Systemic Antibiotics

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Bacteria Responsible for Ocular Infections

- Gram-positive cocci arranged in clusters: Staphylococci
  - *Staphylococcus epidermidis*: Found in high numbers on the skin and mucous membranes.
  - *Staphylococcus aureus*: Also found on the skin and mucous membranes, but in less numbers.

- *S. aureus* is more virulent in nature than *S. epidermidis*.

- ~50% of ocular infections are caused by Staphylococci.

Bacteria Responsible for Ocular Infections

- Gram-positive cocci arranged in chains: Streptococci
  - *Streptococcus pneumoniae*: Diplococci that is a common cause of corneal ulcers and pediatric conjunctivitis.
  - *Streptococcus pyogenes*: Not a frequent cause of ocular infections.
  - *Streptococcus viridans*: Most frequently found on teeth, but can cause ocular findings.
Bacteria Responsible for Ocular Infections

- Gram-negative cocci: Neisseria
  - *Neisseria gonorrhoeae*: Cause of Gonorrhea
  - *Neisseria meningitidis*: Most frequent associated illness is meningitis.
  - Neisseria can penetrate intact cornea in 48 hours!

Other Gram-Positive Bacteria

- Gram-Positive Bacilli:
  - *Bacillus cereus*
  - *Corynebacteria diphtheriae*
  - *Listeria monocytogenes*
  - *Clostridium difficile*
  - *Propionibacterium acnes*

  These are all capable of causing ocular infections, but it is a more rare finding.

Bacteria Responsible for Ocular Infections

- Gram Negative Rods:
  - *Haemophilus influenzae*: Common cause of childhood infections
  - *Pseudomonas aeruginosa*: Most common gram – organism isolated from corneal ulcers.
  - *Moraxella catarrhalis*: Commonly found in alcoholics and debilitated

- Less Common Gram Negative Rods Causing Ocular Infections:
  - *Haemophilus aegypticus*
  - *Serratia marcescens*
  - *Escherichia coli*
  - *Enterobacter species*
  - *Acinetobacter species*
  - *Proteus species*
Additional Causes of Infection

- **Chlamydia trachomatis**
  - Obligate intracellular parasite – must grow and multiply inside the host cells
  - Serotypes A-C = Trachoma
  - Serotypes D-K = Inclusion Conjunctivitis

- **Spirochetes**
  - *Treponema pallidum* is the cause of Syphilis.
  - *Borrelia burgdorferi* is the cause of Lyme Disease

- **Mycobacterium Species**
  - *M. tuberculosis* = Tuberculosis
  - Multiple Ocular Signs from phylectenules to uveitis

Ocular Conditions Often Treated with Systemic Antibiotics

- **Lid Disease:**
  - Meibomian Gland Dysfunction
  - Internal and External Hordeolum
  - Ocular Rosacea
  - Conjunctivitis
    - Hyperacute from *Neisseria gonorrhoeae*
    - Trachoma and Inclusion Conjunctivitis from *Chlamydia trachomatis*
  - Recurrent Corneal Erosions
  - Dacryocystitis
  - Dacryoadenitis
  - Cannaliculitis
  - Orbital and Preseptal Cellulitis

Meibomian Gland Dysfunction

- Cells slough from epithelial lining or meibum thickens to obstruct the drainage of the meibomian glands – this causes stagnation and possible infection.
- Symptoms Include: Irritation, stinging burning, Mild blurry vision due to tear film disruptions, and chronic redness.
- Treatment: Lid hygiene, Topical and Oral Antibiotics
Hordeolum

- **Internal** = Infection of the meibomian gland
  - Deep within the tissues so often requires oral antibiotics
- **External** = Infection of glands of Zeis or Moll
  - More superficial and can be treated with topical therapy
  - Lid hygiene and warm compresses also recommended.

Most common cause: *Staphylococcal*

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Rosacea

- Chronic inflammatory disorder involving the skin and eye of unknown etiology
- Adults: 30-60 years of age
- Three presentations: Facial, Ocular, or Oculo-Facial
- Ocular Signs often include:
  - Dry Eye
  - Blepharitis and Meibomian Gland Dysfunction
- Treatment: Topical and Orals

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Hyperacute Conjunctivitis

- Most common and severe cause: *N. gonorrhoeae*
- Found in neonates, adolescents, and adults.
- Swollen lids, Severe Hyperemia and Chemosis, and Heavy Discharge! Eye is often painful with tenderness to the touch and blurred vision.
- Rapid Onset: 24-48 (up to 72) hours
- Need to perform irrigation to help with symptoms.
- Requires systemic treatment.
Chlamydial Conjunctivitis

- Trachoma: Major cause of preventable blindness in the world, but not frequently seen in the United States.
- Inclusion Conjunctivitis: Results from spreading from the genitals.
  - Signs: Follicular and Papillae Reaction will be extreme. Lid Edema and Discharge will be present.

Recurrent Corneal Erosions

- Peeling off of a large piece of epithelium as the patient blinks or opens eyes when awakening
- Signs and Symptoms: Pain, tearing significantly, photophobia, perilimbal injection, FB sensation or pain when patient wakes in morning.
  - Usually Recurrent
- Treatment regimen may include systemic antibiotics.

Dacryoadenitis

- Dacryoadenitis: Inflammatory process of the lacrimal gland
- Symptoms: Unilateral or bilateral local tenderness and redness with characteristic "S" shape swelling, conjunctival chemosis, pain, and irritation.
Dacryocystitis

- Infection / inflammation of the lacrimal sac
  - Occurs either secondary to or concomitant with stasis of lacrimal outflow system
  - Symptoms and Signs: Pain, Redness of nasal canthus, smoldering unilateral red eye.

Cannaliculitis

- Infection or inflammation within the canaliculus
  - Relatively rare.
  - Symptoms and Signs: Red Eye - usually unilateral and often with history of resistance to antibiotics, epiphora, mild tenderness, and pouting/erythema of the puncta.

Orbital and Preseptal Cellulitis

- Preseptal: Infection of lid structure anterior to the orbital septum
  - Most common causes:
    - S. aureus or S. pyogenes
    - Serious risk of progression to Orbital infection which can cause death
  - Orbital: Infection of the lid structures posterior to the orbital septum
  - Much more serious risk of blindness
Antibiotics

- Compounds that assist the body’s immune system in killing bacteria.
- Even on antibiotics the immune system is responsible for killing the majority of bacterial microbes.

Complications to Antibiotic Treatment:
- Hypersensitivity
- Toxicity
- Superinfections

Spectrum of Activity

- The species against which a drug shows intrinsic activity against.
  - Narrow-Spectrum: Effective against only a few species
  - Broad-Spectrum: Effective against a wide variety of species
  - Extended-Spectrum: Effective against both gram-positive and gram-negative microbes

- Bacteriostatic = Prevents multiplication
- Bacteriocidal = Kills the organism

Antibiotic Resistance

- Microorganism that was originally in the spectrum of activity is no longer susceptible to the drug.

Mechanisms of Resistance Include:
- Producing an enzyme capable of destroying or inactivating the antibiotic.
- Altering the target site receptor for the antibiotic so as to reduce or block its binding.
- Preventing the entry of the antibiotic into the bacterial cell or actively transporting the antibiotic out.
Avoiding Resistance

- Avoid prescribing for non-bacterial infections.
- Avoid sublethal doses (attack to kill all).
- Avoid intermittent use.
- Always complete the full dosage for an appropriate length of time.
  - 7 days minimum recommended.
- NEVER TAPER AN ANTIBIOTIC below recommended dosing schedule!

Antibiotic Treatment

- Empiric Therapy vs. Specific Therapy:
  - Empiric = “shot-gunn” approach; based on an assumed diagnosis and powerful broad-spectrum medications.
  - Specific therapy is based on solid identification of the infecting organism and a “sensitivity analysis” proving the organism’s susceptibility to the antimicrobial.
- Most ocular treatment begins with empiric methods and only moves to specific in cases of high risk or resistance to healing.

Antibiotics Available:

- Antibiotics are designed to capitalize on the differences between bacterial and human cells.
- 5 Main Mechanisms of Action of Bacteria:
  - Inhibiting cell wall synthesis
  - Affecting the cell membrane
  - Affecting Protein Synthesis
  - Affecting Folate Metabolism
  - Affecting Bacterial DNA Synthesis
Antibiotics Inhibiting Cell Wall Synthesis

Medications Affecting Cell Wall Synthesis
- The cell wall of bacteria are not found in any human cells, therefore targeting this results in low levels of toxicity.
- Direct mechanism is targeting the peptidoglycan layer that is necessary for the structural integrity of the cell.
- Peptidoglycan is a mucoprotein made up of linear polysaccharide chains and peptide cross linkages. No peptidoglycan = cell lysis and death.

Drugs Affecting Cell Wall Synthesis
- Class Includes:
  - Beta-Lactams (Penicillins, Cephalosporins, Carbapenems, and Monobactams)
  - Bacitracin
  - Vancomycin
Penicillins

- All penicillins contain a thiazolidine ring and a β-lactam ring connected to a side chain.
  - Side chain primarily decides the antibacterial spectrum.

- MOA: Inhibits the enzymes (penicillin binding proteins or transpeptidases) that create the peptide cross linkage.
  - These enzymes are beneath the cell wall therefore PCN's are most effective when cells are actively dividing.
  - **Bactericidal Medications**

Penicillins

- Generally effective against gram + cocci, gonococci, gram + rods, and many of the spirochetes.

- High levels of resistance:
  - Bacteria produce enzymes called β-lactamases/penicillinase to hydrolyze the ring.
  - Alter transpeptidases (penicillin binding proteins) to no longer bind PCN.

- 4 Main Categories Include:
  - Effective against Gram + Bacteria
  - Resistant to Penicillinase
  - Extended Spectra of Activity
  - Antipseudomonal Activity

PCN's effective against Gram +

- Two Major Medications: Penicillin G and Penicillin V
  - G = not stable in gastric acid and must be administered IV/IM.
  - V = synthetic derivative of G that is able to be administered orally.
PCN's effective against Gram +

- Antibiotics of choice for systemic infections caused by *Streptococcus pyogenes* and *pneumoniae* and *Treponema pallidum* (syphilitic disease).

- Oral Probenecid can be co-administered to inhibit the secretion of these medications at the kidneys, thus prolonging the drug's ½ life and effectively maintaining a higher concentration longer.

PCN's Resistant to Penicillinase

- Modified PCN structure to increase susceptibility of staph that produce penicillinase.
  - Resulted in further resistance forming by altering the penicillin binding proteins = Methicillin Resistance (MRSA).

PCN's Resistant to Penicillinase

- Medications Include: Oxacillin, Cloxacillin, Dicloxacillin, Nafcillin (IV only), and Methicillin (IV or IM only).
  - Dicloxacillin is an excellent oral medication for Staph due to its low MIC value and high absorption. Not good for resistant staph.
  - Oxacillin, Cloxacillin, Nafcillin, and Dicloxacillin are useful in patients with renal failure due to their non-renal routes of clearance.
  - Drugs are designed with staph as spectrum of activity, therefore use is primarily for infections resulting from staphylococci such as internal hordeolums.
PCN’s with Extended Spectra

- Further modified PCNs that increase spectrum to include some gram negatives such as *Haemophilus influenzae*.
- Frequently used to treat ear/respiratory infections in children.

- Drugs Include: Ampicillin (IV, IM, and PO) and Amoxicillin (PO).
  - Amoxicillin is better absorbed from the intestine and yields higher blood/urine levels than does ampicillin when given orally.

PCN’s with Extended Spectra

- These medications are inactivated by penicillinase much like other categories, but often used in combination with clavulanate, tazobactam, or sublactam which bind to and irreversibly inactivate bacterial penicillinase.
  - Amoxicillin + Clavulanate = Augmentin (Oral)
  - Ampicillin and Sulbactam = Unasyn (IV, IM)

- Very useful for ocular infections caused by resistant strains (such as gram positive cocci or *Haemophilus influenza*) that occur with dacryocystitis or sinusitis.

Optometric Uses of PCN’s with Extended Spectra

- Augmentin:
  - Available in 250, 500, and 875 tablets (all have 125 mg of clavulanate) and 125/31.25/5 mL and 250/62.5/5 mL liquid.
  - Adults: 500 mg tablet q8-12 hours or 875 mg tablet q12 hours
  - Pediatrics: 20-40 mg/kg day in three divided doses in children.

- Unasyn IV:
  - Common medication of choice for Orbital Cellulitis.
  - Dosage: 3 grams IV q6 hours in adults
PCN’s with Antipseudomonal Activity

- Active against *Pseudomonas, Proteus*, and *Enterobacter* species unlike other PCNs.
  - Have an additional carboxy group on the side chain that renders them more resistant to the chromosomal beta-lactamases of these species.

Medications Include:
- Carbenicillin
- Piperacillin
- Piperacillin/Tazobactam (Zosyn)
- Ticarcillin/clavulanate (Timentin)

PCN’s with Antipseudomonal Activity

- Carbenicillin (Geocillin) is the only oral formulation available and is reserved for urinary tract infections.

- IV meds such as piperacillin and ticarcillin can be used in the treatment of severe ocular infections.

PCN Side Effects

- Adverse Reactions = Hypersensitivity Types 1 – 4 effect ~5% of patients to some extent.
  - 1: Urticaria, Angioedema, and Anaphylaxis
  - 2: Hemolytic Anemia
  - 3: Interstitial Nephritis, Vasculitis, and Serum Sickness
  - 4: Contact dermatitis and Steven’s Johnson Syndrome

- Once a patient reacts to a PCN they are likely to react to any PCN.
PCN Side Effects

- Rarely may cause oral contraceptives to fail.
- Synergistic with Aminoglycosides in the body, but cannot be given in IV together or they will inactivate.
- Absorption is affected by food thus recommended to give 1 hour before or 2 hours after meals.

PCN Side Effects and Contraindications

- Other Side Effects:
  - CNS symptoms such as HA and dizziness
  - GI Upset
  - Kidney/Liver Toxicity
  - Superinfections (especially with ampicillin) can result in pseudomembranous colitis.
  - Hematologic Toxicity is rare but has occurred.
- CI: History of allergy to PCNs and Cross sensitivity to Cephalosporins

Cephalosporins

- Same MOA as Penicillin’s, but slightly different structure.
  - Replaces the thiazolidine ring with 6-member dihydrothiazine.
- Variable susceptibility to β-lactamase
  - Gram negative bacteria has resistance by hydrolyzing the cephalosporin at a greater level than it does with PCN’s.
- Divided into 4 generations that relate to their characteristics:
  - As you progress from 1st to 4th generation you see the following changes:
    - Decreased gram positive coverage/Improved gram negative coverage
    - Increased toxicity and cost in later generations
    - Increased resistance to beta-lactamase in later generations
1st Generation Cephalosporins

- Effective against gram positive bacteria, with very modest activity against gram negative.
  - Must be concerned with resistance!

- Medications Include:
  - Cephradine (Velosef)
  - Cefadroxil (Ultracef, Duricef)
  - Cefazolin (Ancef) is IV or IM only
    - Topical fortified antibiotics have been used for the treatment of corneal ulcers by compounding into topicals.
  - Cephalexin (Keflex)

Keflex (Cephalexin)

- Commonly used oral medication for Internal Hordeolums or mild preseptal cellulitis

- Recommended Dosages:
  - Adults: 1000 – 4000 mg/day PO divided BID to QID
    - Common to Prescribe: 500 mg PO QID
    - BID provides questionable continuous coverage due to half-life of 1 hour only for this medication.
    - Brand Keflex is available as 750 mg capsule for extended release.
    - Prescribe one capsule BID
  - Pediatrics: 25 – 50 mg/kg/day PO divided BID to QID

2nd Generation Cephalosporins

- Increasing effectiveness against gram negative bacteria including *H. influenzae*, with okay efficacy against methicillin-sensitive *Staph* and *Strep*.

- Drugs include:
  - Oral Medications: Cefuroxime axetil, Cefprozil, and Cefaclor
    - Cefaclor (Ceclor):
      - Brand Name is no longer available.
      - Mild preseptal cellulitis = 250-500 mg TID in adults and 20-40 mg/kg/day in three divided doses for children
    - IV or IM only Include: Cefuroxime, Cefoxitin, and Cefotetan.
3rd Generation Cephalosporins

- Less active against gram positive cocci with much greater effect against gram negative bacteria.
  - Effective against *Haemophilus*

- Available Orally:
  - Cefdinir (Omnicef)
  - Cefixime (Suprax)
  - Ceftibuten (Cedax)
  - Cefpodoxime (Vantin)
    - Optometric Uses: Cefdinir (600 mg daily) and Cefpodoxime (200 mg BID) can be used in the management of preseptal cellulitis.

3rd Generation Cephalosporins

- Optometric Uses for the Treatment of Preseptal Cellulitis:
  - Cefdinir (Omnicef)
    - Adults: 600 mg once daily
    - Children: 14 mg/kg/day in two doses
      - Max daily is 600mg
  - Cefpodoxime (Vantin)
    - Adults: 200 mg BID
    - Children: 10 mg/kg/day in two doses
      - Max Daily is 400 mg

3rd Generation Cephalosporins

- Available IM or IV:
  - Cefotaxime (Claforan)
  - Ceftazidime (Fortaz or Tazicef)
    - Only 3rd generation effective against *Pseudomonas*.
  - Ceftriaxone (Rocephin)
    - Optometric Uses: Ceftriaxone is the drug of choice for *N. gonorrhoeae*.
      - Adults: 1g IM in a single dose (can be repeated if necessary)
      - Neonatal: 125mg in single dose IM or IV
      - Can also be used in severe preseptal or orbital cellulitis
4th Generation Cephalosporins

- Extended spectrum of activity against **gram-positive** and **gram-negative** organisms.
- Drugs Include: Cefepime (Maxipime) available IV and IM.
- FDA recently granted approval for the first “5th generation”
  - Ceftaroline (Teflaro) IV is used for pneumonia and severe skin infections.

Side Effects and Contraindications

- Hypersensitivity Reactions are common.
  - Risk of cross sensitivity with PCN’s is higher for 1st generation, but often overestimated for later medications.
  - Average is about 10 – 15% cross reactivity.
- Other SE’s:
  - GI Upset and/or Superinfection
  - Vitamin K Deficiency by destroying intestinal microflora can lead to bleeding excessively.
  - Reversible Renal Impairment (medications are eliminated by kidneys)
    - Risk is greater if used in combination with a diuretic or aminoglycoside.
  - Adverse Joint and Skin Reactions
- Contraindicated in hemophilia and history of sensitivity.

Bacitracin

- Inhibits bacterial cell wall synthesis by inhibiting the movement of a peptidoglycan precursor through the cell membrane.
- Spectrum: **Gram + Cocci** and possibly **Neisseria**
- **Not** used parenterally due to renal necrosis side effect.
Vancomycin

- Inhibits the mucopeptide portion of peptidoglycan.
- Highly active against gram + cocci, including staph and strep as well as C. difficile.
  - Drug of Choice for MRSA and penicillinase resistant S. pneumoniae.
  - Reserved for severe vision or life threatening situations.
- Generally administered IV due to poor intestinal absorption/oral bioavailability.
  - Can dilute heavily to make a potent topical medication.
- Side Effects: Redman Syndrome, Otoxicity, and Nephrotoxicity
  - Need to assess renal status prior to use.

Antibiotics affecting the Cell Membrane

- Interact with the phospholipids of the cell membrane causing increased permeability and disruption of the osmotic gradient.
- Bactericidal in nature.
- Two Main Drugs both used Topically Only:
  - Polymyxin B
  - Gramicidin
Gramicidin

- Narrow Spectrum bactericidal medication.
  - Effective against Gram + Bacteria.
- Nearly equivalent in effect to Bacitracin.
  - Replaces Bacitracin when solution formulation is desired.
- Available as 0.0025% in combination with:
  - Polymyxin B 10,000 U/ml and Neomycin 0.175%
  - Brand Name: Neosporin

Polymyxin B

- Narrow Spectrum against gram negative bacteria including Haemophilus influenzae, Neisseria, and Pseudomonas.
- No systemic use due to neurotoxicity and nephrotoxicity.
- Only available in ophthalmic combination products with other antibiotics or steroids (Polytrim, Polysporin, etc)
- SE’s: Irritation/allergic reaction of the conjunctiva and eyelids.
  - Pregnancy Category C.

Antibiotics affecting Protein Synthesis
Drugs Affecting Protein Synthesis

- Mechanisms designed to affect bacterial ribosomes that differ in both size and composition from human ribosomes.

- Medication Classes or Single Drugs Include:
  - Aminoglycosides
  - Tetracyclines
  - Macrolides
  - Chloramphenicol
  - Clindamycin

Aminoglycosides

- Inhibit bacterial protein synthesis and the reading of genetic coding by binding to the 30S subunit.

- All must be given IM or IV due to poor oral absorption:
  - Streptomycin
  - Tobramycin
  - Gentamicin
  - Neomycin
  - Amikacin
  - Kanamycin

Aminoglycosides

- Bactericidal and Broad/Extended Spectrum
- Active against:
  - Gram +: Staphylococcus aureus (unless methicillin-resistant)
  - Gram -: P. aeruginosa (except Neomycin), Proteus, Enterobacter, Serratia
  - Inactive against anaerobes, Streptococci, and Enterococci.

- Gram negative bacilli have developed resistance due to the production of inactivating enzymes.
- Achieve an additive effect against gram – bacilli and gram + cocci when combined with penicillins and cephalosporins.
  - Must prepare and administer separately.
Aminoglycosides

- All aminoglycosides are rarely used systemically, unless no other antibiotic is effective.
  - Concentration-dependent, thus high doses are required.
  - High potential for side-effects (Low Therapeutic Index)
    - Nephrotoxicity (excreted by the kidney unmetabolized)
    - Otoxicity = Auditory/Vestibular
- This prevents the widespread resistance seen in other classes of medications.
- Contraindicated with history of hypersensitivity or intolerance.

Aminoglycosides

- Gentamicin is the most commonly prescribed.
  - Gram negative coverage in severe infections such as septicemia, pyelonephritis, or endocarditis.
  - Tobramycin is slightly less nephrotoxic.
- Amikacin is a Semisynthetic molecule that has been adjusted to prevent the inactivating enzymes that cause resistance from having an effect.
  - Less toxic than others for intravitreal injection, thus can be used for endophthalmitis.

Tetracyclines

- Inhibit bacterial protein synthesis by binding to the 30S subunit and blocking attachment of aminoacyl-tRNA to the receptor site.
  - Bacteriostatic properties.
- Increasing amounts of resistance have decreased clinical use for commonly encountered bacteria infections.
  - Broad spectrum against gram – and gram +.
  - Used systemically for treatment of Rocky Mountain Spotted Fever, Typhus, Lyme Disease, and Chlamydia infections.
Tetracyclines

- Divided into three groups based on pharmacokinetics:
  - Short Acting
    - Tetracycline
    - Oxytetracycline
  - Intermediate Acting
    - Demeclocycline
  - Long Acting
    - Doxycycline
    - Minocycline (longest ½ life of all tetracyclines)

Chlamydia Treatment

- Not the Drug of Choice for STD, but can be used:
  - Dosage of Doxycycline 100 mg BID X 7 Days

- In developing countries tetracycline ointment is currently being used to manage Trachoma.
  - Oxytetracycline/Polymyxin B combo drop dosed BID for 5 of 7 days X 6 months.
  - Not showing complete cure that occurs with oral treatment.

Tetracycline vs. Mino/Doxycycline

- ½ life of 6-9 hours
- Dosed QID
- Exits body via kidneys.
  - Caution in poor renal function.
- Must not be taken after meals due to absorption issues.
- Most frequently Rx’d in 250 and 500 mg capsules.

- ½ life of 17 – 20 hours
- Dosed BID – Daily
- Exits body via intestines.
- Less concerned with timing of meals than other tetracyclines.
- Most frequently Rx’d in 50 and 100 mg tablets.
Forms of Doxycycline

- Oracea: 40 mg (30 mg immediate release and 10 mg delayed release)
- Periostat: 20 mg tablet
- Adoxa: 75, 100, 150 mg tablets, 150 mg capsule
- Doryx: 75, 100, and 150 mg enteric coated tablets
- Monodox: 75 and 100 mg capsules
- Vibramycin: Oral syrup and suspension, 100 mg capsule
- Generic: 20, 50, and 100 mg tablets and 50 and 100 mg capsules
  - Generic: Big difference in cost between 30 tablets of 100 mg for $13 and 30 tablets of 20 mg for $41.
  - Oracea: $360 for 30 tablets

Tetracyclines

- Also exhibit anti-inflammatory properties that have caused tetracyclines to become frequently used for managing conditions such as meibomian gland dysfunction, rosacea, and recurrent corneal erosions.

- Tetracyclines:
  - Inhibit chemotaxis (Early step in inflammatory cascade)
  - Inhibit matrix metalloproteases (MMPs), which involved in many inflammatory diseases, wound healing, embryogenesis, tumor invasion, and angiogenesis.
  - Decrease lipase production from staph destruction.

Meibomian Gland Dysfunction/Rosacea

- Helps resolve symptoms by reducing the fatty acids on the surface sebum which are irritating and inflammatory.
  - Decreases lipase production in S. epidermidis
- 100 mg of doxycycline BID for ~ 2 weeks, taper to 100 mg daily for 2-4 weeks and then a taper to daily 50 mg dosages if possible.
  - MGD often requires 6 months of treatment whereas Rosacea can be for 1 – 2 months.
  - Some pts can discontinue their medication without recurrence of symptoms, others must continue on low dose maintenance for extended periods.
Recurrent Corneal Erosions

- By acting as metalloproteinase inhibitors tetracyclines blocks the action of corneal collagenases and promotes epithelial adhesion.
  - Useful for promoting resolution of non-infected corneal ulcers and for reducing the recurrence of corneal erosions.

- Dosage Recommended:
  - 50 mg BID X 2 weeks followed by daily X 2 months.

Side effects of Tetracyclines

- Relatively non-toxic, but most common side effects are:
  - Photosensitivity reactions (exaggerated sunburn)
    - Educate to avoid the sun exposure.
  - GI irritation
    - Consuming with food can help reduce the irritation BUT...
      - Tetracyclines form complexes with divalent cations thus cannot consume with dairy products or anything containing iron, magnesium, aluminum, or calcium.
      - Reduced absorption with certain antacids such as TUMS.

Side Effects of Tetracyclines

- Intracranial hypertension (pseudotumor cerebri)
  - Often returns to normal after discontinuation.
- Vestibular Toxicity (only with minocycline).
- Must use Doxycycline in reduced kidney function due to others causing azotemia (high levels of nitrogen such as urea).
- Tetracyclines can interact significantly with other drugs.
  - Increase the effects of coumadin-type anticoagulants and seriously interfere with blood clotting.
Side Effects of Tetracyclines

- Pregnancy Category D.
  - Tetracyclines are attracted to embryonic and growing bone tissue.
  - Depress growth of long bones in pregnant women/children.
  - Cause changes in both deciduous and permanent teeth during the time of tooth development (Includes discoloration and increased cavities)

- Contraindicated in:
  - Women in the last half of pregnancy
  - Lactating women
  - Children under 8 years of age

Macrolides

- Macrolides inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit and preventing elongation of the peptide chain.

- Drugs Include:
  - Erythromycin
  - Clarithromycin
  - Azithromycin

Macrolides

- Spectrum of Activity
  - Active against gram + cocci (except enterococci).
    - Also active against Mycoplasma, Chlamydia, and Borrelia.
    - Azithromycin and Clarithromycin are also active against some gram negatives, such as H. influenzae and Moraxella.

- Resistance has formed due to a change in bacterial ribosomal DNA that causes poor binding to the drug.
**Erythromycin**

- Bacteriostatic against *most* organisms.
- Available for oral, topical, and IV use.
  - Oral is not commonly used:
    - Used if patient cannot take tetracycline due to pregnancy/age.
    - Occasionally in Chlamydial infections in infants and children.
    - Adult dose is 500 mg QID X7 days.
    - Used if allergic to PCNs and Cephalosporins.
    - Internal Hordeolums 250 mg QID.
  - Inactivated by gastric acid, therefore it is administered in a variety of formulas to increase absorption.
    - Ex: Erythromycin ethylsuccinate has better absorption than estolate

**Clarithromycin (Biaxin)**

- Derivative of Erythromycin that is more stable in gastric acid with a ½ life that is nearly twice that of Erythromycin.
- Effective against gram positive and gram negative more so than Erythromycin (better with *H.Influenza, Helicobacter pylori*, etc.).
  - Used for respiratory and skin infections mainly, but can be used for Chlamydia if needed.
  - Dosage is 250 – 500 mg BID
- *BIAXIN* is available as immediate-release tablets, extended-release tablets, and granules for oral suspension.

**Azithromycin (Zithromax)**

- Rapidly absorbed if given on an empty stomach.
  - Long ½ life of ~ 68 hours = Once Daily Dosing
- Derivative of erythromycin that has good gram + coverage with much improved gram negative.
- Available in:
  - Z-pac: Six 250 mg tablets packaged for patient compliance
  - Tri-pak: Three 500 mg capsules
  - Zmax (extended release) oral suspension of 1000 or 2000 mg
Azithromycin (Zithromax)

- Drug of Choice for Chlamydia Urethritis/Cervicitis/Conjunctivitis:
  - 1 g PO for adults
  - 20 mg/kg for children

- Also indicated for mild to moderate infection of the respiratory tract and skin.

Macrolide Side Effects

- GI irritation is the most common adverse event with all macrolides.

- Hypersensitivity can occur, but is not common.

- Common findings only with Azithromycin are:
  - Palpitations, Headache, Dizziness, and Fatigue.

- Pregnancy Category B (Clarithromycin is Category C).

Chloramphenicol

- Inhibits protein synthesis by binding to the 50S subunit and blocking aminoacyl-tRNA binding.

- Broad Spectrum: Gram + and Gram –
  - Also: Rickettsia, Chlamydia, spirochetes, and Mycoplasma
  - Resistant to P. aeruginosa.

- Bacteriostatic

- Great ocular penetration and can pass through the blood-aqueous and blood-vitreous barrier easily due to lipophilic nature.
Chloramphenicol

- Rarely prescribed in U.S. due to risks and safer options that are available.

- Side Effects:
  - Bone marrow depression by inhibiting mitochondrial protein synthesis which is reversible.
  - Aplastic anemia which is irreversible.
  - Gray Baby Syndrome

Clindamycin

- Inhibits protein synthesis by binding to a portion of the 50S ribosome subunit.

- Available IV, IM, and orally.

- Occasionally used in the treatment of Ocular Toxoplasmosis but not FDA approved.
  - Main use is in patients allergic to Sulfa drugs.

- High levels of side effects such as serious pseudomembranous colitis and superinfections.

Antibiotics affecting Folate Metabolism
Drugs Affecting Folate Metabolism

- Folic acid is required for synthesis of nucleic acid and proteins.
  - Human cells are capable of absorbing folic acid from food, but bacterial cells synthesize the folic acid.

- Three Main Medications Include:
  - Sulfonamides
  - Pyrimethamine
  - Trimethoprim

- Each of the three classes/drugs above is bacteriostatic in nature – however, if combined together can be bactericidal.

Medications that Interrupt Folate Metabolism

Sulfonamides

- 1st group of chemotherapeutic agents used for the treatment of bacterial infections.
  - All medications are structural analogs of para-aminobenzoic acid (PABA).

- Competitively inhibit the first step of folic acid synthesis.
  - Block the conversion of PABA into dihydrofolic acid.

- Examples Include:
  - Sulfacetamide (Topical)
  - Sulfamethoxazole
  - Sulfadiazine
  - Sulfisoxazole
Sulfonamides

- Originally had a broad spectrum of activity against both gram positive and gram negative, but now widespread resistance has occurred.

- These medications are well absorbed orally, but due to the resistance and side effect profile uses are limited.

Sulfonamides

- If allergic to one sulfonamide antibiotic, likely allergic to the entire class of medications.
  - No cross-sensitivity to trimethoprim or pyrimethamine.

- Most common adverse effects:
  - GI Disturbances
  - Photosensitivity

- Skin reactions such as rash are common and can be more severe to the point of Stevens Johnson Syndrome (even from topicals).

Sulfonamide Ocular Side Effects

- Induce Myopia
  - Occurs rarely and with or without inducing astigmatism.
  - Refractive Error returns to normal following discontinuation of the medication.
Sulfonamides

- Contraindications:
  - History of Hypersensitivity or Intolerance
  - Pregnancy at Term, Nursing Mothers, or infants < 2 months.
    - Promotes kernicterus by displacing bilirubin from plasma proteins.
  - Documented blood dyscrasias
    - Orals can cause hemolytic anemia, aplastic anemia, leukopenia, etc.
  - Caution should be taken in patients on oral hypoglycemic drugs or coumadin-type anticoagulants.

Trimethoprim and Pyrimethamine

- Reversibly inhibit the synthesis of folic acid by inhibiting the enzyme dihydrofolate reductase.
- Pyrimethamine is used in combination with sulfadiazine for the treatment of Toxoplasma gondii as well as for the prevention of malaria.
- Oral Trimethoprim is used mainly as 2nd line therapy for urinary tract infections.

Side Effects of Trimethoprim/Pyrimethamine

- Less frequent than with sulfonamides due to higher affinity for bacterial enzymes than human enzymes.
- Similar side effects of Folate Deficiency are possible.
  - Can cause blood dyscrasias – anemia, leukopenia, etc.
  - Do not use in patients with history of problems.
Trimethoprim

- Broad spectrum against gram + and some gram – bacteria.
  - 20 – 50X more potent than the sulfonamides.
  - Not effective against Pseudomonos.

- Available topically in solution combined with Polymyxin B.
  - Gives excellent coverage against H. influenzae and S. pneumoniae.

Trimethoprim/Sulfa Combinations

- Medications working together become bactericidal.
  - Combining the sulfonamides and trimethoprim or pyrimethamine creates a synergistic effect.
  - Causes sequential blockage of the pathway
  - Helps prevent resistance – Drug of Choice for many MRSA related infections.

- Combination of Sulfamethoxazole and Trimethoprim most commonly found.
  - Brand Names Include: Co-trimoxazole, Bactrim, and Septra

Ocular Use for Combination Treatment: Preseptal Cellulitis

- If patient is allergic to PCN’s and Cephalosporins
  - Bactrim or Bactrim DS (double strength tablets)
    - Bactrim DS: 160 mg trimethoprim/800 mg sulfamethoxazole
    - Bactrim: 80 mg trimethoprim/400 mg sulfamethoxazole.
    - Generic Suspension of 40 TMP/200 Sulfa/5 mL.

- Recommended Dosage:
  - Adults: 1 tablet Bactrim DS BID X 1 week
  - Children: 8–12 mg/kg/day Trimethoprim with 40 – 60 mg/kg/day Sulfa
Antibiotics affecting Bacterial DNA Synthesis

Drugs Affecting Bacterial DNA Synthesis

- Only Class of Medications: Fluoroquinolones
- Fluoroquinolones are synthetic derivatives of the quinolone nalidixic acid – created by adding a fluorine atom to the carbon ring.
- Bactericidal
- Concentration Dependent

Mechanism of Action for Fluoroquinolones

- Interfere with DNA synthesis by inhibiting DNA gyrase (topoisomerase II) and/or topoisomerase IV activity.
- Both gyrase and topoisomerase help maintain the superhelical structure of DNA during synthesis.
- Newer fluoroquinolones have a dual-binding mechanism of action.
  - Inhibit both DNA gyrase and topoisomerase IV in gram-positive species which prevents resistance from developing.
  - Must avoid overuse to help maintain efficacy.
Fluoroquinolones

- Divided into 4 generations, largely based on the indications for use.
- Broad spectrum against gram negative and gram positive bacteria.
- Ophthalmic use is largely reserved to topical therapy, despite good ocular penetration from systemic routes.

Oral Fluoroquinolones

- 1st Generation: Nalidixic Acid
  - Poor for systemic infections

- 2nd Generation: Ciprofloxacin, Ofloxacin, Norfloxacin, and Enoxacin
  - Used primarily in the treatment of UTI's, soft tissue infections, and chlamydia.

- 3rd Generation: Levofloxacin (Levaquin), Sparfloxacin, and Gemifloxacin
  - Used for UTI's, sinusitis, and respiratory infections such as bronchitis and pneumonia.

- 4th Generation: Moxifloxacin (Avelox)
  - "Respiratory Fluoroquinolones" - Used for sinusitis, pneumonia, chronic bronchitis, and skin infections.
    - Have improved effect against Pneumococci compared to Levofloxacin.
  - Gatifloxacin (Tequin) was removed from the market in 2006 for causing Hypoglycemia/Hyperglycemia.

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Oral Fluoroquinolones in Eye Care

- Levofloxacin and Moxifloxacin may be used for Preseptal Cellulitis (reserved for cases in which a patient cannot take the other available medications due to allergies, etc.)
- Dosage of Levaquin: 500 mg Daily X 10 days in Adults
- Dosage of Avelox: 400 mg Daily X 10 days in Adults
  - Moxifloxacin is eliminated primarily by non-renal mechanisms = Good for Renal Pts!

Fluoroquinolones Side Effects

- Well tolerated, but have high amount of SE’s in comparison to other commonly used oral antibiotics.
- GI Upset: Anorexia, Nausea, and Indigestion most common.
- CNS Reactions: Headaches, dizziness, mild tremor, or drowsiness.
- Neuropsychiatric Events such as psychosis, depression, and suicidal ideation.
- Phototoxicity Reactions, along with rashes and itching can occur.
- Liver Enzyme Abnormalities in 2 – 3% of patients.
- Arthropathy in weight-bearing joints.

Fluoroquinolones Side Effects

- Additional Side Effects:
  - Block cardiac potassium channels and cause QT prolongation.
  - Avoid use in patients with history of prolonged intervals, those taking medications to prolong, hypokalemia, patients taking anti-arrhythmics, and those with a history of heart attack or bradycardia.
Fluoroquinolones Side Effects

- **BLACK BOX WARNINGS:**
  - Tendonitis or Tendon Rupture in all ages
  - Increased risk >60 or taking corticosteroids.
  - Exacerbates weakness in patients with myasthenia

- Much like PCN's and Tetracyclines you need to warn patients of the possible decrease in efficacy of Birth Control Pills.

- Ocular SE's include: Corneal perforations, optic neuropathy, retinal hemorrhages and retinal detachments

Fluoroquinolone Contraindications

- Not recommended in children < 18 years of age or pregnant women due to side effects shown in animals (Category C).

- Absorption is reduced by antacids, iron, and zinc salts.

- Avoid in history of CNS disorders (due to adverse reactions such as convulsions occurring).

- Avoid in patients taking other medications that may cause QT prolongation such as Amiodarone.

- Avoid in history of hypersensitivity.

The Oral Drug Of Choice is...

- **Internal Hordeolum**
  - Common Choices:
    - 250 mg Dicloxacillin QID
    - 500 mg Keflex TID - QID
    - 250 mg Cefaclor TID
    - 100 mg Doxycycline BID
  - Additional Options:
    - Azithromycin Z-Pak
    - Bactrim DS (Sulfamethaxazole 800 mg/Trimethoprim 160 mg) BID
The Oral Drug Of Choice is...

- **Mild Preseptal Cellulitis or Dacryoadenitis**
  - Afebrile, systemically healthy adult (>40 kg typically)
    - Drug Of Choice:
      - Augmentin (Amoxicillin + Clavulanate): 500 mg TID or 875 mg BID
      - Cefdinir (Omnicef): 600 mg once daily
      - Cefpodoxime (Vantin): 200 mg BID
    - Additional Options:
      - Cephalexin (Keflex): 500 mg QID
      - Cefaclor (Generic Only): 250 mg TID
      - Azithromycin Z-Pak
      - Moxifloxacin (Avelox): 400 mg daily
      - Doxycycline: 100 mg BID
      - Bactrim DS (Sulfamethaxazole 800 mg/Trimethoprim 160 mg) BID

The Oral Drug of Choice Is...

- **Mild Preseptal Cellulitis, Dacryoadenitis, Dacryocystitis, or Canaliculitis**
  - Afebrile, systemically healthy child >5 and less than 40 kg
    - Drug of Choice:
      - Augmentin: 20 – 40 mg/kg/day in three divided doses
      - Cefpodoxime (Vantin): 10 mg/kg/day (MAX 400)
      - Cefdinir (Omnicef): 14 mg/kg/day (MAX 600)
    - Additional Options:
      - 20 – 40 mg/kg/day Cefaclor (Up to 1 gram) in three divided doses
      - 8 – 12 mg/kg/day Trimethoprim and 40 – 60 mg/kg/day Sulfa
      - 10 – 30 mg/kg/day Clindamycin

The Drug of Choice Is...

- **Chlamydia Treatment**
  - Azithromycin 1 g PO
  - Doxycycline 100 mg BID
  - Erythromycin 500 mg QID