Interaction Considerations

- Antiarrhythmics (e.g. amiodarone, quinidine, sotalol)
 - May cause QT prolongation (dangerous, irregular, fast heartbeat)
 - Azithromycin – carries risk of QT prolongation; higher in elderly and those with hx of heart arrhythmia
 - Combination: increase risk of QT prolongation and cardiac arrhythmias
- Antacids (those with aluminum, magnesium or calcium salts) (e.g. Rolaids, Mild of Magnesia)
 - Bind to azithromycin, affecting absorption, resulting in less effectiveness
- Statins (e.g. atorvastatin=Lipitor, simvastatin=Zocor)
 - Statins may result in rhabdomyolysis
 - With azithromycin may increase risk of rhabdomyolysis
- Warfarin (Coumadin)
 - With azithromycin potential risk of increased bleeding

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

CDC: 2021 Guideline Chlamydial Infections

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

Moham Bahrany Karakou,¹ Ali Jafar Fazel,¹ Victoria Kovach,¹ Marjesh Hegazi,² Laila Ghazem²

ABSTRACT
To assess the efficacy and safety of azithromycin compared with doxycycline in patients with meibomian gland dysfunction (MGD), we conducted a randomised double-masked open-label clinical trial. The primary end point was the percentage of patients achieving complete resolution of MGD after 5 days of treatment. Secondary end points included the percentage of patients achieving complete resolution of MGD after 1 month of treatment. The trial was conducted in a tertiary care hospital in Cairo, Egypt. The trial was conducted in a tertiary care hospital in Cairo, Egypt. The trial was conducted in a tertiary care hospital in Cairo, Egypt.

INTRODUCTION
Meibomian glands have an important role in the health of the ocular surface by secreting a lipid and proteinaceous tear film. Dysfunction of these glands can lead to meibomian gland dysfunction (MGD), which is a common cause of dry eye disease. MGD is a chronic condition that can lead to significant discomfort and visual impairment. The aim of this study was to compare the efficacy and safety of oral azithromycin and doxycycline in the treatment of MGD.

MATERIALS AND METHODS
This was a randomised, double-masked, open-label clinical trial. The trial was conducted in a tertiary care hospital in Cairo, Egypt. The trial was conducted in a tertiary care hospital in Cairo, Egypt. The trial was conducted in a tertiary care hospital in Cairo, Egypt.

- 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

Oral azithromycin vs doxycycline in meibomian gland dysfunction: a randomised double masked open label clinical trial (BJO 2015;99:199–204/2014 on line)

- Some antibiotics with anti-inflammatory effects may help:
 - to control bacterial colonization and
 - lid inflammation
- Tetracyclines decrease inflammation and inhibit matrix metalloproteinases
 - Doxycycline treats MGD through its antimicrobial, anti-inflammatory and antimetalloproteinase properties
 - Has fewer side effects than tetracycline.
- Azithromycin inhibits pro-inflammatory cytokines
 - Topical and oral azithromycin reported to improve the sign and symptoms of MGD and posterior blepharitis.

JAMA Ophthalmology | Original Investigation

Pulsed Oral Azithromycin vs 6-Week Oral Doxycycline for Moderate to Severe Meibomian Gland Dysfunction: A Randomized Clinical Trial

Phit Upapong, MD, Chulaluck Tangtrakongkong, MD, Pichayut Phayo, MD, PhD

Intervention:
Azithromycin (1g once per week) x 3 weeks OR
Doxycycline (200 mg daily) x 6 weeks

Conclusion:
*Azithromycin equivalent effect compared to doxycycline for MGD
*No more GI adverse effects with azithromycin
*Reduced dosing with azithromycin supports its use as alternative to doxycycline

Key Points
Question: Are the adverse effects of a 3-week course of weekly oral azithromycin equivalent to that of the 6-week course of oral doxycycline in treating moderate to severe meibomian gland dysfunction (MGD)?
Findings: In this randomized clinical trial that included 137 eyes, at the 6- and 8-week follow-ups, the mean differences in total MGD scores between azithromycin and doxycycline were -0.33 and 0.13, respectively. At both time points, the differences were within the prespecified equivalence margin of 2.
Meaning: A 3-week course of weekly oral azithromycin was equivalent to a 6-week course of oral doxycycline in treating moderate to severe MGD.

Meta Analysis/Systematic Review: Azithromycin vs Doxycycline for Meibomian Gland Dysfunction

Purpose: review efficacy and safety of oral doxycycline vs azithromycin for MGD

Background:

- Tetracyclines (esp minocycline and doxycycline): downregulate inflammatory response (including matrix metalloproteinase and cytokines), leucocyte proliferation, granuloma formation and angiogenesis
- Macrolides: immunomodulatory impact, decrease leucocyte concentration, downregulate cytokine and MMP production
- Both affect oc immune response and meibum quality, but via slightly different pathways

Findings:

- Azithromycin better: TBUT, staining, MG secretion, other signs/symptoms, ad
- Dosage of doxy varied among studies (vs azithromycin same)

Conclusion:

- Both macrolides and tetracyclines are effective for tx MGD
- Macrolides have better efficacy and safety profile vs tetracyclines

Antibacterials Affecting Intermediary Metabolism (Folic Acid)

Drugs Affecting Intermediary Metabolism (Folic Acid)

-Sulfonamides

-Pyrimethamine

-Trimethoprim

Principles of Pharmacology, Golan et al. 2012

Drugs Affecting Intermediary Metabolism (Folic Acid)

■ Inhibition of nucleic acid synthesis

■ Sulfonamides

■ Trimethoprim

Antibacterials Affecting Intermediary Metabolism

Sulfonamides and Trimethoprim

Sulfonamide Pharmacology

Inhibit synthesis of folic acid (chemical required for synthesis of nucleic acid and protein)

Humans: absorb preformed folic acid

Minimal effect on host cells

Bacteriostatic

Trimethoprim Pharmacology

Inhibit folic acid synthesis

Block a sequential step in pathway

Effectivity MRSA

Source: Bertram G. Katzung, Anthony J. Trev
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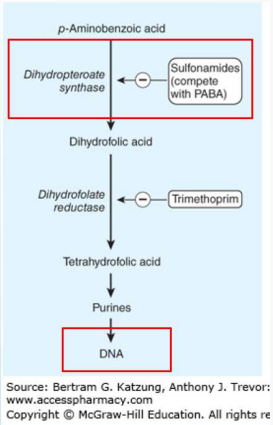
Antibacterials Affecting Intermediary Metabolism
Sulfonamides

Drugs Affecting Intermediary Metabolism
Sulfonamides

- Oral:
 - Sulfamethoxazole
 - Sulfadiazine
- Topical:
 - Sulfacetamide
 - Combination with steroids

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.



Drugs Affecting Intermediary Metabolism
Pyrimethamine and Trimethoprim

sulfamethoxazole/trimethoprim
generic

Adult Dosing ⓘ
Dosage forms: TAB: 400 mg/80 mg, 800 mg/160 mg; SUSP: 200 mg/40 mg per 5 mL; INJ: various

Treatment option for MRSA

- Dacryoadenitis, canaliculitis, dacryocystitis

Treatment Example

- Dacryocystitis (MRSA)
- Trimethoprim/sulfamethoxazole 160/800 mg BID

Bactrim DS
sulfamethoxazole/trimethoprim

Adult Dosing ⓘ
Dosage forms: TAB: 800 mg/160 mg

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

Bactrim
sulfamethoxazole/trimethoprim

Adult Dosing ⓘ
Dosage forms: TAB: 400 mg/80 mg

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
- Arthroplasty
- Idiosyncratic reactions (hepatitis)

May be related to chemical moiety of the molecular structure of the FQ

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Fluoroquinolones and Tendinopathy

Journal of Clinical Pharmacy and Therapeutics
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Fluoroquinolones and Tendinopathy: A Guide for Athletes and Sports Clinicians and a Systematic Review of the Literature

Trevor Lewis, MSc, MCSP*, Jill Cook, PhD†

*Physiotherapy Department, Arden University Hospital National Health Service Foundation Trust, University Hospital Arden, Liverpool, United Kingdom; †Department of Physiotherapy, Monash University-Patrick Campus, Preston, Victoria, Australia

Context: Fluoroquinolone antibiotics have been used for several decades and are effective antimicrobials. Despite their widespread use, however, a growing body of evidence has accumulated that the use of these drugs may be associated with tendinopathy and tendon rupture. The aim of this review is to provide a guide for athletes and sports clinicians and a systematic review of the literature.

Objectives: To discuss the clinical pharmacology, complications, and the evidence for tendinopathy and tendon rupture associated with the use of these drugs in sports. To provide a guide for athletes and sports clinicians and a systematic review of the literature.

Keywords: Fluoroquinolones, tendinopathy, tendon rupture.

Abstract: Fluoroquinolone antibiotics have been used for several decades and are effective antimicrobials. Despite their widespread use, however, a growing body of evidence has accumulated that the use of these drugs may be associated with tendinopathy and tendon rupture. The aim of this review is to provide a guide for athletes and sports clinicians and a systematic review of the literature.

Keywords: Fluoroquinolones, tendinopathy, tendon rupture.

Abstract: Fluoroquinolone antibiotics have been used for several decades and are effective antimicrobials. Despite their widespread use, however, a growing body of evidence has accumulated that the use of these drugs may be associated with tendinopathy and tendon rupture. The aim of this review is to provide a guide for athletes and sports clinicians and a systematic review of the literature.

- Fluoroquinolones have a high affinity for connective tissue, esp cartilage and bone
- Cause of tendinopathy effects of fluoroquinolones is unclear
- Proposed mechanisms:
 - Ischemia
 - Degradation of tendon matrix
 - Alteration of tenocyte activity
- Matrix metalloproteinases have degrading properties that are important in homeostasis and response to injury of tendon tissue
- Fluoroquinolones facilitate expression of matrix metalloproteinases in tendon tissue
 - Ciprofloxacin in particular increases the expression of matrix metalloproteinase-3 in human Achilles tendon derived cells
- Reduces collagen synthesis via inhibition of tenocyte proliferation

What tendon pathology is seen on imaging in people who have taken fluoroquinolones? A systematic review

Journal of Clinical Pharmacy and Therapeutics
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What tendon pathology is seen on imaging in people who have taken fluoroquinolones? A systematic review

Articles were used for this review: twenty-six papers met the eligibility criteria. The Achilles tendon was most commonly affected, and ciprofloxacin and levofloxacin were the most commonly implicated FQs. Mean time to onset of symptoms was 16 days following first FQ dose. Imaging modalities used included magnetic resonance imaging (MRI), B-mode ultrasound (US) and computed tomography (CT).

Keywords: Fluoroquinolones, imaging, tendinopathy, tendon.

Abstract: Fluoroquinolones (FQs) are highly effective broad-spectrum antibiotics. Clinical data reveal an increased incidence of tendon pain and rupture in those taking FQs, yet little is known about tendon structural changes. This review synthesises published data on tendon structural changes in people who have taken FQs. Eight databases were searched for potentially relevant articles (Medline, CINAHL, Biological Abstracts, AMED, Web of Knowledge, SCOPUS, SportDiscus and EMBASE) using MeSH and free-text searches. Inclusion and exclusion criteria determined which articles were used for this review. Twenty-six papers met the eligibility criteria. The Achilles tendon was most commonly affected, and ciprofloxacin and levofloxacin were the most commonly implicated FQs. Mean time to onset of symptoms was 16 days following first FQ dose. Imaging modalities used included magnetic resonance imaging (MRI), B-mode ultrasound (US) and computed tomography (CT). Tendon measurements were rarely reported, and intratendinous imaging findings were not reported in a consistent manner. Few studies imaged tendons bilaterally, and only two studies were longitudinal in design. Future studies should report imaging measures such as thickness and cross-sectional area and use consistent descriptions of intratendinous changes during and post-FQ treatment.

Fluoroquinolone (Oral) and Tendon Pathology

- Mean time following FQ use to symptoms: 2 weeks to months
 - Risk factors
 - >60 yo
 - Concomitant steroid therapy
 - Renal disease
 - Males
 - Magnesium deficiency
 - Hyperthyroidism
 - Gout
 - Systemic disease eg. DM, RA
 - Most common: levofloxacin and ciprofloxacin use

Antibacterial Considerations

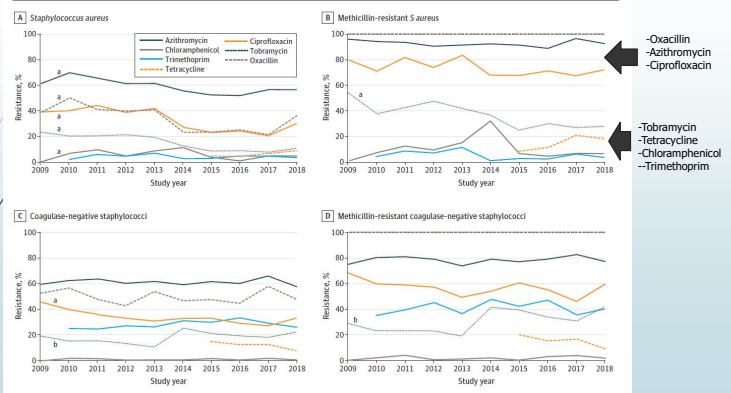
JAMA Ophthalmology | Original Investigation
Trends in Antibiotic Resistance Among Ocular Microorganisms
in the United States From 2009 to 2018

- Resistance was observed to ciprofloxacin in 33.5% and to azithromycin in 59.7% of *S aureus* isolates
 - although all were susceptible to vancomycin.
- Resistance greater than 70% for fluoroquinolones (not applicable for besifloxacin) and 92.9% for azithromycin.
- The later-generation fluoroquinolones (besifloxacin, gatifloxacin, and moxifloxacin) had lower MIC90s overall
- Compared with the earlier ones (ciprofloxacin, levofloxacin, and ofloxacin), Besifloxacin showed the lowest MIC90s, and ciprofloxacin showed the highest.

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

Original Investigation Research

Figure 4. Antibiotic Resistance Among Isolates Over Time

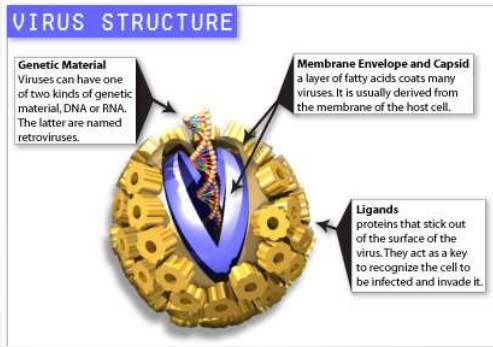


Anti-infective Drugs
AntiViral Drugs

Viral Overview

Virus: Overview

- Virus:
 - Obligate parasites - cannot multiply outside the living cells
 - Lack cell wall and cell membrane
 - Consists of proteins and nucleic acids
 - Are either double or single stranded DNA or RNA (nucleic acids) encased in protein coat (capsid)



Viral Replication

- 1-Virus binds to host cell
- 2-Viral particle penetrates host cells
- 3-Duplication of viral DNA or RNA
- 4-New viral particle released
- 5-Cell death or survival (latency)

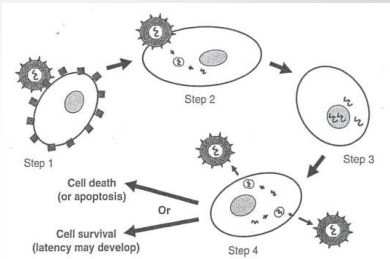
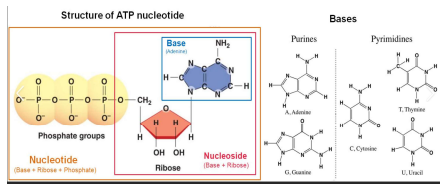


Figure 11-2 Steps in viral replication. Step 1: Attachment of virus to host cell using specialized receptors on the virus and host cell. Step 2: Penetration of virus into host cell and uncoating of virus. Step 3: Duplication of viral DNA or RNA using host DNA/RNA. Step 4: Assembly of viral genome and capsid within host cell and then release of progeny. (The host cell can then either die or survive, depending on the virus and host cell type.)

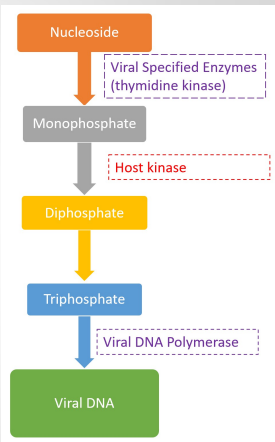
Quick Review of the Basics....



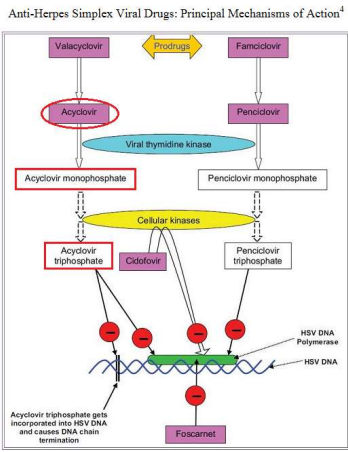
- Nucleoside:
 - Purine (adenosine or guanosine) OR Pyrimidine (cytosine, thymine, uracil) base PLUS
 - Sugar (ribose or deoxyribose)
- Nucleotide:
 - Nucleoside + phosphate group
- Nucleic acid: bonded together nucleotides (e.g. DNA)
- Function nucleotide: structural unit for DNA/RNA and part of cell function.
- Function nucleic acid: storage and expression of genetic information (e.g. DNA, RNA)

Viral Life Cycle (DNA/Herpes)

- Nucleoside triphosphates are incorporated into new viral genomes by viral or cellular polymerase
- HS:
 - Generation of deoxyribonucleoside triphosphates involves phosphorylation of nucleosides by viral thymidine kinase;
 - Viral DNA polymerase then adds deoxyribonucleoside triphosphates to the growing DNA genome



AntiViral Overview



Medical Pharmacology Chapter 36: Antiviral Drugs/<http://www.pharmacology2000.com/Antiviral/antiviral400.htm>#Antiviral_Drugs

AntiVirals (Herpes)

Oral Antiviral Agents

Acyclovir (Zovirax)
Valacyclovir (Valtrex)
Famciclovir

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



Antiviral Drugs
Acyclovir

- Activity: HSV, VZV
- Selective against herpes (low toxicity)
- Guanosine (nucleoside) analog

- 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

Acyclovir (ACV)

↓
Thymidine kinase

ACV-monophosphate

↓
Cell enzymes

ACV-triphosphate

↓
Viral DNA polymerase

Viral DNA

→
Chain Termination

ACV-triphosphate is most incorporated into the growing strand of viral DNA. Because acyclovir-GMP lacks a 3' hydroxyl group, it causes chain termination, preventing acyclovir-GMP from being incorporated into the growing strand of viral DNA.

Antiviral Drugs
Acyclovir

2 mechanisms that results in viral DNA chain termination:

- Competitively inhibits and inactivates viral DNA polymerase
- Incorporates into and termination of growing viral DNA chain

Pharmacology

- ACV (guanosine analog) >>>
- Is selectively phosphorylated by herpes specific (HSV/HZV) thymidine kinase to ACV monophosphate >>>
- Subsequent formation of ACV triphosphate by cellular enzymes>>>
- ACV triphosphate inactivates/inhibits (herpes) viral DNA polymerase and
- Incorporates into causing chain termination

Acyclovir (ACV)

↓
Thymidine kinase

ACV-monophosphate

↓
Cell enzymes

ACV-triphosphate

↓
Viral DNA polymerase

Viral DNA

→
Chain Termination

ACV-triphosphate is most incorporated into the growing strand of viral DNA. Because acyclovir-GMP lacks a 3' hydroxyl group, it causes chain termination, preventing acyclovir-GMP from being incorporated into the growing strand of viral DNA.

Antiviral Drugs
Acyclovir

- Clinical Use:
 - Primary and recurrent episodes of genital herpes
 - Primary varicella (chickenpox)
 - Herpes zoster
- Off label:
 - HSV keratitis
 - Acute retinal necrosis
 - Herpes zoster ophthalmicus
 - Bell palsy
 - HZ ophthalmicus
 - HSV prophylaxis

Courtesy of A.P. Dunn, MD
©1993 Warner Eye Institute

Antiviral Drugs
Acyclovir

- Adverse Reactions
 - Safe
 - Nausea, vomit, diarrhea
 - HA
 - Skin rash
- Caution in renal impairment and dehydration
- 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

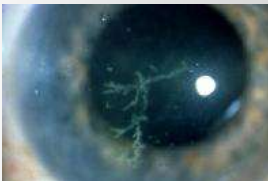
Lactation

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 Active HSV Keratitis

- Oral acyclovir 400 mg 5 times daily for treatment of HSV epithelial keratitis
- Does not prevent stromal disease during active keratitis
- Does not benefit stromal keratitis in patients receiving topical Viroptic and steroids



Acyclovir-resistant HSV-1 keratitis: a concerning and emerging clinical challenge. Am J Ophthal 2022

- **Purpose:** To describe the clinical and virological profiles of patients with herpes simplex keratitis (HSK) caused by acyclovir-resistant (ACVR) strains of herpes simplex virus 1 (HSV-1).
- **Background:**
 - ACV 400 mg BID causes 2 fold decrease in recurrences
 - Valacyclovir (prodrug of ACV) 500 mg QD can replace ACV
 - ACV resistance may be due to mutations in thymidine kinase or viral DNA polymerase
- **Conclusions:**
 - Suspect resistance in cases with highly frequent recurrences despite ACV prophylaxis
 - Resistance is more likely in patients with long-standing disease and multiple recurrences
 - Resistance develops more rapidly in immunocompromised

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 For Herpes

Herpes zoster:

- 800 mg 5 x/day (7 days)

Herpes Simplex keratitis:

- 400 mg 5x/day (7 days)
- Prophylactic:
 - 400 mg BID

Clinical Practice Guideline: Bell's Palsy

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Kumar, MD, FRCS, FRCR¹⁴, Alan Riccio, MD¹⁵,
Debra Russell, DHS, PA-C¹⁶,
Steven Rosenbaum, MD¹⁷, and
William Vaughan¹⁸

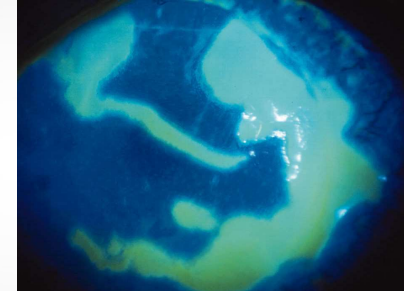
Bell Palsy

- Prescribe oral steroids within 72 hours of symptom onset
- New onset: steroids and oral antiviral (not antiviral alone)
- Initiate within 72 hours (benefit after 72 hours less clear)
- Etiology: viral etiology suspected; exact mechanism unknown
 - Inflammation and edema causing compression
- Oral steroid
 - Prednisolone 50 mg for 10 days OR
 - Prednisolone 60 mg for 5 days with 5 day taper
- Acyclovir: 400 mg 5x/day for 10 days

Otolaryngology—Head and Neck Surgery 149(35) 51-527 American Academy of
Otolaryngology—Head and Neck Surgery Foundation 2013

Acyclovir Treatment Summary

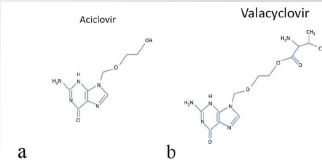
- **HSV keratitis (off label)**
 - 400 mg 5x/day
 - Prophylactic: 400 mg BID
- **Herpes zoster ophthalmicus (off label)**
 - 800 mg 5x/day x 7 days
- **Bell palsy (new onset) (off-label)**
 - 400 mg 5x/day for 10 days in combination with corticosteroids (not alone)
 - Begin within 3 days of symptom onset



Antiviral Drugs

Valacyclovir (Valtrex)

- Pharmacology
 - Prodrug of acyclovir
 - L-valyl (valine) ester of acyclovir
 - Metabolized to acyclovir
 - Higher bioavailability than acyclovir by 3-5 fold compared to oral ACV
 - Rapidly converted to ACV after oral consumption
 - 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
 - E.g. Treatment effect for HZ:
 - 800mg ACV 5x/day vs VAL 500mg BID (or 250mg QID)
- Caution: renal disease and dehydration



valacyclovir
generic

Pregnancy/Lactation ⁽ⁱ⁾

Pregnancy

Clinical Summary
may use during pregnancy; no known risk of teratogenicity based on limited human data and on animal data at 4x and 7x MRHD

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

Absorption of Valacyclovir

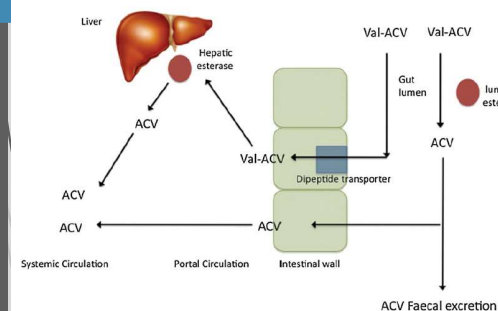


Figure 8. The pharmacokinetics of acyclovir (ACV) and valacyclovir (Val-ACV). Oral administration of valacyclovir yields systemic ACV through uptake by dipeptide transporters in the gut lumen and hydrolysis by esterases present in the gut lumen, intestinal wall and liver.

- Reported that more than 95% of Valacyclovir is converted to ACV
- The high bioavailability of Valacyclovir is similar to IV ACV

Antiviral Drugs
Valacyclovir (Valtrex)

Caution: renal disease and dehydration

valacyclovir
generic

Pregnancy/Lactation[Ⓢ]
Pregnancy
Clinical Summary
may use during pregnancy; no known risk of teratogenicity based on limited human data and on animal data at 4x and 7x MRHD
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

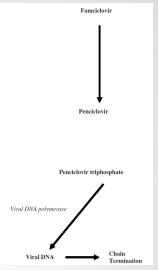


Antiviral Drugs
Valacyclovir (Valtrex)

- Dosage:
 - HS keratitis: 500 mg TID
 - HZ: 1000mg TIDs (within 72 hours, max efficacy w/in 48 hrs)
 - 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
 - PCV=nucleoside analogue, similar mechanism of action as ACV
 - Effective against some ACV-resistant HSV strains
 - 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
 - Unlike ACV does not cause 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 1.4-10.0x systemic exposure and 1.1-0.8x MRHD
Lactation
Clinical Summary
weigh risk/benefit while breastfeeding; no human data available to assess risk of infant harm or effects on milk production

Antiviral
Drug:
Famciclovir

- Dosage:
 - HS keratitis: 250 mg TID x 7-10 days
 - HZ: 500 mg tid x 7 days (72 hrs onset, max efficacy w/in 48h)
- Bell's Palsy: 500mg tid x 7 days (within 3 days of onset) with oral steroid

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
 - Prodrug of penciclovir
 - HS Keratitis: 250 mg TID x 7 days
 - Prophylactic consider: 250mg BID
 - HZ: 500 mg TID x 7 days

Note for all HZ:

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

Oral Antiviral Agents and Caution

Acyclovir (Zovirax)
Valacyclovir (Valtrex)
Famciclovir

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

Herpes Simplex Studies

- 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

Herpes Simplex Studies

- HSV recurrent eye disease
 - Prophylactic oral ACV decreases
 - Long term oral ACV effective in decreasing recurrence
- HSV epithelial keratitis
 - Oral ACV may be effective tx
- HSV iridocyclitis
 - Add oral ACV with topical steroid and trifluridine, may be beneficial

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

Zoster Eye Disease Study: Rationale and Design

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Kathryn A. Colby, MD, PhD,* and Bennie H. Jeng, MD,§ on behalf of The ZEDS Trial Research Group

Purpose: The purpose of this study was to describe the rationale and design of the Zoster Eye Disease Study (ZEDS).

Methods: ZDIs in a National Eye Institute-sponsored randomized clinical trial designed to determine whether 1 year of suppressive antiviral therapy with valacyclovir in patients with herpes zoster ophthalmicus (HZO) reduces complications because there is currently no high-quality evidence that suppressive therapy reduces the risk of complications. All patients had immunosuppression, have a history of a typical rash at disease onset, and have had a record of active ophthalmic or stomatal keratitis or intraocular inflammation within 1 year before enrollment. Exclusion criteria include concurrent ocular disease, prior HZO, prior HZO treatment, or prior HZO-related complications. The study ran for 1 year. The primary end point was the time to first occurrence of new or worsening dendritic epithelial keratitis, stromal keratitis without HZO, or treatment-related ocular toxicity, or this or HZO without 12 months of treatment. Secondary end points were the time to first occurrence of new or worsening dendritic epithelial keratitis, stromal keratitis without HZO, or treatment-related ocular toxicity, or this or HZO without 12 months of treatment. The study has 80% power to detect a 30% difference between treatment groups, with a 30% rate of events by 1 year assumed among controls. Secondary and exploratory questions include whether the percentage of patients with ocular toxicity is higher before or after treatment, whether development of postherpetic neuralgia varies by treatment group, and whether vaccinations against herpes zoster affect study outcomes and coronavirus disease 19 rates.

Results: Over approximately 4 years, over 400 study participants have been enrolled.

Conclusions: ZEDS aims to provide scientific evidence on whether suppressive valacyclovir treatment improves outcomes in HZO and should become the standard of care.

Key Words: Herpes zoster ophthalmicus, Zoster Eye Disease Study, suppressive valacyclovir treatment, clinical trial

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Herpes zoster ophthalmicus (HZO) is a condition affecting millions of Americans and is associated with unilateral acute and chronic eye disease and pain, with potential complications that can significantly impair functioning, especially among older adults. An estimated 200,000 new cases of HZO occur in the United States annually, and the incidence of herpes zoster (HZ) is increasing.¹⁻³ Although there is considerable consensus on the treatment of acute HZO in immunocompetent adults, there is no standard approach to the treatment of HZO sequelae such as ocular disease and postherpetic neuralgia (PHN), a severely debilitating chronic pain syndrome.

RATIONALE FOR ZEDS

Several factors call for evaluating long-term suppressive antiviral treatment to prevent HZO complications in a prospective, randomized, double-masked, placebo-controlled clinical trial, including recent data that the infection is a source of complications. Complications of HZO have not been well characterized. It has been suggested that HZ results from acute reactivation of latent varicella-zoster virus (VZV), it was confirmed only relatively recently that complications of HZ may be caused by a direct effect of the virus on the nerve, but manifestations of inflammatory, immune, neuropathic, and vascular sequelae do infrequently. For example, a 1993 study showed that late dermoford epithelial keratosis (DEK) lesions are often polymorphic chain reaction positive for VZV, and have been associated with the development of malignancy. It has been found to be responsive to topical and systemic antiviral treatment, which provides further evidence that it is caused by active VZV infection.^{5,6} There is also evidence associating chronic, active VZV infection with PHN, vasculopathy after stroke, and in potentially fatal strokes, and giant cell (temporal) arteritis.⁷⁻¹⁰

HZO and herpes simplex virus (HSV) infection have some common similarities it is that primary infection (which differs herpes viruses) is followed by latency and recurrent infection is frequently associated with chronic and/or recurrent eye disease, both of which can lead to loss of vision. In the Herpesic Eye Disease Study (HEDS), prolonged suppressive antiviral treatment was most beneficial in preventing recurrence of HSV stromal keratitis, suggesting that active viral infection is an important factor contributing to stromal keratitis, although the mechanism is not well understood.¹¹ Given the similarities of the infections of these 2 viruses, it is likely that suppressive antiviral treatment can also prevent

Zoster Eye Disease Study

- ZEDS aims to provide scientific evidence on whether suppressive valacyclovir treatment improves outcomes in HZO and should become the standard of care.

TABLE 3. (Continued) Participating Clinical Centers Approved to Screen and Enroll Participants in the United States, Canada, and New Zealand

United States			
State	City	PCC Name	Principal Investigator
New Jersey	Montclair	EyeCare MD of NJ	Maria Lupatky, MD
New York	Albany	Albany VA MC	Jacqueline Biersing, MD
	Camden	The Eye Care Center	Holly Hindman, MD
	Great Neck	Northwell Health	Anne Steiner, MD
	New York	New York Eye and Ear Infirmary	Agnes Wen, MD
	New York	NYC Langone Health	Rose Hershman, MD
	New York	SUNY - Stony Brook University	Azra Ashari, MD
	New York	Walt Conell Eye Associates	Jessica Criskey, MD

GLAUCOMA MEDICATIONS

CARBONIC ANHYDRASE INHIBITORS

Carbonic Anhydrase

Carbonic anhydrase:

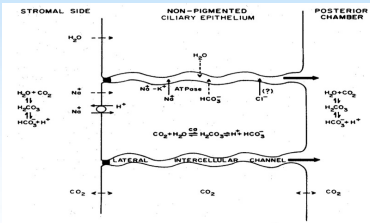
- Important in many physiological processes, including:
 - ◆ pH and bicarbonate homeostasis
 - ◆ Respiration
 - ◆ Bone metabolism
 - ◆ Tumorigenesis
- There are 16 CA isoforms in humans
 - ◆ Isoform II is the most relevant for ocular hypertension
 - ◆ CA II, IV and XII are expressed in many tissues/organs
 - ◆ This explains why systemic administration of CAIs has numerous side effects
 - ◆ Isoforms II, IV and XII isoforms expressed in ciliary body

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
 - ◆ Open angle glaucoma
 - ◆ Angle closure glaucoma
 - ◆ Secondary glaucomas
 - ◆ Macular edema
 - ◆ Pseudotumor cerebri
 - ◆ Altitudinal sickness
 - ◆ Seizure disorder
- Decrease aqueous production: 27%
- Decrease IOP: 20-30%
- 95% bound to plasma proteins

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- Use:
- Altitudinal sickness
 - ◆ Prevents altitudinal sickness by increasing ventilation
 - ◆ Increases alkali (bicarbonate) excreted in urine, making blood more acidic>drives ventilation
 - Epilepsy
 - ◆ Appears to retard abnormal, excessive discharge from CNS neurons
 - ◆ Not sure if related to CAI effect on CNS or acidosis
 - Pseudotumor cerebri
 - ◆ Decreases intracranial pressure

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
 - ◆ Probable result of ciliary body edema producing forward displacement of lens-iris diaphragm

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- **Common Side Effects:**
 - ◆ GI irritation:
 - ◆ Abdominal cramps, nausea, diarrhea
 - ◆ Help:
 - Food
 - Sustained release
 - Sodium bicarbonate

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- **Side Effects**
 - ◆ Metabolic acidosis
 - ◆ Results from bicarbonate loss
 - ◆ Hypokalemia
 - ◆ Renal Calculi
 - ◆ Blood dyscrasias
 - ◆ Dermatitis
 - ◆ Depression
 - ◆ Reduced libido

Carbonic Anhydrase Inhibitors
Systemic: Acetazolamide

- **Contraindications/Cautions:**
 - ◆ Hypersensitivity to sulfonamides (e.g. Stevens-Johnson syndrome, blood dyscrasias)
 - ◆ Impaired renal function, kidney stones
 - ◆ Liver disease
 - ◆ Severe COPD
 - ◆ Sick cell
 - ◆ And hyphema in sickle cell patient

acetazolamide

generic

Pregnancy/Lactation ⓘ

Pregnancy

Clinical Summary

may use during pregnancy; risk of teratogenicity not expected based on limited human data, though possible risk of transient neonatal metabolic acidosis based on limited or conflicting human data and drug's mechanism of action

Lactation

Clinical Summary

weigh risks/benefits while breastfeeding; no known risk of infant harm based on limited human data w/ PO form and drug properties; no human data available to assess effects on milk production

Drugs.com (4-23-24)

Acetazolamide Breastfeeding Warnings

Benefit should outweigh risk.

Excreted into human milk: Yes

Some authorities believe this drug is compatible with breastfeeding when used to treat glaucoma. However, product manufacturers advise against, or advise use with extreme caution while breastfeeding due to the potential for serious adverse effects in nursing infants.

US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

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: Methazolamide

- Clinical Uses
 - ◆ Consider as 1st CAI for systemic glaucoma treatment
- Better tolerated than acetazolamide
- > Lipid and water solubilities than acetazolamide
- 55% binds to plasma proteins (vs 90-95% acetazolamide)
- IOP effect slightly less than acetazolamide

Carbonic Anhydrase Inhibitors
Systemic: Methazolamide

- Side effects (similar but less than acetazolamide):
 - ◆ Paresthesia
 - ◆ Kidney stones
 - ◆ Aplastic anemia (rare)
 - ◆ Skin rash
 - ◆ Drowsiness
 - ◆ Metabolic acidosis

Carbonic Anhydrase Inhibitors
Systemic: Methazolamide

- Caution:
 - ◆ COPD
 - ◆ Pulmonary impairment
 - ◆ Diabetes
 - ◆ Sulfa allergies

Neptazane
methazolamide

Pregnancy/Lactation[®]

Pregnancy
Clinical Summary
weigh risk/benefit during pregnancy; no human data available; risk of teratogenicity based on animal data at 40x recommended human dose

Lactation
Clinical Summary
consider alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production

Methazolamide Pregnancy Warnings
Animal studies have revealed evidence of teratogenicity; there are not controlled data in human pregnancy.
US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
This drug should be used during pregnancy only if the benefit outweighs the risk to the fetus.
US FDA pregnancy category: C
See references

Methazolamide Breastfeeding Warnings
A decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.
Excreted into human milk: Unknown
Excreted into animal milk: Data not available
Comments: The effects in the nursing infant are unknown.

Carbonic Anhydrase Inhibitors
Systemic: Methazolamide

- Methazolamide (Neptazane=brand d/c)
 - ◆ 25 or 50 mg tablets
- Dosage: 50-100 mg BID,TID
 - ◆ Onset: 2-4 hour
 - ◆ Duration: 10-18 hours

HYPEROSMOTICS:
SYSTEMIC

Hyperosmotics
Systemic

- Oral:
 - ◆ Glycerin*
 - ◆ Isosorbide*
- Intravenous
 - ◆ Mannitol
 - ◆ Urea **

*Not available?
**Not available ocular use

Hyperosmotics
Systemic

- Indications:
 - ◆ Acute angle closure glaucoma
 - ◆ Intraocular surgery
- Mechanism:
 - ◆ ^ serum osmolality
 - ◆ Osmotic gradient between ocular fluids (aqueous and vitreous) and plasma
 - ◆ Result: fluid movement from eye to hyperosmotic plasma via retinal and uveal blood vessels

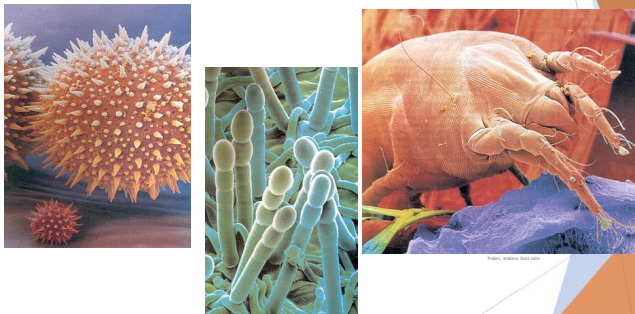
Hyperosmotics: Systemic-Orals

- 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

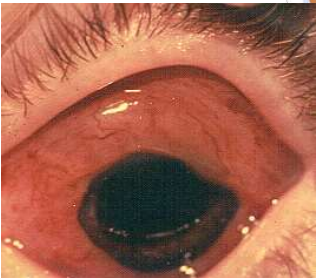
- Topical treatment
 - ◆ Beta Blocker (e.g. timolol), alpha 2 agonist (e.g. brimonidine or apraclonidine),
 - ◆ CAI (e.g. dorzolamide),
 - ◆ cholinergic agonist (note pilocarpine does not work when IOP >60)
 - ◆ 3 rounds separated by 15 minutes
- Oral acetazolamide: 2x 250 mg (NOT extended release) (not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

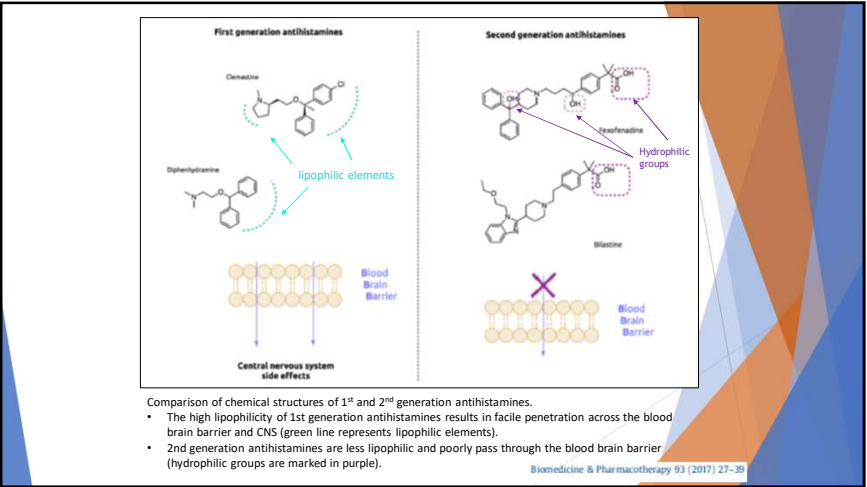
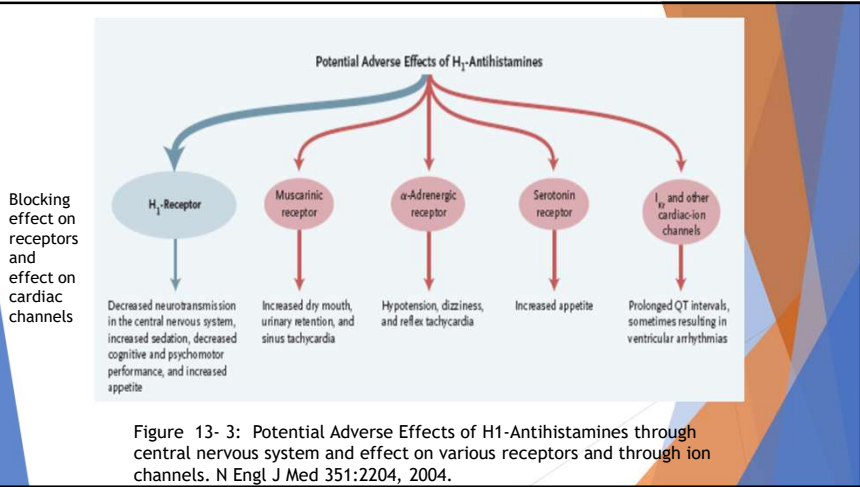
Antiallergy:
Antihistamines



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

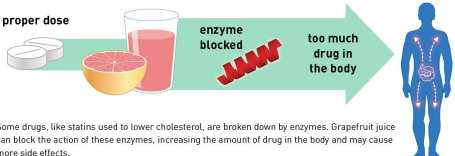
Grapefruit Juice

- Grapefruit juice decreases cytochrome P450 activity and metabolism of the drug is decreased
 - Blood levels of drug may rise
- Side effects vary and depend on drug involved and may include:
 - abnormal heart rhythms, stomach bleeding, kidney damage, difficulty breathing, sedation, dizziness
- Effect of grapefruit juice on medications can last for over 24 hours
- Usually other juices do not have this type of interaction, but orange or apple juice can interact with fexofenadine (Allegra)
 - Blood levels with fexofenadine go DOWN and the effectiveness is reduced
 - This interaction occurs by a different mechanism than CYP450 3A4 === but still recommend take with water and not fruit juice

How Grapefruit Juice Affects Some Drugs

When drugs are swallowed, they may be broken down (metabolized) by enzymes and/or absorbed using transporters in cells found in the small intestine. Grapefruit juice can cause problems with these enzymes and transporters, causing too much or too little drug in the body.

proper dose

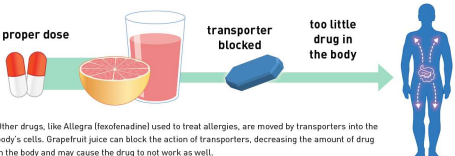


enzyme blocked

too much drug in the body

Some drugs, like statins used to lower cholesterol, are broken down by enzymes. Grapefruit juice can block the action of these enzymes, increasing the amount of drug in the body and may cause more side effects.

proper dose



transporter blocked

too little drug in the body

Other drugs, like Allegra (fexofenadine) used to treat allergies, are moved by transporters into the body's cells. Grapefruit juice can block the action of transporters, decreasing the amount of drug in the body and may cause the drug to not work as well.

Increasing drug in blood

- Enzyme's ability to metabolize drug is decreased==not mechanism for Fexofenadine

Decreasing drug in blood == Fexofenadine

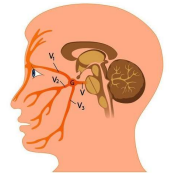
- Grapefruit juice affects proteins in body (drug transporters) that help move drug to cells for absorption
- Less drug enters the blood
- Orange or Apple juice has similar interaction as grapefruit juice with fexofenadine (not always true for other drugs)

Analgesic Treatment Ocular Pain

NonOpioid Analgesics

Opioid Analgesics

Opioid Crisis



Pain Assessment and Management

Pain Mechanism

History

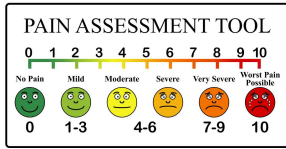
Clinical Presentation

Level of Pain

The Drugs

- Narcotic vs Non Narcotic

PAIN ASSESSMENT TOOL



The visual analog scale (VAS) is a subjective measure for acute and chronic pain. A patient is asked to indicate his/her perceived pain intensity (=VAS score).

World Health Organization (WHO) Analgesic Ladder

The three main principles of the WHO analgesic ladder are: "By the clock, by the mouth, by the ladder."

By the clock: To maintain constant pain relief, drugs should be given "by the clock" or "around the clock" rather than only "by the pain." This means that the pain is not allowed to build up between doses. The frequency will depend on whether it is a long- or short-acting preparation.

By the mouth: The oral route is usually the preferred route for most of pain (ability of oral dosing). However, if a drug is not available for oral use (e.g. paracetamol, morphine, codeine, fentanyl) then the drug should be given by other routes (e.g. intravenous, intramuscular, subcutaneous, rectal, transdermal, etc.).

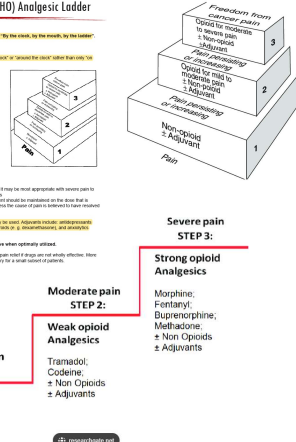
By the ladder: A pain action plan should be prepared for each patient. It should include:

- 1. Non-opioid analgesics (e.g. paracetamol, NSAIDs)
- 2. Weak opioid analgesics (e.g. codeine, tramadol)
- 3. Strong opioid analgesics (e.g. morphine, fentanyl, buprenorphine, methadone, etc.)

Drug selection should be guided by the severity of the pain. It may be most appropriate with severe pain to start at the top of the ladder with a strong opioid. It is not always necessary to start at the top. When pain is controlled, the patient should be stepped down the ladder as far as possible. In a pain action plan, it is important to include the need for adjuvants (e.g. antiemetics, anticholinergics, etc.).

The three step approach is appropriate and effective when used.

Original formulation of analgesic ladder may provide when pain relief is not achieved, effective, then consider other of adjuvant (e.g. sedatives) may be necessary for a small subset of patients.



Step 1: Non-opioid Analgesics
Aspirin; Paracetamol; NSAIDs; ± Adjuvants

Step 2: Weak opioid Analgesics
Tramadol; Codeine; ± Non Opioids ± Adjuvants

Step 3: Strong opioid Analgesics
Morphine; Fentanyl; Buprenorphine; Methadone; ± Non Opioids ± Adjuvants

Principles of analgesic ladder:

- By clock: drugs given around clock (NOT prn)
- By mouth: preferred route
- By ladder: prompt administration of drugs in the following order:
 - non-opioids (e. g. acetaminophen, NSAID)
 - as necessary, mild opioids (e. g. codeine)
 - then strong opioids (e. g. morphine or hydromorphone) until the patient is free of pain
- Along any step in the ladder adjuvants may include:
 - Antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentin), corticosteroids (e.g. dexamethasone), and anxiolytics (e.g. diazepam).

Diane T. Adamczyk, OD © 2025

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Analgesic Drugs

Peripherally acting agents

- Act on peripheral pain receptors
- Prevent sensitization and discharge of nociceptors
- NSAIDs

Anesthetic agents

- Nociceptive signal interrupted between peripheral source and brain or spinal cord
- Limited long term use

Centrally acting agents

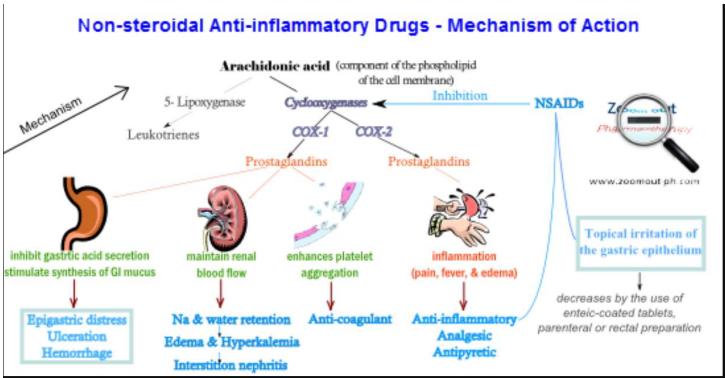
- Act on CNS
- Opioid (narcotic) analgesics

Nonopioid (NonNarcotic) Analgesics

Treat mild to moderate pain

NSAIDs

Short term use



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

NSAIDs

- Analgesic doses are small and have a ceiling
- Anti-inflammatory doses are higher
- Note: inflammation does not equal pain

Analgesic ceiling of ibuprofen: 400mg/dose (max 1200/day)

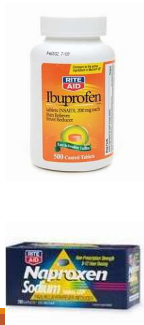
STUDY ARMS	IBUPROFEN DOSE	MEAN PAIN SCORE BEFORE MEDS	MEAN PAIN SCORE AFTER 60 MIN	DIFFERENCE (95% CI)
Group 1	400 mg	6.48	4.36	2.12 (1 to 7)
Group 2	600 mg	6.35	4.50	1.85 (2 to 7)
Group 3	800 mg	6.46	4.50	1.97 (3 to 7)

Table 1: Results showing the difference in pain score before and after administration of Ibuprofen at three different doses.
<https://epmonthly.com/article/the-ibuprofen-analgesic-ceiling/>

Nonopioid (NonNarcotic) Analgesics

Nonsalicylate NSAIDs

- Mechanism
 - Inhibit cyclooxygenase
 - Reduce production of sensitizers for peripheral nociceptors
- Metabolized by liver and eliminated through kidney
- Superior to aspirin in analgesic efficacy, lower incidence and severity of side effects
- Propionic acid derivatives: ibuprofen and naproxen



Nonopioid (NonNarcotic) Analgesics

Nonsalicylate NSAIDs

Naproxen

- 500mg, then 250 q6-8h or 500 q12h



Ibuprofen

- Lower GI complications (bleeding) compared to other NSAIDs when ≤ 1200 mg/day
- However odds double when ≥ 1800 mg/day
- Anti-inflammatory ceiling dose (2400-3200 mg/day) is higher than analgesic ceiling dose
- 200-400 mg q4-6h
- **Ibuprofen 400mg QID=acetaminophen 300mg/codeine 30 mg (formerly Tylenol 3)**



Nonopioid (NonNarcotic) Analgesics

Nonsalicylate NSAIDs

- Side Effects:
 - GI effects
 - Inhibit platelet function (reversible vs. aspirin which is irreversible)
- Contraindications
 - Peptic ulcer, renal insufficiency





Nonopioid (NonNarcotic) Analgesics

Acetaminophen

- Site and mechanism of analgesic action is unclear
- Weak inhibitor of prostaglandin synthesis
- Little or no inflammatory effect
- Does not:
 - inhibit platelet aggregation,
 - affect prothrombin time,
 - produce GI irritation



Nonopioid (NonNarcotic) Analgesics

Acetaminophen

- Dosage: 325-1000mg Q4-6H
- Max: 1g/4h and 4g/day
- Side effects:
 - Liver toxicity
- Contraindications
 - Chronic alcoholism

FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure

- Acetaminophen:
 - Maximum: 4 g/day
 - Maximum: 325 mg per dose when in combination with opioids

acetaminophen
generic

Adult Dosing ⓘ

Dosage forms: CAP: 325 mg, 500 mg; TAB: 325 mg, 500 mg, 650 mg; ER TAB: 650 mg; CHEWABLE: 80 mg, 160 mg; SUSP: 100 mg per mL, 120 mg per 5 mL, 160 mg per 5 mL; SOL: 160 mg per 5 mL, 500 mg per 15 mL; INJ: various

pain

[PO route, immediate-release form]

Dose: 325-1000 mg PO q4-6h prn; Max: 1 g/4h and 4 g/day from all sources

[PO route, extended-release form]

Dose: 650-1300 mg ER PO q8h prn; Max: 4 g/day from all sources

FDA Mandate on Acetaminophen-Opioid Combinations Appeared Effective

— Hospitalizations for liver toxicity declined after FDA limited acetaminophen dose

by Jeff Miner, Contributing Writer, MedPage Today
March 7, 2023



Mandate: limited amount of acetaminophen in combination products to 325mg (from prior 750mg), with boxed warning of liver injury risk

- Prior mandate: acetaminophen/opioid toxicity increased by 7% per year
- Post mandate: acetaminophen/opioid toxicity decreased by 16% per year
- Prior mandate: acetaminophen/opioid hospitalization increased by 11% per year
- Post mandate: acetaminophen/opioid hospitalization decreased by 11% per year
- Safe dose of acetaminophen not established, but product label advises 4g/24 hours
 - Age, genetics, nutritional status, use of alcohol can be factors that influence drug safety

Acetaminophen Dosing			
Acetaminophen	AMOUNT	DOSE & FREQUENCY	DAILY LIMIT
Acetaminophen regular strength for example: Tylenol Regular Strength	325 mg per pill	2 pills every 4 to 6 hours while symptoms last	Do not take more than 10 pills in 24 hours, unless directed by a doctor
Acetaminophen extra strength for example: Tylenol Extra Strength	500 mg per pill	2 pills every 6 hours while symptoms last	Do not take more than 6 pills in 24 hours, unless directed by a doctor
Acetaminophen extended release for example: Mobic-BE, Actavis-Pan	650 mg per pill	2 pills every 8 hours	Do not take more than 6 pills in 24 hours

The daily limit of acetaminophen is **4,000 mg**
for most adults, and not take more
than this amount in 24 hours

ACETAMINOPHEN DOSING CONSIDERATIONS

As a healthcare professional, you may use your discretion to recommend acetaminophen up to 4,000 mg in a 24-hour period for patients whose pain or fever persists.

• The OTC maximum daily dose of acetaminophen remains 4,000 mg.

Condition	Recommended ibuprofen dosage for adults	Ibuprofen Maximum dosage for adults
Pain relief	200-400 mg orally every 4-6 hours as needed	1200 mg per day (OTC); 3200 mg per day (prescription strength)
Fever	200-400 mg orally every 4-6 hours as needed	1200 mg per day
Dysmenorrhea (menstrual cramps)	200-400 mg orally every 4-6 hours as needed	1200 mg per day (OTC); 3200 mg per day (prescription strength)
Arthritis (osteoarthritis and rheumatoid arthritis)	1200-3200 mg orally per day in several doses	3200 mg per day

The ibuprofen Rx maximum daily dose is 3,200 mg, while the OTC maximum daily dose is 1,200 mg.

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
- Contraindications
- Bronchial asthma, COPD

Opioid Analgesics: Codeine



- Codeine
- Potential for addiction is low
 - 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 (Codeine) or
 - Schedule III (products with less than 90mg Codeine)
 - 30mg+acetaminophen(300mg) (Tylenol 3-brand d/c)
 - Q4H
 - Use in ocular pain

Opioid Analgesic: Tramadol

- Tramadol (Ultram=brand d/c)
- Schedule IV
- Exact mechanism of action unknown
- Pharmacology:
- Analgesia from both: parent drug tramadol AND its M1 metabolite
 - Tramadol:
 - Weakly inhibits norepinephrine/serotonin reuptake (>>>increasing serotonin)
 - Metabolism depends on cytochrome P-450 isoenzyme
 - M1:
 - Binds to mu opioid receptors
 - Production depends on cytochrome P-450 isoenzyme
- Pain, moderate-mod. Severe [50-100 mg PO q4-6h prn]

Important Considerations for Use of: Tramadol and Oral Medications

- Important Considerations:
- “Poor metabolizers”: 7% of the population has reduced activity of CYP2D6 isoenzyme of cytochrome P-450
 - Concentrations of tramadol are 20% higher,
 - While M1 concentrations were 40% lower
 - Drug Interactions
 - Concomitant use of serotonin reuptake inhibitors and MAO inhibitors with tramadol >>>enhance risk of adverse events including seizures and serotonin syndrome
 - Concomitant use erythromycin (a CYP3A4 inhibitor) may reduce metabolic clearance of tramadol >>>increased risk for seizures and serotonin syndrome
 - Liver/Kidney disease
 - Liver/kidney disease affects clearance and metabolism of tramadol
 - Age
 - Tramadol in those 75 and older: adjust daily dose because serum concentrations are elevated and elimination prolonged

And with privilege
goes responsibility.

John F. Kennedy

Best wishes...



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