OCULAR PHARMACOLOGY & THERAPEUTICS

Wills Review Course 2021
Daniel Lee, M.D.

I. Pharmacologic Principles

- Pharmacokinetics – The study of the absorption, distribution, metabolism, and excretion of a drug. The *lifecycle* of the drug.
- Pharmacodynamics – The study of the biological effects of drugs. The mechanism of action.
- Bioavailability – The ability of the drug to reach the target tissue.
- Toxicity – The adverse effects of a drug
    - Local
        - Type I hypersensitivity – IgE mediated
        - Type IV hypersensitivity – Cell-mediated
        - Preservatives
    - Systemic
        - Topical drops can bypass the first-pass mechanism in the liver
    - Preservatives
        - Can be toxic to the ocular surface
        - Enhances corneal permeability (increased bioavailability)
        - Quaternary cationic surfactants: benzalkonium chloride (BAK), benzododecinium bromide
        - Mercurial: thimerosal, chlorobutanol, parahydroxybenzanoates
        - Aromatic alcohols
- Age-related differences
    - Infants/Children
        - A reduced ability to eliminate medications
            - Low cytochrome P450 activity
            - Low glomerular filtration rate (GFR)
            - Low glucuronide levels - Aids in elimination of drug through urine or bile
    - Elderly
        - Less body mass
            - Less muscle, body water, albumin
            - Increased adipose tissue
            - Affects binding and distribution of drug
        - Reduced kidney function extends the half-life
            - Declining GFR
                - 20s: 116 mL/min/1.73m^2
                - 40s: 100 mL/min/1.73m^2
                - 70+: 75mL/min/1.73m^2

- How much medication is in each drop?
    - Converting % value to grams and milligrams

        - X% denotes X grams of medicine in 100mL of solvent
        - Example
            - Atropine 1% = 1g/100mL = 10 mg/1mL = 0.5 mg/50 ul (drop)
        - Simple approach → Add a "0" after the % value to get the mg/ml

II. Routes of Drug Delivery

- Delivery Routes (Outside – In)
    - Transcorneal/Transconjunctival
    - Subconjunctival
    - Subtenon
    - Intrastromal (cornea)
    - Intracameral
    - Intravitreal
    - Retrobulbar

- **Topical Administration: Eyedrops**
    - Concentration gradient from tear reservoir to cornea/conjunctiva drives passive absorption
    - 20% of a drop is retained in the eye
        - 10ul or a 50ul drop remains in the tear reservoir
    - Half of the medicine remains in the eye after 3-4 minutes
        - The turnover rate of topical medicine is ~15% per minute
- Patient methods to improve absorption (bioavailability) of topical drops
    - Allow at least 5 minutes between drops
    - Gently close the eye for 5 minutes
        - Prevents nasolacrimal pump action of blinking
    - Compress the nasolacrimal duct with pressure to the medial canthus
        - Reduce systemic absorption
        - If serious adverse event (asthma & beta blocker) is of concern avoid/discontinue
    - Drug delivery vehicles which prolong presence of drug on ocular surface
        - contact lens, collagen shield, inserts, etc.

- Barriers to drug delivery and absorption through the cornea
    - **There are several obstacles preventing drug from entering the eye**
    - Getting the drop on the eye
        - Medication non-adherence is prevalent (80%)
    - Keeping the medicine on the eye
        - Washout of medicines from reflex tearing or consecutive dosing
        - Small cul-de-sac
        - Tear turnover time
    - Bypassing the cornea
        - Hydrophobic and hydrophilic layers of the cornea
        - Adjusting the pH of a medicine can optimize the rate of drug penetration by changing the proportion of ionized and nonionic particles

        - "Burning" sensation with certain medications due to different pH than tear film (i.e. dorzolamide)
- Factors affecting the amount of medication penetrating the cornea
    - Concentration and solubility of drug
    - Viscosity
    - Lipid solubility
    - pH
    - Ionic and steric forms
    - Molecular size
    - Chemical structure and configuration
    - Vehicle
    - Surfactants (preservatives)
- Concentration and Solubility
    - Limits to raising concentration
    - Reflex tearing due to tonicity of medication
    - Drugs have solubility limits above which they precipitate out of solution
        - Presence of precipitate makes the drug a *suspension*
            - E.g. prednisolone acetate and brinzolamide
            - Shake the bottle to evenly distribute the medicine
        - Emulsions – The combination of two immiscible (poorly soluble) liquids
            - Emulsifying agents are required to keep them homogeneous
            - No shaking necessary
            - E.g. Cyclosporine and difluprednate
- Viscosity
    - Increasing viscosity by adding substances such as methylcellulose or polyvinyl alcohol increases drug retention and contact time
    - Ointments and gel-forming solutions
    - Common trade-off is often blurring and sticky sensation
- Lipid Solubility
    - More important than water solubility for corneal penetration
    - E.g. Latanoprost as a prodrug has 2-3x more lipophilicity than latanoprost acid and 25-40x increased corneal permeability
    - **Remember water is a polar molecule. Charged molecules are more water-soluble than uncharged molecules.
- pH
    - pH of tears = 7.4
    - Lower pH (acid) has higher concentration of hydrogen ions and have low lipid solubility. Higher pH are less ionized and more lipid-soluble.
    - The range of tolerability is narrow
    - Dorzolamide and Tropicamide are optimally effective at lower pH (common issue of burning)
- Surfactants (Preservatives)
    - Preservatives disrupt the cell membranes of bacteria and epithelium
        - Prevents bacterial contamination
        - Reduces barrier effect of the corneal epithelium

    - Preservative-free medications are in general less efficacious
- Reflex Tearing
    - pH and preservatives may cause irritation and tear washout of drugs.
    - Formulations have to be carefully selected
- In summary, there are many hurdles and challenges to achieving a therapeutic level of medicine while balancing tolerability and compliance.

- **Local Administration**
    - Ocular Barriers to Medicines
        - Epithelial barrier – Tight junctions between corneal epithelial/endothelial cells
        - Blood-ocular barrier
            - Vascular endothelium of the retina is non-fenestrated and are bound by tight junctions
            - Choroidal vessels are fenestrated but tight junctions at the retinal pigment epithelium (RPE) and non-pigmented epithelium serve as the barrier
            - Damage to blood-ocular barrier is manifested as aqueous flare on exam (protein leakage into aqueous)

    - Periocular Injection **-**Subconjunctiva/Sub-Tenon/Retrobulbar
        - Bypasses the ocular barriers
            - Especially for hydrophilic drugs (e.g. Penicillins) which have more difficulty bypassing the ocular surface
        - Acts as reservoir for slow release of medications
        - Delivery of medication closer to site of action
            - Sub-Tenon injection of steroid for macular edema
            - Subconjunctival injection of 5-FU or MMC after trabeculectomy
            - Retrobulbar injection of anesthesia or alcohol
    - Intraocular Injections
        - Tradeoff between systemic and ocular adverse effects
            - Toxicity to internal structures
            - Infection and inflammation risk
        - Primarily for intra-operative applications but much more common in office recently
        - Intracameral – Anterior chamber
        - Intravitreal – Vitreous cavity
            - Most common form of intraocular drug delivery
        - Post-cataract antibiotics – Cefuroxime, moxifloxacin, vancomycin
            - Hemorrhagic occlusive retinal vasculitis (HORV)
                - A very rare complication thought to occur after intracameral vancomycin
                    - Delayed onset of vision loss
                    - Retinal hemorrhage and non-perfusion

        - Tendency for venule and peripheral involvement
        - Mild anterior and vitreous cell
    - Toxic Anterior Segment Syndrome (TASS)
        - Autoclave contamination, preservative,s and excessively high drug concentrations
        - Exuberant inflammatory response seen early post-operative period

Table 15-1 Examples of Medications Delivered by Intracameral and Intravitreal Routes

Route of Administration	Clinical Application
Intracameral	
Antibiotics (eg, cefuroxime, moxifloxacin, vancomycin)	Prevent endophthalmitis in cataract surgery
Acetylcholine	Constrict pupil in intraocular surgery
Carbachol	Same as above
Balanced salt solution	Intraocular surgery, re-form anterior chamber
Ophthalmic viscosurgical devices (OVDs)	Same as above
Epinephrine (preservative- and bisulfite-free[a])	Dilate pupil in intraocular surgery
Phenylephrine 1%/ketorolac 0.3%	Maintain pupil dilatation in intraocular surgery (added to irrigation solution)
Lidocaine (preservative-free)	Intraocular surgery, anesthesia
Trypan blue	Stain anterior capsule in cataract surgery
Tissue plasminogen activator (tPA) (off-label use)	Assist fibrinolysis of fibrin in anterior chamber and subretinal hemorrhage
Intravitreal	
Anti–vascular endothelial growth factor	Choroidal neovascularization, diabetic retinopathy, diabetic macular edema, retinal vein occlusion
Corticosteroids (eg, triamcinolone acetonide; sustained-release intraocular implants such as dexamethasone in poly(lactic-*co*-glycolic acid) (PLGA) matrix and fluocinolone acetonide in a polyvinyl acetate/silicone laminate)	Cystoid macular edema, diabetic macular edema, retinal vein occlusion, posterior uveitis, postoperative inflammation
Foscarnet injection	Cytomegalovirus retinitis
Ganciclovir injection	Same as above
Silicone oil	Vitreoretinal surgery
Intraocular gases	Same as above
Perfluorocarbon	Same as above
Various antibiotics	Intraocular infection

[a] Preservative-free epinephrine with 0.1% bisulfite ampules of 1:1000 epinephrine can be safely injected intracamerally if it is diluted 1:4 with either balanced salt solution (BSS) or fortified BSS (BSS Plus).

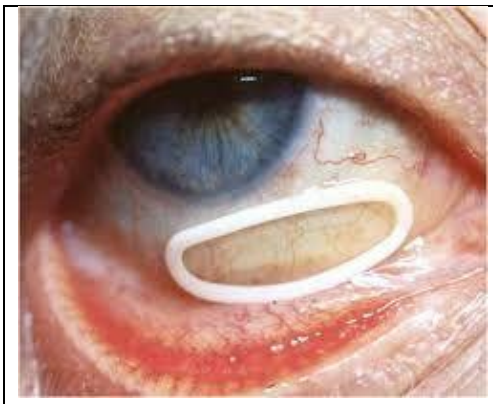
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III. Ocular drug design

- New medications employ several strategies to reduce toxicity and improve compliance
- Prodrugs
    - Ophthalmic prodrugs are relatively inactive forms of a drug molecule that facilitates passage into the eye and in some cases reduce ocular surface toxicity
        - Parent drug is conjugated with an ester or amide pro-moiety which are hydrolyzed by corneal esterase and amidases respectively

- Latanoprost → latanoprost acid
- Dipivefrin → epinephrin

- Liposomes
  - Small lipid vesicles composed of a phospholipid bilayer and aqueous core containing medications
  - Anterior – Improves residence time and permeability
  - Posterior – Improves intravitreal half-life
- Contact lens and Collagen Shields
  - Permeates with drug and increases residence time of medication
  - Used to promote healing of corneal ulcers
  - BAK becomes concentrated in soft contact lenses
- Sustained-release medications
    - Ocular inserts
      - Drug reservoir that allow for steady and sustained diffusion
      - Drawback: foreign body sensation
      - Pilocarpine (Ocusert, Alza Corp.) – 1970s
      - Bimatoprost (Forsight Vision5)
    - Intraocular Implants
      - Designed to circumvent the issue of repeated injections
      - Gancyclovir intravitreal implant -- *discontinued*
        - Surgically implanted
        - Cytomegalovirus (CMV) retinitis
        - 5-8 months
      - Fluocinolone acetonide implants
        - Retisert (0.59mg; 0.6-0.3ug/d)
          - Surgically implanted30-monthh duration
          - Noninfectious posterior uveitis
        - Iluvien (0.19mg; 0.2ug/d)
          - Intravitreal injection
          - 36 months
          - Diabetic macular edema
      - Dexamethasone (biodegradable)
        - Biodegradable
        - Ozurdex (0.7mg)
        - Polylactic-co-glycolic acid (PLGA) matrix loaded with dexamethasone
        - Degrades to lactic acid + glycolic acid + dexamethasone
      - Bimatoprost SR
        - FDA approved 2020
        - PLGA matrix
        - Injection into anterior chamber

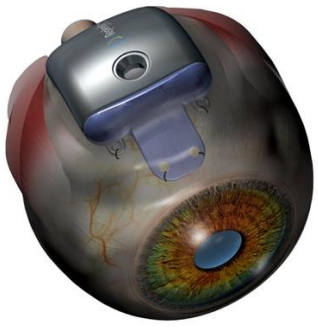


Pilocarpine ocular insert (Ocusert)

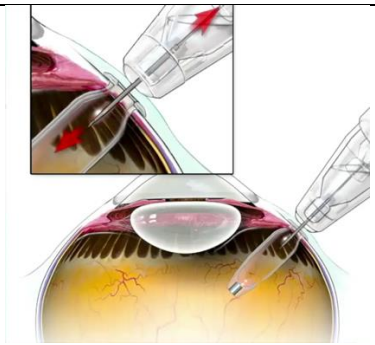


Bimatoprost ring (Forsight Vision5)

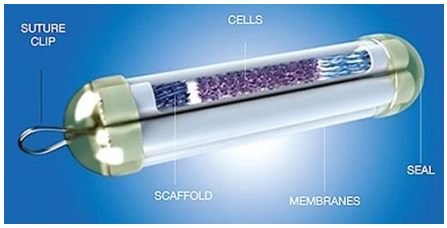
- Punctal-plug mediated delivery
  - Generally a polymeric core loaded with drug surrounded by impermeable shell
  - Open cap or permeable membrane for drug release into cul-de-sac
  - Dexamethasone (Dextenza, Ocular Therapeutix) for cataract surgery
  - Glaucoma applications currently under evaluation
- Encapsulated Cell Technology (ECT)
  - Surgical implant with genetically engineered cells in a permeable capsule which secretes therapeutic material into the vitreous
  - Cells are viable for several years
- Refillable Sustained Release
  - Microelectromechanical Systems (MEMS)
    - Delivery device implanted in a similar manner as tube shunts
    - Surgically implanted through the pars plana
    - Has a refillable subconjunctival reservoir, battery, and electrolysis chamber to deliver desired dose of medication
  - Port Delivery System
    - Permanently refillable implant
    - Non-inferior to monthly ranibizumab injections



Refillable MEMS (Replenish Inc.)



Port Delivery System (Genentech)



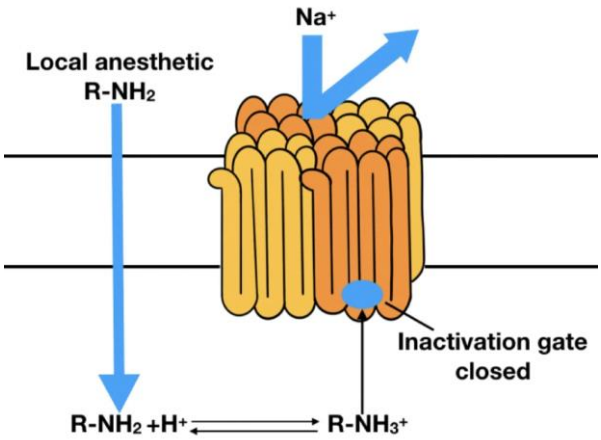
Encapsulated cell technology

IV. FDA Approval Process

- Phase 1
  - Involves a small cohort (20-80ppl) of healthy volunteers
  - Collecting toxicology and pharmacokinetic data on dosage range, absorption, and metabolism
- Phase 2
  - Randomized control trial (50-100ppl)
  - Determine safety and efficacy of drug
- Phase 3
  - Larger cohort (>100ppl)
  - Different populations, doses, combinations with other treatments, etc.
  - Outcomes serve as basis for labeling and New Drug Application (NDA)
- Off-label use
  - The use of drug for an indication that was not approved through the FDA process.
  - Many drugs are used off-label in ophthalmology
    - E.g. Bevacizumab (Avastin) for neovascular disease, doxycycline for ocular rosacea, glaucoma drops for angle-closure glaucoma, etc.
  - Often financial constraints prevent drug sponsors from seeking FDA approval for new indications

V. Local anesthetics

- An essential component of the ophthalmic exam and is extensively used in the office and OR.
- Prevents the generation of action potential by blocking transmembrane sodium channels
- Unmyelinated and short nerves are blocked more quickly
  - Action potentials are continuous in unmyelinated nerves and a small portion of nerve needs to disrupt the signal
  - Pupillary dilation after intracameral lidocaine → Shorter postganglionic fibers of parasympathetic system
- The pKa of local anesthetics is >7.4
  - Lipophilic anesthetics work better as they must traverse the cell membrane prior to inactivating the sodium channels
  - In the acidic environments (inflamed tissues), ionized form of drugs have increased difficulty penetrating lipid-rich cell membranes and myelin sheaths



Voltage-gated sodium channels are inactivated from the cytoplasmic side of the transmembrane protein

Topical Anesthesia (Drops)

- Never for home use
  - Inactivates superficial corneal microvilli
  - Inhibits mitosis and cellular migration
  - Results in significant corneal toxicity
- **Proparacaine 0.5%**
  - Onset - 15 seconds
  - Duration – 15-20 minutes
  - Cross-sensitization does not occur for those allergic to other anesthetics due to difference in molecular structure
  - Does not inhibit bacterial growth – May be preferable to use prior to obtaining cultures from a corneal ulcer
  - Least irritating and better tolerated than other topical anesthetics
- **Benoxinate 0.4% with Fluorescein**
  - Used primarily for tonometry
  - Onset & duration same as proparacaine
- **Tetracaine 0.5%**
  - Onset - 30 seconds
  - Duration - 20 minutes
- **Cocaine 1-4%**
  - No longer used due to risk of adverse effects and drug abuse
  - Sympathomimetic effect – Blocks reuptake of norepinephrine
    - Pupillary dilation and vasoconstriction
  - Toxicity

        - CNS stimulation, anxiety, convulsions, circulatory and respiratory collapse
        - Dose >1gm may be fatal
    - Test for Horner's Syndrome
- Longer acting anesthetics such as lidocaine and bupivacaine have a higher likelihood of corneal toxicity and is more often used for procedures

Local Injection

- Amide vs. ester anesthetics
    - Amide anesthetics are metabolized by the liver and not locally
    - Results in a longer residence time and less systemic toxicity
    - Ester anesthetics are metabolized by local serum cholinesterases as well as the liver
        - Toxicity may occur in lower doses in patients on anti-cholinesterase medications such as echothiophate (irreversible inhibitor)

Amide linkage	Ester linkage
Lidocaine Mepivacaine Bupivacaine Etidocaine	Cocaine Proparacaine Procaine (Novocaine) Tetracaine

- **Lidocaine 1-4%**
    - Onset – 1 minute
    - Duration – 45-60 minutes
    - Maximum tolerated dose – 500mg
        - Do not exceed 50ml at 1%
    - Toxicity – Decrease BP, cardiac arrhythmia, nausea/vomiting, respiratory depression
- **Mepivacaine 1-3% (Carbocaine)**
    - Onset – Faster than lidocaine
    - Duration – 2 hours
    - Maximum safe dose 25ml at 2%
- **Bupivacaine 0.25-0.75% (Marcaine)**
    - Onset – Slower than lidocaine
    - Duration – 8 hours
    - Maximum safe dose 25ml at 0.75%
- **Hyaluronidase (Wydase)**
    - Mucopolysaccharide enzyme
    - Promotes better diffusion of anesthesia providing better sensory and motor blockade
    - Limits posterior pressure from the orbit
        - Post-op hypotony may be accentuated
    - Duration of local anesthesia is shortened due to increased diffusion of medication from site of injection

- Retrobulbar and Peribulbar Anesthesia
    - Typically Lidocaine + Bupivacaine +/- Hyaluronidase
        - Lidocaine provides rapid anesthesia
        - Bupivacaine provides prolonged anesthesia
    - Draw back on plunger before injecting
        - Heme – Possible intravascular entry
            - Intra-arterial injection may cause rapid onset seizures
        - Clear fluid (CSF) – Possible subdural entry
            - Respiratory depression (apnea) and cranial nerve palsies

VI. General Anesthesitics (GA)

- All systemic agents cause a reduction in intraocular pressure
- **Ketamine, Succinylcholine, and nitric oxide** may potentially increase IOP
- **Succinylcholine**
    - Neuromuscular blocking agent that facilitates intubation during GA
    - Competitively binds to nicotinic receptor
    - Causes initial receptor depolarization and extraocular muscle contraction
        - Risk of short-term increase in IOP and extrusion of ocular contents in setting of open globe
    - Contraindicated in patients on phospholine iodide (irreversible cholinesterase inhibitor) due to prolonged respiratory paralysis

Malignant Hyperthermia

- 50% Autosomal Dominant and 50% de novo mutation
- 1:2000 have genetic markers but variable expressivity and penetrance
    - Mutation on ryanodine receptors on skeletal muscle sarcoplasmic reticulum
- 1:100,000 adult and 1:30,000 pediatric cases
- Hypermetabolic activity of skeletal muscles after exposure to a triggering agent
    - Triggering agents: Halogenated gases and succinylcholine
- Sharp increase in unbound Ca^{2++} from sarcoplasmic reticulum leading to sustained muscle contracture
- Hyperthermia from increased metabolic rate
- Lactic metabolic acidosis → Rhabdomyolysis → Hyperkalemia + Myoglobinuria → Acute renal failure
- Early signs: Tachycardia and end-tidal carbon dioxide level
- Other signs: Labile BP, tachypnea, sweating, muscle rigidity, blotchy discoloration of skin, cyanosis, dark urine, hyperthermia (late finding)
- Disseminated intravascular coagulation and death
- Treatment
    - Stop triggering medicine
    - Hyperventilate, high flow 100% O_2
    - Administer Dantrolene 2.5-10mg/kg
        - Prevents calcium release from SR
        - Reduces mortality rate from 80% to 5%

        - Avoid calcium channel blockers – hyperkalemia and myocardial depression
    - Administer sodium bicarb 1-2mEq/kg
        - Controls acidosis and hyperkalemia
    - Cool down patient with Ice baths, IV iced saline
    - Insulin may be given to control hyperkalemia



VII. Cholinergic Drugs

- Acetylcholine (ACh) receptors are found throughout the somatic and autonomic nervous system
    - ACh is provided by preganglionic neurons in both sympathetic and parasympathetic nerves
    - Released by postganglionic parasympathetic nerves and somatic nerves
- Two types of acetylcholine receptors: Nicotinic and Muscarinic
- Muscarinic receptors are at end organs of parasympathetic nervous system
- Nicotinic receptors are on postganglionic neurons of both sympathetic and parasympathetic nerves, adrenal medulla, and striated muscle.

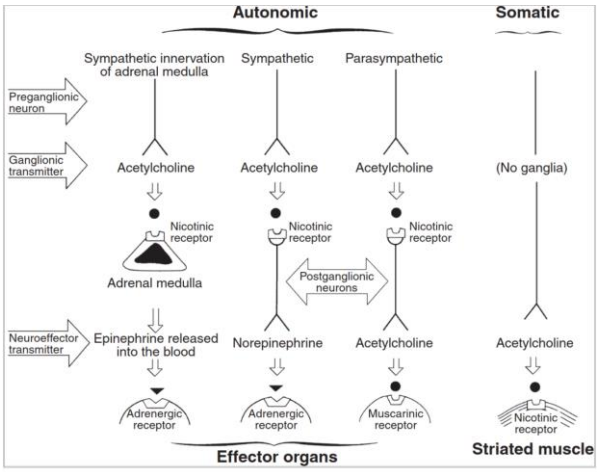


Figure 16-1 Summary of the neurotransmitters released and the types of receptors found within the autonomic and somatic nervous systems. *(Reproduced with permission from Mycek MJ, Harvey RA, Champe PC, eds. Pharmacology. 2nd ed. Lippincott's Illustrated Reviews. Philadelphia: Lippincott-Raven; 1997:32.)*

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- Three types of cholinergic drugs:
    - Direct agonists – Acts on receptor to elicit an excitatory response
    - Indirect agonists – Increases endogenous levels by blocking acetylcholinesterase
    - Antagonists – Block action at the receptor

Muscarinic Drugs

- Direct agonist
    - Three actions
        1. Contraction of iris sphincter (miosis)
        2. Contraction of circular fibers of ciliary muscle (accommodation)
        3. Contraction of longitudinal fibers (lowers IOP)
    - **Acetylcholine 1% (miochol)**
        - Intracameral use – broken down by corneal cholinesterases
        - Duration: 10 minutes
    - **Carbachol 0.01% (miostat)**
        - Resistant to cholinesterases
        - Duration: 24 hours
        - 100X more potent and longer lasting
        - Lowers IOP better
    - **Carbachol 1.5%, 3% (Isopto carbachol)**
        - Topical use for glaucoma – same mechanism as pilocarpine
    - **Pilocarpine 0.25-4%**
        - Up to 4x/day; was available as extended-release ocular insert (Ocusert)
        - Lowers IOP: Tightening of the longitudinal fibers of the ciliary muscle stretches of the trabecular meshwork → Improves outflow facility
            - Tension on peripheral retina can lead to retinal tears and detachments
        - Its use in angle closure glaucomas are controversial

        - Low conc. – Reduces crowding at the angle by tightening iris
        - Higher conc. (>2%) - Anterior movement of lens-iris diaphragm may worsen angle closure
    - Decreases uveoscleral outflow
    - Increased permeability of blood-aqueous barrier
        - Increased post-operative inflammation
  - Adverse effects of cholinergics
    - Ocular: Miosis, nyctalopia, cataracts, induced myopia, induced accommodation, retinal detachment, uveitis, iris cysts (echothiophate)
    - Systemic:
        - SLUDGE (Salivation, Lacrimation, Urination, Defecation, GI distress, Emesis)
        - Bronchiolar spams, pulmonary edema
        - Bradycardia
        - Can make Parkinson's symptoms worse (more ACh than Dopa)
  - Treatment for cholinergic toxicity/overdose
    - Atropine
    - Pralidoxime (Protopam, P2AM)
        - Separates anti-AChE drug from bound cholinesterase
- Indirect agonists
  - Longer duration and more potent than direct agonists
  - Inhibits cholinesterase
  - Irreversible inhibitors
    - **Echothiophate 0.03-0.25% (Phospholine Iodide)**
        - Phosphorylates acetylcholinesterase and forms a stable bond
        - Iris cysts at pupillary margin noted in children
            - Concomitant phenylephrine reduces severity
        - Can treat lice infestation of lashes with echothiophate – organophosphates are used as pesticides
    - RISK with local and systemic anesthesia with use of irreversible AChE inhibitors
        - Ester anesthetics (i.e. procaine) are normally inactivated by plasma cholinesterases
        - Succinylcholine (competitively binds to ACh receptor) will not be metabolized leading to prolonged respiratory paralysis
  - Reversible inhibitors
    - **Physostigmine 0.25%, 0.5% gtt**
    - **Physostigmine 1-4mg subQ and IV**
        - Temporarily inactivates cholinesterase
        - Miosis for 12-36hrs
        - Very potent. Risk of toxic effects with high frequency and dose.

        - Used as antidote to anticholinergic overdose
    - **Neostigmine and Edrophonium** – See Nicotinic agonists
- Antagonists
    - Competitively blocks effect of ACh at muscarinic receptors
    - Iris sphincter is paralyzed and dilator muscle is unopposed causing pupillary dilation (*mydriasis*)
    - Ciliary muscles are paralyzed and loss of accommodation (*cycloplegia*)
    - Used in setting of anterior uveitis
        - Reduces contact between posterior iris and anterior capsule to prevent formation of *posterior synechiae*
        - Reduces permeability of the blood-aqueous barrier
        - Paralyzes ciliary muscle – helps relieve pain from iridocyclitis
    - Inhibits accommodation for refraction in children
    - Treats malignant glaucoma
    - Moves lens-iris diaphragm posteriorly
    - Increased IOP especially in POAG patients (opposite effect of pilocarpine)
    - Systemic Adverse Effects
        - Fever, flushing, tachycardia, constipation, urinary retention, reduced sweating, dry mouth, delirium
        - "Hot as a hare, red as a beet, dry as a bone, blind as a bat, mad as a hatter"
        - Fatal dose ~100mg in adult and ~10mg in child
        - Physostigmine is used to treat for anticholinergic poisoning

	Onset	Duration
Atropine	45-120 min	7-14 days
Scopolamine	30-60 min	4-7 days
Homatropine	30-60 min	4-7 days
Cyclopentolate	30-60 min	1-2 days
Tropicamide	20-40 min	4-6 hours

Nicotinic Drugs

- Indirect-acting agonists
    - **Edrophonium**
        - Short-acting inhibitor of muscarinic receptors (see above) but also inhibits nicotinic receptors at higher doses
        - Used to diagnose myasthenia gravis – Autoimmunity to Nicotinic ACh receptors in the neuromuscular junction
        - Watch out for muscarinic adverse effects
            - SLUDGE Mnemonic
            - Keep Atropine around for reversal of medication
- Antagonists
    - Neuromuscular blocking agents typically used to aid in intubation during general anesthesia
        - Non-depolarizing agents
            - **Rocuronium, vecuronium, and pancuronium**

        - Bind to nicotinic receptors on striated muscles but DO NOT cause contraction
    - Depolarizing agents
        - **Succinylcholine and decamethonium**
        - Causes initial muscle contraction prior to relaxation
        - Muscle fibers with multiple innervation may have a sustained contraction
            - 20% of extraocular muscles (EOM) are multiply innervated
            - EOM contraction may cause expulsion of intraocular contents in open globe scenarios
            - Same mechanism also increases IOP

VIII. Adrenergic Drugs

- Adrenoreceptors

α1	α2	β1	β2	β3
Smooth muscle contraction - Vasoconstriction - ↑Peripheral resistance - ↑Blood pressure - Mydriasis	Feedback inhibition of presynaptic nerve - Inhibition of norepinephrine and release of norepinephrine	Stimulates the heart - ↑Heartrate - ↑Myocardial contractility - Lipolysis	Relaxes smooth muscle - Vasodilation - ↓Peripheral resistance - Bronchodilation - ↑Glycogenolysis - ↑Release of glucagon	Lipolysis

Alpha-adrenergic Drugs

- Direct-acting α1-agonists
    - Main role is to dilate the pupil by stimulating iris dilator muscle
    - **Phenylephrine 2.5%, 10%**
        - Dilation with phenylephrine alone can be overcome by pupillary light reflex → iris sphincter is stronger than iris dilator
        - Systemic adverse effects
            - Increase BP, stroke, myocardial infarction, cardiac arrest
            - Use with caution in patients with increased sensitivity to α-agonists
                - Orthostatic hypotension
                - Medications: TCA, cocaine, MAO inhibitors
    - **Omidria (phenylephrine 1%/ketorolac 0.3%)**
        - Intracameral use during cataract surgery
        - Added to irrigating solution
        - Particularly helpful in setting of floppy iris syndrome

- Direct-acting α2-agonists
    - **Apraclonidine 0.5%, 1% (**α2>α1)
        - Derivative of clonidine
        - Blocks norepinephrine release at presynaptic nerve terminals
        - Lowers IOP by decreasing aqueous production and reducing episcleral venous pressure but tachyphylaxis over time
        - Prevents IOP spikes following laser procedures (iridotomy, trabeculoplasty, capsulotomy) and cataract surgery
        - High rate of topical sensitivity
            - Follicular conjunctivitis occurs in 40%
            - Suited well for short-term use
        - Used to diagnose Horner's syndrome
            - Apraclonidine is a weak α1 agonist and under normal conditions has no effect on pupil dilation
            - Denervation hypersensitivity to α1 results in dilation in setting of Horner's
    - **Brimonidine tartrate 0.1-0.2% (selective α2)**
        - Less tachyphylaxis than apraclonidine
        - 15% incidence of follicular conjunctivitis
            - Low cross-sensitivity in patients with known hypersensitivity with apraclonidine
        - Decreases aqueous production and increases uveoscleral outflow
        - Possible neuroprotective effect to optic nerve and retina
        - More lipophilic and may cause sedation due to central α2 receptors
        - <u>Contraindicated in infants and children younger than 6yrs</u>
            - May lead to somnolence/coma, hypotension, bradycardia, and hypothermia
        - Pregnancy CLASS B (other glaucoma meds are CLASS C)
    - **Brimonidine tartrate 0.1, 0.15% with Purite (Alphagan P)**
        - BAK 0.004% replaced with Purite 0.003%
        - 40% less conjunctivitis compared to Brimonidine 0.2%
- Indirect-acting adrenergic agonists
    - **Cocaine 1-4% and Hydroxyamphetamine 1%**
    - Test for Horner's – Refer to Neuro-Ophthalmology
- Antagonists
    - **Thymoxamine 0.5% and Dapiprazole 0.5%**
        - Competitively binds against alpha-receptors vs. norepinephrine
        - Constricts pupil without affecting ciliary body
        - No change in aqueous production and IOP
        - No change in accommodation
        - Uses:
            - Reverses phenylephrine mydriasis
            - Treat angle closure
            - Lid retraction from thyroid eye disease

Beta-adrenergic drugs

- β2 Agonists

- **Epinephrine – Nonselective α&β agonist**
  - Increased outflow facility at the trabecular meshwork
  - Increases intracellular cAMP
  - Adrenochromes – Dark colored conjunctival deposits – Oxidized epinephrine
  - Tachyphylaxis – Downregulation of β receptors with chronic use
- **Dipivefrin (Propine)**
  - Pro-drug of epinephrine
  - 17-fold improved penetration
  - Reduced incidence of optical side FX
  - Note: Echothiophate (AChE inhibitor) blocks corneal esterases that converts dipivefrin to epinephrine

- β-Antagonists (β-blockers)
  - Reduced aqueous humor production
  - Tachyphylaxis
    - 47% reduction in aqueous production in 1 week vs. 25% at 1 year
  - Low allergy rate <5%
  - No effect on IOP and aqueous production during sleep
    - Aqueous production at basal levels overnight
  - Contraindications
    - Asthma, pulmonary disease
    - OK to use in CHF (unless severe disease)
    - Bradycardia, arrhythmias
  - Toxicity
    - Depression, decreased HR, decreased forced expiratory volume (FEV)
    - Anxiety, confusion, impotence, hair loss
    - Exacerbates myasthenia gravis
    - Altered response to hypoglycemic episodes
    - Adversely effects lipid profiles (↑LDL, ↓HDL)
  - Nonselective β1/β2-antagonists
    - **Timolol 0.25, 0.5%**
      - Available in gel which increases cul-de-sac residence time and reduces systemic absorption
    - **Levobunolol 0.25, 0.5%**
    - **Metipranolol 0.3%**
    - **Carteolol 1%**
      - Has intrinsic sympathomimetic activity
      - Tempers cardiovascular and respiratory effects
        - Less reduction in HR and BP
        - Still avoid in presence of
      - Less of an effect on cholesterol levels
  - Selective β1-antagonist
    - **Betaxolol 0.5% soln, 0.25% susp**
      - 85% as effective as timolol at lowering IOP

IX. Carbonic Anhydrase Inhibitors (CAIs)

$$CO2 + H2O \underset{C.A.}{\rightleftharpoons} H+ + HCO3-$$

- Carbonic anhydrase (CA) is an enzyme that catalyze the interconversion of carbon dioxide and water and bicarbonate (HCO_3^-) and hydrogen ions
- CA is present in pigmented and non-pigmented epithelium of the ciliary body
    - 33% reduction in aqueous production
    - Hypotensive action is <u>not</u> due to diuretic action
- Used for the treatment of glaucoma, idiopathic intracranial hypertension (IIH), and macular edema (i.e. retinitis pigmentosa)
- 99% of CA activity must be inhibited for clinical effect
    - The amount of CA enzyme present is 100x higher than required
- Renal metabolic acidosis
    - Thought to contribute to reduction in IOP
        - Unclear mechanism – Likely related to effects on Na+/K+ ATPase
    - May exacerbate sickle cell crisis and diabetic ketoacidosis
    - Worsened in setting of COPD due to reduced ability to expel CO_2
- Hypokalemia
    - Check metabolic panel at regular intervals with primary care physician
    - Higher risk in patients using other diuretics, steroids or ACTH
    - Potentially deadly arrhythmias in patients using digitalis
- Kidney stones
    - 11x increased incidence compared to those not using oral CAIs
    - Due to pH changes and decreased citrate excretion
    - Typically occurs within the first year of therapy
    - History of renal stone >5 years ago not associated with increased risk of recurrence
- CNS and GI side effects (Most common side effect; ~50% affected)
    - Numbness and tingling (paresthesias) of hands, feet and lips
    - Metallic taste with carbonated drinks
    - Nausea
    - Somnolence and depression
- Adverse effects associated with sulfonamides
    - Rash, Steven Johnson's Syndrome
    - Transient myopia (shallowed AC due to ciliary body swelling)
    - Thrombocytopenia
    - Aplastic anemia (very rare)

- Systemic CAIs
    - **Acetazolamide 125, 250, 500mg**
        - Onset of action 1-2 hours
        - Duration 8-12 hours
        - 500mg extended release (E.R.) lasts 18-24 hours

- **Methazolamide 25, 50mg**
  - Duration 10-18 hours
  - More lipid soluble so lower doses required
  - Metabolized in the liver (unlike acetazolamide)
  - Less effective for IOP lowering but lower rate of renal stones
- Topical CAIs
  - IOP reduced by ~15%
    - Effect potentiated in combination with prostaglandin analog
  - Systemic effects of sulfonamides rarely seen in topical medications
    - Use of topical CAIs in sulfa allergic patients is a controversial topic
  - Likely no additive effect in combination with oral CAI
  - May worsen condition in setting of compromised corneal endothelium
  - **Dorzolamide 2% soln.**
    - 33% experiencing burning sensation
      - pH ~5.6 – Optimized for ocular penetration
      - Less efficacious at physiologic pH
  - **Brinzolamide 1% susp.**
    - Less burning compared to dorzolamide
      - pH ~7.5 – Closer to physiologic levels
    - Blurring of vision due to opacity of suspension

X. Prostaglandin Analogs (PGA)

- Currently first-line drop for glaucoma
  - Favorable safety profile and efficacy
  - Once daily dosing – Superior diurnal control of IOP compared to timolol
  - Approximately 1/3 of patients will require a second drop within first year
- PGF_{2a} reacts with FP receptors
- Increases uveoscleral outflow and conventional outflow to a smaller degree
- Upregulates MMP-9 (matrix metalloproteinase) and promotes remodeling of the extracellular matrix
  - Increased intermuscular space in ciliary body muscles
  - Trabecular meshwork remodeling with improved outflow facility (controversial)
- Adverse Effects
  - Red eye (most common)
  - Hypertrichosis
  - Darkening of iris color (*irreversible) and extraocular skin
    - Increased number of melanosomes within melanocytes
    - Hypertrophy of melanocytes <u>not hyperplasia</u>
    - More common is “mid-toned” irises → Medium brown, hazel, and green
  - Periocular fat atrophy
  - CME
    - Pseudophakic and aphakic patients
    - Pre-existing conditions such as RVO, diabetes, etc.

    - Uveitis
    - Pregnancy Category C – PG may cause uterine contraction
- Relative lack of systemic side effects
- Prodrug PGAs
    - Becomes biologically active after being hydrolyzed by corneal esterases
    - **Latanoprost 0.005%** -- Available with mild preservative Potassium sorbate (Xelpros)
    - **Travoprost 0.004%** -- Available with mild preservative SofZia (Travatan Z)
    - **Tafluprost 0.0015%** -- Preservative free (Zioptan)
- **Bimatoprost 0.01%, 0.03%**
    - Not a prodrug – More lipid soluble
    - Interacts with prostamide receptor
    - Possibly greater effect on TM outflow compared to others

XI. New Glaucoma Drops

Nitric Oxide (NO) Donors

- NO is a ubiquitous signaling molecule
- Relaxes juxtacalanicular TM improving outflow facility
- **Latanoprostene bunod 0.024% (LBN; Vyzulta)**
    - NO donating moiety attached to latanoprost
    - LBN is cleaved by corneal esterases to latanoprost and butenediol mononitrate
    - Two mechanisms of action
        - ↑Uveoscleral outflow (latanoprost)
        - ↑Conventional outflow (NO)
    - 1.2mmHg more reduction of IOP compared to latanoprost (Phase II)
- NO donating moieties attached to other PGA, beta blockers and CAIs are being investigated

Rho Kinase (ROCK) Inhibitors

- **Ripasudil 0.4%**
    - Approved in Japan in 2014 – Not available in US
    - BID dosing
- **Netarsudil 0.02% (Rhopressa)**
    - Daily dosing
- ROCK plays a role in smooth muscle contraction, cell migration and cell survival by regulating stress fiber formation
- Multiple mechanisms of IOP reduction
    - Relaxes trabecular meshwork to increase conventional outflow
    - Reduces aqueous production through inhibition of norepinephrine transporter inhibition
    - Decreases episcleral venous pressure
- Other potential indications (Mostly pre-clinical studies)
    - Increased blood flow through vascular endothelial smooth muscle relaxation

    - Neuroprotective for retinal ganglion cells (RGC)
    - Reduce scarring after glaucoma surgery by inhibiting collagen deposition and blocking production and contraction of stress fibers
    - Promotion of corneal endothelial cell proliferation
- Adverse effects
    - Hyperemia (53%)
    - Corneal verticillata (20%)
    - Petechial subconjunctival hemorrhage
    - Irritation
    - Blurred vision

XII. Fixed-Combination Glaucoma Medications

- Medications of different classes are being combined in a single bottle
- Increasingly becoming second-line treatments of choice
    - Improved compliance due to increased convenience, efficacy, and potentially costs

Generic	Trade
Dorzolamide-Timolol	Cosopt
Brimonidine-Timolol	Combigan
Brimonidine -Brinzolamide	Simbrinza
Netarsudil-Latanoprost	Rocklatan

XIII. Osmotic Drugs

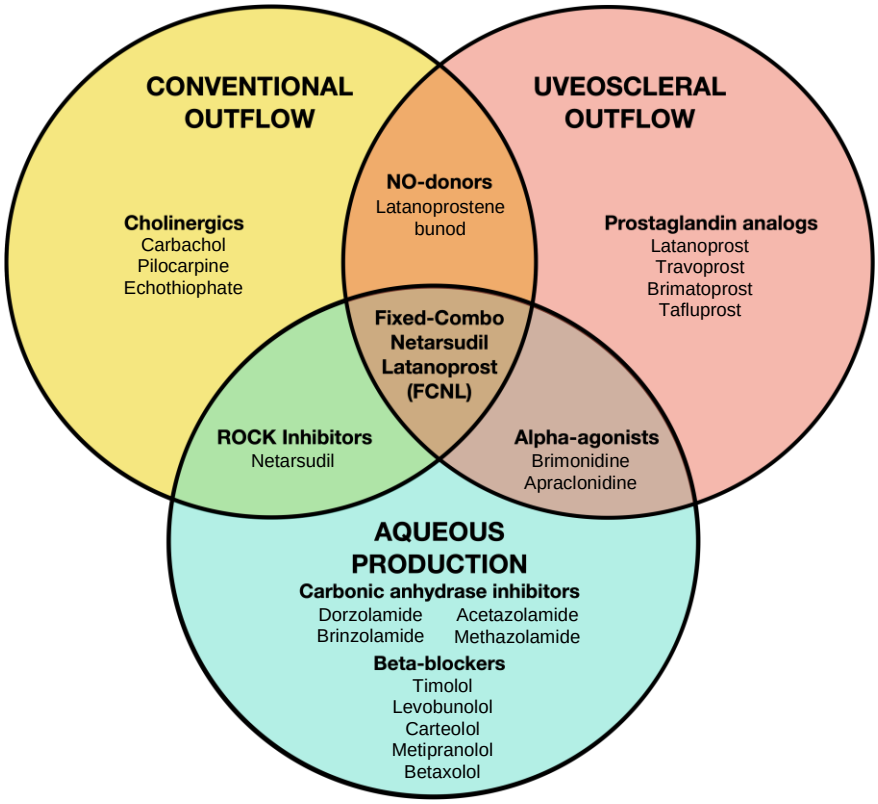
- Increase in serum oslmolarity draws fluid from the eye through vascular barriers of the eye
- Approved for short-term management of acute glaucoma
- Also used to reduce vitreous volume prior to surgery
- Increased cardiovascular load due to expansion of plasma volume
    - Use with caution in patients with CHF and/or recent MI
- **Intravenous route**
    - **Mannitol**
        - Cannot be absorbed through GI tract
        - Dose: 0.5-2mg/kg
        - Drip – 20% (200mg/ml) over 30-60 minutes
        - IV Push – 25% solution injected over 3-5 minutes
        - Onset: 20-60 minutes; Duration: 6 hours
        - Rapid infusion may lead to shift of intracellular water to extracellular space leading to:
            - Hyponatremia
            - Cardiovascular overload
            - CHF
            - Pulmonary edema
            - Intracranial bleeding – Subarachnoid hemorrhage
    - **Urea**

        - Rapid onset of action
        - Not commonly used anymore
            - Tissue necrosis with extravasation
            - Rebounding IOP
                - Reversal of osmotic gradient after kidneys clear the excess urea
    - Be aware that Mannitol and Urea cause increased diuresis/urine output when using peri-operatively

- **Oral route**
    - **Glycerin**
        - 50% No longer available in the U.S. but can be diluted from 100% solution
        - Serve with crushed ice to mitigate overwhelmingly sweet taste
        - Hyperglycemia is a concern especially for diabetics
            - **Isosorbide** was preferred option for diabetics but no loner available

XIV. Overview of Glaucoma Medications

- Based on current understanding, IOP is determined by the rate of aqueous production (the loading force) and overall resistance to outflow generated by the conventional and uveoscleral outflow systems.
- All glaucoma treatments exert an effect on one or more of these components.



XV. Anti-Inflammatory Drugs

Glucocorticoids

- Corticosteroids are administered topically, injected locally, and systemically
- Controls early and late tissue effects of inflammation
    - Early: Reduces hyperthermia, hyperemia, edema, and pain
    - Late: Capillary proliferation, fibroblast proliferation, collagen deposition, and scarring
- Inhibits arachidonic acid release from phospholipids which is a potent mediator of inflammation
- Inhibits degranulation of mast cells, basophils and neutrophils
- Suppresses lymphocyte proliferation and macrophage movement
- Acetate vs. Alcohol vs. Phosphate
    - Biphasic compounds such as acetate and alcohol penetrate cornea better than phosphates
    - Prednisolone acetate > Prednisolone phosphate

Table 16-15 Comparison of Anti-inflammatory[a] and IOP-Elevating[b] Potencies

Glucocorticoid	Relative Potency	Rise in IOP, mm Hg
Dexamethasone, 0.1% (equivalent to betamethasone, 0.1%, less than or equivalent to difluprednate, 0.05%)	24.0	22
Fluorometholone, 0.1%[c]	21.0	6
Prednisolone acetate, 1%	2.3	10
Medrysone, 1%[d]	1.7	1
Tetrahydrotriamcinolone, 0.25%	1.4	2
Hydrocortisone, 0.5%	1.0	3

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- Adverse effects
    - Ocular
        - Ocular hypertension/glaucoma
        - Posterior subcapsular cataract
        - Exacerbation of infections (bacterial/viral/fungal)
        - Ptosis
        - Mydriasis
        - Scleral/corneal melting
        - Skin atrophy (also conjunctival atrophy)
        - Central serous chorioretinopathy
    - Systemic
        - Adrenal insufficiency (suppression of pit-adrenal axis)
        - Gluconeogenesis leads to:

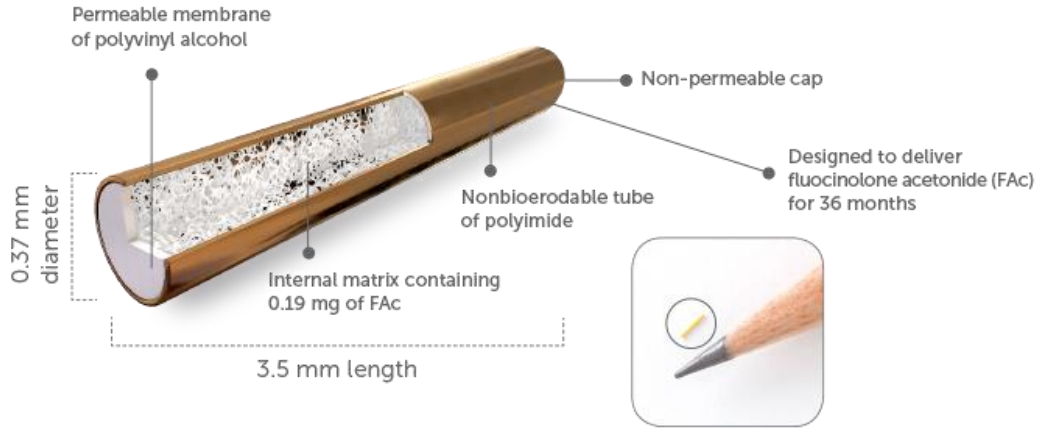
                - Hyperglycemia
                - Osteoporosis
                - Muscle wasting
            - Fat redistribution from periphery to trunk
            - Aseptic necrosis of hip
            - Peptic ulcer
            - Worsens diabetes and hypertension
            - Hirsutism
            - Euphoria, insomnia, psychosis
    - Steroid induced IOP elevation
        - Deposition of extracellular matrix materials (glycosaminoglycans) in the trabecular meshwork
        - Long-term use (>1 year) may be irreversible
        - In general, higher the potency, higher the risk of steroid response
        - Higher risk of steroid response:
            - History of glaucoma
            - Glaucoma risk factors (ocular trauma, family history, etc.)
            - Myopia
            - Type I diabetics
            - Children especially 4-6 years of age
            - Fuch's, keratoconus, history of PK
- **Rimexolone 1%**
    - Lower incidence of elevated IOP
- **Loteprednol etabonate 0.2%, 0.38%, 0.5%**
    - 0.2% (Alrex) is indicated for allergic conjunctivitis
    - 0.5% (Lotemax) has a low incidence of significantly elevated IOP when used in steroid responders
        - Available as gel drop or ointment (preservative free)
- **Difluprednate 0.05%**
    - Emulsion (no need to shake bottle)
    - Addition of fluorine atoms and ester groups
        - Improved receptor affinity
        - Improved corneal penetration
    - Most potent topical steroid drop
- **Triamcinolone 40mg/ml (preservative free)**
    - Useful for macular edema secondary to diabetes, RVO, and inflammation
    - IOP rise seen in 50% with increase in IOP >30%
    - Most IOP increases can be managed with medications
        - 1% require glaucoma surgery
    - Cataract progression is seen more frequently in those with IOP rise
    - Pseudo-hypopyon with triamcinolone crystals setting inferior AC
    - Effect may last >6 months with intravitreal injection
    - Helpful for intraoperative visualization of the vitreous and aids with membrane peeling during macular hole repairs
- **Fluocinolone acetonide**
    - Available as intraocular implants

- High cataract and glaucoma rate
- 0.59mg (Retisert) – Surgically placed in the pars plana region
    - Indicated for non-infectious posterior uveitis
    - Releases steroid at 0.6ug/d initially and reaches 0.3-0.4ug/day steady state
    - Lasts 30 months



Fluocinolone 0.59mg (Retisert)

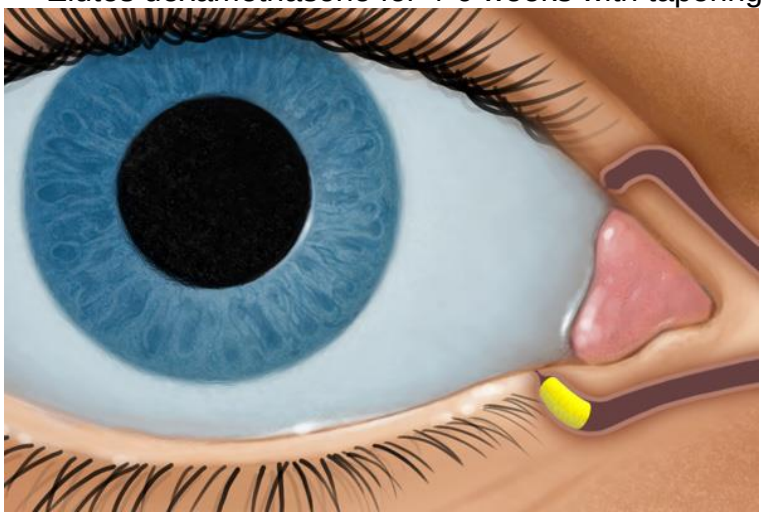
- 0.19mg (Iluvien)
    - Non-biodegradable
    - Approved for the treatment of diabetic macular edema
    - 0.2 ug/d and lasts for 36 months



Fluocinolone 0.19mg (Iluvien)

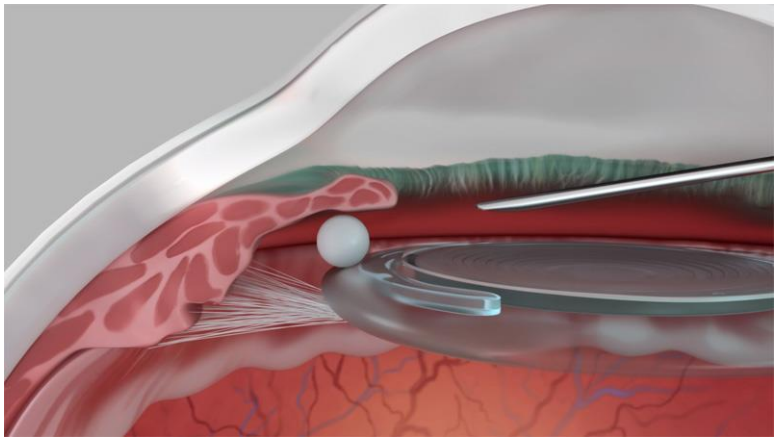
- **Dexamethasone**
    - **0.7mg (Ozurdex)**
        - Biodegradable polymer which slowly releases medicine for 6 months
        - Approved for macular edema secondary to CRVO, diabetic macular edema, and non-infectious uveitis

- **0.4mg ophthalmic insert (Dextenza)**
  - Approved for post-operative inflammation
  - Punctal plug made of hydrogel polymer
  - Elutes dexamethasone for 4-6 weeks with tapering effect



Dexamethasone 0.4mg (Dextenza)

- **Dexamethasone ophthalmic suspension 9% (Dexycu)**
  - Approved for post-operative inflammation
  - Injected in posterior chamber following cataract surgery
  - Self organizes into a sphere (proprietary "Verisome" technology) which dissolves over time
  - Self-tapering effect



Dexamthasone intraocular suspension (Dexycu)

XVI. Immunomodulatory Therapy (IMT)

- To be considered in patients who are having significant adverse effects from steroids and/or unable to be weaned off of them
- Absolute indications for IMTs
  - Behcet's disease

    - Sympathetic ophthalmia/VKH
    - Necrotizing scleritis
    - Peripheral ulcerative keratitis (PUK)
    - Granulomatosis with polyangiitis (GPA; a.k.a. Wegener's granulomatosis)
    - Polyarteritis nodosa (PAN)
    - Ocular cicatricial pemphigoid (OCP)
- There are potentially serious adverse effects associated with IMT
    - Confirm absence of infection, recent live vaccine, hepatic/renal/hematologic issues, pregnancy/breast feeding
    - Family planning and contraception is often needed
    - Close follow-up with evaluation and labs
- Potency of medicine is correlated with risk of adverse events
    - *Antimetabolites* have lowest potency but is safer
    - *T-cell inhibitors* have intermediate efficacy but more side effects compared to antimetabolites
    - *Alkylating agents* are powerful with serious risks (malignancies) – Reserve for life/sight threatening disease

- Antimetabolites
    - Interferes with DNA synthesis
    - Cells with high turnover rates are especially vulnerable (i.e. hair follicles, bone marrow, neoplasms)
    - Weaker anti-inflammatory activity compared to other IMTs but a relatively favorable safety profile
    - Cytopenias and hepatitis are common adverse effects – Monitor CBC and Liver Enzymes
    - **Azathioprine**
        - Purine nucleoside analog →
        - Dosing 2-3mg/kg per day PO or IV
        - Variable response based on thiopurine-S-methyltransferase (TPMT) activity
            - High TPMT activity require higher doses
            - If low/no TMPT activity avoid use
        - Complications
            - Hepatitis
            - Hepatic vaso-occlusive disease
            - GI Upset
            - Bone marrow suppression
    - **Methotrexate**
        - Inhibits dihydrofolate reductase which converts folic acid to tetrahydrofolic acid
        - Dosing starts at 15mg per week PO, SubQ, IM, or IV
            - Maximum dosing 25mg/kg
        - 6 months for full effect
        - First line for pediatric uveitis
        - Complications

                - Hepatitis
                - Bone marrow suppression
                - Fatigue/Malaise
                - Nausea
        - **Mycophenolate mofetil (CellCept)**
            - Blocks synthesis of purines → depletes guanosine nucleotides
                - Inhibits inosine monophosphate dehydrogenase
            - Dose: 1-1.5g BID PO
            - 4 months for full effect
            - Better tolerability with <20% experiencing adverse effects
            - Good alternative to MTX for pediatric population
            - Complications
                - Hepatitis
                - Bone marrow suppression
                - GI upset/Diarrhea
- Alkylating agents
    - Attaches an alkyl group to guanine and disrupts all phases of the cell cycle
    - Increased risk of malignancies
        - 13.5x increased risk for leukemia (chlorambucil)
        - 33x increased risk for bladder CA (cyclophosphamide)
    - High rate of sterility → consider sperm or embryo banking
    - Limited use for severe and recalcitrant disease may be justified
    - Indications
        - Necrotizing scleritis
        - Intermediate uveitis
        - VKH/Sympathetic ophthalmia
        - Behcet disease
    - **Cyclophosphamide**
        - Likely more effective PO compared to pulsed IV dosing
        - Dose titrated to keep leukocytes between 3000-4000cell/ul
        - Complications
            - Hemorrhagic cystitis
            - Bladder cancer
            - Myelosuppression
            - Hairloss
            - Sterility
            - Hematologic malignancies
            - Opportunistic infections → Pneumocystis jirovecii (TMP/SMX)
        - Check urinalysis and CBC
    - **Chlorambucil**
        - Long-acting alkylating agent
        - Dose: 0.1-0.2mg/kg per day
        - Check UA and CBC
- T-cell inhibitors

- Calcineurin inhibitors which halt IL-2 production and subsequently reduces T-cell proliferation
- **Cyclosporine**
  - Product of fungus Beauveria nivea
  - Complications
    - Hypertension
    - Nephrotoxicity
    - Paresthesias
    - GI upset
    - Hypertrichosis
    - Gingival hyperplasia
  - Monitor BP, Creatinine, and CBC
  - Available topically for dry eye syndrome (Restasis)
- **Tacrolimus (FK506)**
  - Product of Streptomyces tsukubaensis
  - Increased potency and lower dose compared to cyclosporine
  - Better safety profile
    - Nephrotoxicity, HTN, HPL is less common
- TNF inhibitors
- Tumor necrosis factor alpha (TNF-a) is thought to play a major role in the pathogenesis of JIA, ankylosing spondylitis and other spondyloarthropathies
- Associated adverse effects
  - CNS demyelination
    - Unmasks or worsens multiple sclerosis
  - Increased risk of malignancy
  - Reactivation of tuberculosis, histoplasmosis, hepatitis B and fungal infections
  - Congestive heart failure (CHF)
- **Adalimumab**
  - Human monoclonal IgG1 antibody
  - SubQ injection
    - 80mg initial dose
    - 40/0.8 mg/ml every 2 weeks for maintenance dosing
  - 88% success rate for JIA
  - 100% success rate for adults with Behcet, Posterior, and Panuveitis
  - SYCAMORE study
    - Used adjunctive with MTX for JIA associated uveitis
    - Less likely to have treatment failure w/ adalimumab
    - More likely to eliminate use of steroids
- **Infliximab**
  - Mouse/human chimeric IgG1-kappa antibody
  - Infusions
    - Week 0, 2, 4, then every 4-8 weeks for maintenance dosing
  - Similar efficacy as adalimumab but nearly half unable to tolerate long-term due to adverse events

        - Complications
            - Drug-induced lupus
            - Systemic vascular thrombosis
            - CHF
            - New malignancy
            - Demyelinating disease
            - Vitreous hemorrhage
        - 75% develop anti-nuclear antibodies after 3 infusions
    - **Etanercept**
        - Not effective for ocular inflammatory disease
- Lymphocyte inhibitors
    - **Rituximab**
        - Chimeric monoclonal antibody against CD20+ cells (B lymphocytes)
        - IV infusion
        - Used in necrotizing scleritis (associated granulomatosis with polyangiitis, PAN), pemphigoid, JIA-associated uveitis
        - Intravitreal injection for primary vitreoretinal lymphoma
    - **Interferon (IFN) α2a/2b**
        - SubQ
        - α2a – antiviral, immunomodulatory and antiangiogenic effect
            - Well tolerated and efficacious for Behcet's – 90% controlled
        - α2b – may treat uveitic macular edema
        - Complications
            - Flu-like syndrome in first few weeks
            - Leukopenia and thrombocytopenia
            - Depression
    - **Abatacept**
        - T-cell co-stimulation inhibitor
        - IV infusion
        - Mixed results treating JIA-related uveitis

XVII. Nonsteroidals Anti-Inflammatory Drugs (NSAID)

- Arachidonic acid mediate a variety of functions
    - Smooth muscle tone
    - Platelet aggregation
    - Hormone release
    - Inflammation
- Arachidonic acid is released from phospholipids by phospholipase A_2 (PLA_2)
- Corticosteroids exert their anti-inflammatory effect by blocking PLA_2
- Cycloxygenase (COX) converts free arachidonic acid to a variety of prostaglandins which mediate inflammation
    - COX-1 - Constitutively expressed and is present in various tissues (including stomach lining → gastric ulcers)
    - COX-2 – Induced in setting of pro-inflammatory signals
- Classic NSAIDS inhibit COX-1 and COX-2

- COX-2 specific inhibitors lack gastrointestinal toxicity but have been associated with cardiovascular complications such as myocardial infarction
- COX-1 inhibition prevents thromboxane production which is necessary for coagulation
    - Platelets lack nuclei and cannot replenish COX
    - COX-2 inhibitors does not alter platelet activity
    - After stopping NSAIDs, COX activity recovers by 10% per day (rate of platelet turnover)
- Reye syndrome
    - Sudden acute brain and liver damage
    - Associated with aspirin use in children who are recovering from a viral illness (influenza and chicken pox)
- NSAIDs are less effective for scleritis than steroids in treating scleritis and uveitis
- Topical NSAIDs
    - May be used pre-operatively to reduce PG mediated miosis
    - Prevention and treatment for cataract-related CME (Irvine Gass)
    - Associated with delayed wound healing and corneal melt
    - **Ketorolac 0.4-0.5%**
        - BID-QID
        - Burning/Stinging in 40%
        - pH 6.8 – Optimize drug delivery in deionized form
    - **Bromfenac 0.07% (Prolensa, Bromday)**
        - Once daily use
        - Bromine is added to the molecule which makes it more lipophilic
        - Burning/Stinging in 1.4%
    - **Nevanac 0.3% (Ilevro)**
        - Once daily use
        - Prodrug for amfenac → improved corneal penetration
        - Low incidence of burn/sting
        - Good posterior activity for CME treatment

XVIII. Anti-Allergic Drugs

- 20% of the U.S. population have allergies and more than half require treatments
- 50 million mast cells on the human eye
- Antigens bind with IgE and trigger release of histamine, PG, leukotrienes from mast cells and basophils
    - Type I hypersensitivity reaction
- Leads to hyperemia and swelling
- Corticosteroids, mast-cell stabilizers and antihistamines are effective agents
- Corticosteroids
    - Very effective but higher risk for adverse effects compared to others
    - **Loteprednol 0.2% (Alrex)** is designed for allergy use
    - Severe and recalcitrant cases such as atopic and vernal conjunctivitis may require stronger topical steroids
- Antihistamines (H1-receptor antagonists)
    - Onset of action is within minutes of use

    - Duration is approximately 4 hours
    - **Emedastine difumarate 0.05% (Emadine)**
        - 4 times daily dosing
        - Headache (11%), blurred vision, burn/sting, corneal infiltrates, rhinitis and sinusitis
    - **Levocobastine HCl 0.05% (Livostin)**
        - 4 times daily dosing
        - Discontinued in U.S.
    - **Antazoline (Vasocon-A) and Pheniramine (Naphcon-A)**
        - H1-antagonist combined with naphazoline (decongestant)
- Mast-cell stabilizers
    - Prevents degranulation and mediator release by blocking calcium influx across mast cell membranes
    - Slow onset – May take days to weeks to reach peak efficacy
        - Need topical steroids or H1 blockers for immediate relief
    - Good side effect profile – Well tolerated medications
    - **Cromolyn sodium 4% (Crolom)**
    - **Lodoxomide 0.1% (Alomide)**
        - 4 times daily dosing
        - 2500x more effective than cromolyn
        - More rapid and less stinging compared to cromolyn
        - More effective against vernal
    - **Pemirolast 0.1% (Alamast)**
        - 2 times daily dosing
        - Burning, photophobia, headaches
- Combined antihistamine and mast-cell stabilizers
    - Headache and burning sensation is a common side effect
    - **Olopatadine 0.1%, 0.2%**
        - **0.1% (Patanol)** – 2 times daily dosing
        - **0.2% (Pataday)** – 1 time daily dosing
    - **Ketotifen (Zaditor)**
    - **Azelastine (Optivar)**
    - **Epinastine (Elestat)**
    - **Bepotastine 1.5% (Bepreve)**

XIX. Antifibrotic Drugs

- Indications
    - Conjunctival intraepithelial neoplasia
    - Phototherapeutic keratectomy (PTK) to reduce corneal haze
    - Pterygium to prevent recurrence
    - Glaucoma surgery to control scarring
- **Fluorouracil (5-FU)**
    - Fluorinated pyrimidine nucleoside analog
    - Blocks thymidylate synthase and causes thymine deficiency
    - Interrupts RNA and DNA synthesis
    - Blocks S-phase of cell cycle

    - Increased success rate when used during and after glaucoma surgery
    - Has been evaluated for preventing PVR associated with retinal detachments with inconclusive outcomes
    - Complications – Corneal epithelial toxicity (especially with repeat application)
        - Fluorouracil Filtering Surgery Study (FFSS)
            - 5mg injections BID daily x 1 week then daily x 1 week
            - Total 21 post-op injections
- **Mitomycin C (MMC)**
    - Derived from Streptomyces caespitosus
    - Alkylating agent – Crosslinks DNA
    - Interrupts all phases of the cell cycle
    - Weak immunosuppressive properties but strong antifibrotic
    - Complications: Wound/bleb leakage, hypotony, endophthalmitis, localized scleral/corneal melt, corneal edema, cataract, anterior uveitis

XX. Dry Eye Syndrome

- **Cyclosporine 0.05% emulsion (Restasis)**
- Calcineurin inhibitor → Reduced T-cell function
- Available as a multidose bottle or single use vial
- Targets the inflammatory etiology of dry eye
- Histologic findings
    - Repopulation of goblet cells
    - Decreased number of lymphocytes
    - Decreased conjunctival cell turnover

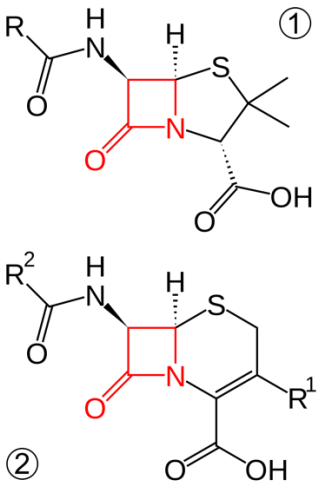
- **Lifitegrast 5% (Xiidra)**
- Lymphocyte function-associated antigen 1 antagonist (LFA-1)
- Inhibits intercellular adhesion molecule-1 (ICAM-1) to LFA-1
    - ICAM-1 is a transmembrane protein that aids in leukocyte endothelial transmigration

XXI. Ocular Decongestants

- Causes temporary decongestion of conjunctival vessels
- Mediated by α1-receptors
- **Naphazoline**
- **Oxymetazoline**
- **Tetrahydrozoline**
- **Phenylephrine**
- **Brimonidine 0.025% (Lumify)**
- Adverse effects
    - Rebound vasodilation
    - Ocular surface toxicity
- Advise against use of ocular decongestants in general. Make efforts to determine the etiology of red eye and address the underlying factors.

XXII. Antimicrobials

- Penicillins and Cephalosporins
  - β-lactam containing that disrupt synthesis of the peptidoglycan layer of the bacterial cell wall
  - Hydrophilic compounds that have difficulty penetrating the ocular surface and blood-ocular/brain barrier → Not effective as eyedrops
  - Difficulty bypassing the lipopolysaccharide (LPS) outer layer of gram-negative bacteria
  - Some bacteria produce β-lactamases (penicillinase) which cleave and inactivate this class of antibiotics
  - Potentially fatal anaphylactic hypersensitivity reactions can occur
    - 10% cross-reactivity with cephalosporins



Beta-lactam group in Penicillins and Cephalosporins

- Penicillins (5 Classes)
  - Natural Penicillins
    - **Penicillin G**
      - Produced directly from *Penicillium crysogenum*
      - Inactivated by stomach acids
    - **Penicillin V**
      - Derivative of Penicillin G with similar spectrum of activity
      - Better absorption by mouth
    - Inactivated by β-lactamase
    - Effective against most gram + and gram – cocci, anaerobes, listeria, actinomyces, leptospira, and treponema (syphilis)
      - Staphylococci, neisseria and enterococci becoming increasingly resistant
    - Short half-lives and excreted by the kidneys
      - Probenecid inhibits renal tubular excretion and increases serum concentrations

- Penicillinase-resistant Penicillins
  - Addition of isoxazyl side chain gives intrinsic resistance to β-lactamases
  - **Methicillin and Nafcillin**
    - Acid labile → Better administered by injection rather than PO
  - **Oxacillin, Cloxicillin, Docloxicillin, and Floxacillin**
  - Effective against penicillinase producing organisms
  - Better gram-positive coverage
    - More effective against staphylococci compared to Penicillin G
    - Less effective against organisms susceptible to the natural penicillins but still works
    - Not effective against enterococci
  - Almost no activity against gram negatives and anerobic bacteria
  - Methicillin-resistant staph aureus (MRSA) and staph epidermidis (MRSE) are very common now
- Aminopenicillins (Broader spectrum)
  - **Ampicillin, amoxicillin, and bacampicillin**
  - Similar to Penicillin G but addition of amino group expands the spectrum
    - More effective against enterococci
    - Better gram-negative coverage
      - H. influenza, E. coli, Salmonella, Shigella, and Proteus
  - Susceptible to β-lactamases with increasing resistance to this class of medications
  - Can be given with beta-lactamase inhibitors such as clavulanic acid or sulbactam
- Carboxypenicillins
  - **Carbenecillin and ticarcillin**
  - Carboxyl group replaces amino group
    - Greater gram-negative spectrum than aminopenicillins → especially against pseudomonas, enterobacter, and indole-positive strains of Proteus
    - Less effective against enterococci and other gram positives
  - Susceptible to β-lactamases
- Ureido- and Piperazine penicillins
  - **Piperacillin, azlocillin, and mezlocillin**
  - Ureido group further expands gram negative coverage
    - Coverage = Carboxypenicillins + Klebsiella, Serratia, Enterobacter, Enterococcus + Increased anaerobic coverage
  - Susceptible to β-lactamases

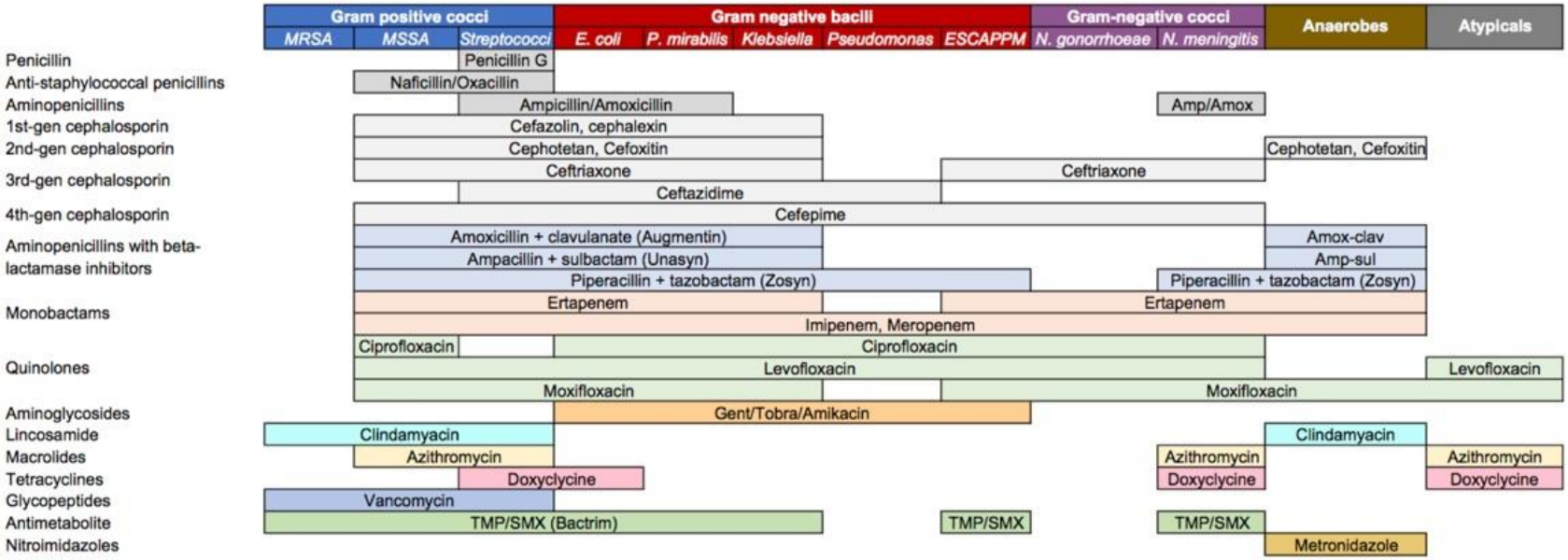
- Cephalosporins (5 Generations)
  - With each progressing generation, there is increasing gram negative coverage

- First generation
  - **Cefazolin (Ancef), cephalexin (Keflex), cephalothin, cefadroxil, cephadrine**
  - Strong activity against gram+ organisms (e.g. Staph and Strep)
  - Moderate activity against gram- organisms (E. coli, Proteus, Klebsiella)
  - No anaerobic coverage
  - Cephalothin is most resistant to β-lactamase among the group but can only be given IV
    - Painful when given IM and unstable with gastic acids
  - Cefazolin has a longer half-life and tolerated both IM and IV
  - Cephalexin is stable in gastric acid and can be taken PO
  - Indications: Skin infections, endocarditis prophylaxis
- Second generation
  - **Cefamandol, cefoxitin, and cefuroxime**
  - Better gram-negative coverage
    - Greater activity against H. influenza, Enterobacter, and Neisseria
  - Same gram-positive coverage
  - Anaerobic coverage
  - Cefuorxime is effective against penicillinase producing N. gonorrhoeae and ampicillin-resistant H. influenzae
  - Cefuroxime also crosses blood-brain-barrier well and is useful against pneumococcal/meningococcal/H influenzae meningitis
  - Indications: Intra-abdominal infections
- Third generation
  - **Cefotaxime, ceftriaxone, ceftazidime, cefoperazone, and ceftizoxime**
  - Similar spectrum activity against gram+ and gram -
    - Further enhanced activity against gram-negative compared to second generation
    - Less effective against gram-positive compared to first generation
  - No anerobic coverage
  - Ceftazidime and cefoperazon work well against Pseudomonas
  - Cefotaxime penetrates blood-brain-barrier better than others
  - Indications: Lung infections
- Fourth generation
  - **Cefepime and cefpirome**
  - Very good broad-spectrum antibiotic
    - Strong level of gram-positive coverage (similar to gen1)
    - Strong level of gram-negative coverage (similar to gen3)
  - Great Pseudomonas coverage
  - Better resistance against β-lactamases
  - No anaerobic coverage
  - Indications: Serious infections, Fever of unknown origin (FUO)

    - Fifth generation
        - Ceftolozane - Strongest Pseudomonas coverage
        - Ceftaroline – Covers MRSA
        - + Anaerobic coverage
- Fluoroquinolones
    - Interferes with bacterial DNA replication
        - Inhibits bacterial topoisomerase II (DNA gyrase) and topoisomerase IV
    - **Ofloxacin, ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, norfloxacin, and besifloxacin**
    - Potent activity against gram + and gram – bacteria
    - Not effective against MRSA
    - Increasing resistance for other bacteria (Mycobacterium, Pseudomonas, C.diff, Salmonella, E.coli, etc.)
    - Indicated for:
        - Corneal ulcers → Effective against 90% of common pathogens
        - Bacterial conjunctivitis
    - High rate of penetration into ocular tissues
    - Ciprofloxacin and norfloxacin can cause white crystalline deposits in the cornea
    - Systemic adverse effect: Tendonitis and tendon rupture
    - Avoid use in children → potential damage to growth plate cartilage
- Sulfonamides
    - Bacteria cannot use exogenous folic acid and must synthesize it from para-aminobenzenesulfonamide (PABA)
    - Sulfonamides are structural analog of PABA and a competitive antagonist of dihydropteroate
        - Disrupts synthesis of folic acid
    - Broad spectrum for gram positive and gram negative
    - Bacteriostatic
    - Sulfonamides are bacteriostatic only and is often combined with bacterial dihydrofolate reductase i.e. trimethoprim and pyrimethamine
        - Trimethoprim/Sulfamethoxazole (TMP/SMX)
    - **Sulfacetamide ophthalmic solution and ointment (10-30%)**
    - **Sulfadiazine and TMP/SMX (Bactrim)**
        - Used for ocular toxoplasmosis
    - Sulfonamide sensitivity (~5%)
        - Erythema nodosum/multiforme
        - Steven Johnson Syndrome (SJS)
        - Toxic epidermal necrolysis (TEN)
    - Antibiotic and non-antibiotic sulfonamides do not have much cross-reactivity
        - Type 1 hypersensitivity to antibiotics is to N1 heterocyclic ring and non-antibiotic sulfonamides do not have this feature
    - There is no cross-sensitivity between sulfonamide and sulfate groups
- Tetracyclines

    - **Tetracycline, doxycycline, minocycline**
    - Bacteriostatic
    - Inhibits protein synthesis by binding to ribosomal subunit 30S
    - Enters bacteria by active transport across the cytoplasmic membrane
        - Host cells lack the active transport system and are less affected
    - Indicated for syphilis, chlamydial infections, Lyme diseae, mycoplasma, rickettsia, malaria
    - Poorly water soluble → penetrates corneal epithelium well
    - Excreted into oil glands
        - Used for staphylococcal infections of the meibomian gland
    - Anti-inflammatory properties
        - Decreased leukocyte migration
        - Reduced production of ROS
        - Inhibition of MMP
        - Inhibition of PLA_2
    - Adverse effects
        - Photosensitivity
        - Renal toxicity – Fanconi syndrome
        - Idiopathic intracranial hypertension
        - Deposits in bone and teeth which may inhibit bone growth and discolor teeth
            - Avoid in children and pregnant women
- **Chloramphenicol**
    - Inhibits protein synthesis by binding to 50S
    - Bacteriostatic
    - Used less often due to potential for aplastic anemia and availability of safer and more effective alternatives
- Aminoglycosides
    - **Gentamycin, tobramycin, kanamycin, and amikacin**
    - Transported across the cell membrane and blocks 30S and 50S subunits of bacterial ribosome
    - Good gram - coverage
    - Bactericidal
    - Co-administration with antibiotics that affect cell-walls increase penetration (PCN/Cephalosporins)
    - Not well absorbed orally → Given IV/IM
    - Does not cross blood ocular barrier → Topical and local injection
    - Adverse effects
        - Hearing loss
        - Vertigo
        - Nephroticity
- Macrolides
    - **Erythromycin, clarithromycin, azithromycin**
    - Originally used for patients allergic to Penicillin
    - Blocks 50S subunit of bacterial ribosome
    - Bacteriostatic

    - Good choice for atypical respiratory pathogens
        - Mycobacteria, Legionella, Chlamydia
    - Used for toxoplasma infections
    - Available as topical ointments for bacterial conjunctivitis and blepharitis
- **Vancomycin**
    - Drug-class: Glycopeptide
    - Inhibits peptidoglycan synthesis
    - Bactericidal active against aerobic and anaerobic G+ bacteria including MRSA
    - Resistance is rising and is transmitted among bacteria by conjugative plasmid
        - Vancomycin resistant enterococcus (VRE)
        - Vancomycin resistant S. aureus (VRSA)
        - Linezolid, daptomycin, TMP/SMX
    - Ophthalmic uses
        - Empiric treatment for endophthalmitis (Vancomycin with Ceftazidime or Amikacin)
        - Bacterial keratitis
        - Irrigating solution during cataract surgery
    - Adverse effects
        - Flushing ("red man syndrome") → rapid infusion causes histamine release
        - Otoxocity
        - Nephrotoxicity
- **Polymyxin B**
    - Cationic detergent that disrupts phospholipid layer of bacterial cell walls
    - Sensitivity is related to phospholipid content and resistance depends on presence of cell wall
- **Bacitracin**
    - Inhibits bacterial cell wall synthesis
    - Available as ophthalmic ointment
        - Combination with polymyxin, neomycin, and hydrocortisone
- **Providone-Iodine 5%, 10%**
    - The only compound shown to reduce risk of postoperative endophthalmitis
    - Reported allergies to iodine, seafood, or contrast dye is NOT a contraindication
    - Consider sending patient for allergy testing especially if repeated procedures are needed (i.e. intravitreal injections)



See github.com/aetherist/antibiogram for details. For educational purposes only. TMP/SMX = Trimethoprim-sulfamethoxazole, MRSA = Methicillin-resistant Staphylococcus aureus, MSSA = Methicillin-sensitive Staphylococcus aureus, ESCAPPM = Enterobacter spp., Serratia spp., Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp. and Morganella morganii.

XXII. Antifungals

- Polyenes
  - Oldest class of antifungal medications
  - Binds to sterols of cell walls of susceptible fungi causing damage followed by leakage of nutrients
    - Potentiates other antifungals which pass more easily through cell membranes
  - Effective topical agent against:
    - Filamentous fungi - Aspergillus, Cephalosporium, Curvularia, Fusarium, Penicillium
    - Yeast - Candida
  - **Natamycin 5% suspension (Natacyn)**
    - For topical ophthalmic use
  - **Amphotericin B 0.25-0.5% (Fungizone)**
    - Delivered topical, intravitreal injection, and systemic
    - Systemic – Aspergillus, Blastomyces, Candida, Coccidioides, cryptococcus, and histoplasma
    - Intravitreal – Association with retinal toxicity

- Imidazoles and Triazoles
  - Increase fungal cell membrane permeability and disrupt membrane bound enzyme activity
  - Triazole have less activity against human sterols than imidazoles
  - Imidazoles
    - **Miconazole**
      - Available topical or local injection (subconj or intravitreal)
    - **Ketoconazole (Nizoral)**
      - Oral dosing
      - Does not cross the blood-ocular barrier but enhances penetration in setting of inflammation
  - Triazoles
    - **Itraconzaole (Sporanox)**
      - Oral, IV
      - Less toxic and broader spectrum than ketoconazole
    - **Fluconazole (Diflucan)**
      - Oral, IV, Subconj
      - Good bioavailability but limited spectrum
    - **Voriconzaole (Vfend)**
      - Topical, Intravitreal, Oral, IV
      - Excellent bioavailability, intraocular penetration, and broad spectrum coverage
      - Rapidly replacing other antifungal options

- Echinocandins
  - **Caspofungin, Micafungin, & Anidalafungin**
  - IV only

- Inhibits glucan, a component of the fungal cell wall
- Primarily active against Aspergillus and Candida
- Used prophylactically in stem cell recipients and in candidemia

- **Flucytosine (5-flucytosine)**
  - Converted to 5-fluorouracil (5-FU) by cytosine deaminase then to 5-fluorodeoxyuridylate
    - Blocks DNA synthesis by inhibiting thymidylate synthase
    - Host cells lack cytosine deaminase activity
  - Most aspergillus and candida are resistant
  - Used as an adjunct to amphotericin B

XXIII. Antivirals

- Topical nucleoside/nucleotide analogs
  - Compete with natural nucleotides for incorporation into viral and human DNA
  - Treatments for herpes simplex virus (HSV) epithelial keratitis
  - Cross resistance does not occur among these medications
  - **Idoxuridine 0.1% (IDU) and Vidarabine 3% and**
    - Less commonly used.
    - Available as powder for compounding
  - **Trifluridine 1% (Viroptic)**
    - 9x/day for 10-14 days
  - **Ganciclovir 0.15% (Zirgan)**
    - 5x/day for 1 week then 3x/day for 1 week
- Topical DNA polymerase blockers
  - **Gancyclovir 0.15% (Zirgan)**
    - Guanosine analog
    - Blocks viral DNA polymerase when triphosphorylated by cellular kinases
    - Approved for HSV keratitis and CMV endotheliitis/anterior uveitis
  - **Acyclovir 3% ointment (not available in US)**

- Systemic
  - **Acyclovir**
    - Guanosine analog
    - Viral thymidine kinase has high affinity to acyclovir
    - Crosses blood-ocualr/brain-barrier well
      - CSF and Aqueous concentration is ½ and 1/3 of plasma concentration respectively
    - Mainly excreted by kidneys
      - Increased half-life with probenecid and anuria
      - Interferes with other drugs with renal excretion (i.e. methotrexate)
    - HSV keratitis: 200-400mg 5x/day x 7-10 days

        - Zoster ophthalmicus: 600-800mg 5x/day x 10 days
        - Maintenance dose to prevent recurrence: 400mg BID
    - Herpetic retinopathy: 13 mg/kg IV divided q8h daily; 10-40ug/0.1mg
    - Adverse systemic effects (especially IV)
        - Nephrotoxicity – Crystal formation
        - Neurotoxicity
    - **Valacyclovir**
        - Amino-acid prodrug of acyclovir
        - Higher bioavailability (50% vs. 20%)
        - Adverse effects: Nephrotoxicity and thrombocytopenia
    - **Famciclovir**
        - Oral prodrug of penciclovir
        - Used for acute HSV and HZV (off label)
        - Penciclovir (like acyclovir) needs to be activated by phosphorylation by viral thymidine kinase
        - Reduces duration of post-herpetic neuralgia (unlike acyclovir) when administered during HZV
    - **Ganciclovir**
        - Mechanism discussed above
        - Mostly used for CMV retinitis and CMV prophylaxis in HIV patients
            - Other treatments have better safety profile so not routinely used for other herpes viruses
        - Adverse effects: Bone marrow suppression
    - **Valganciclovir**
        - Prodrug of ganciclovir
        - Better bioavailability (60% vs. 9%) when taken orally
        - Converted to ganciclovir by intestinal/hepatic esterases
        - Used as an outpatient alternative to ganciclovir for CMV retinitis
            - Note: Valacyclovir and Valganciclovir have improved outpatient management of HSV and CMV retinitis
    - **Foscarnet**
        - Inhibits DNA polymerase, RNA polymerase, and reverse transcriptase
        - Approved for HIV patients with CMV retinitis and HSV in immunocompromised patients
        - Effective against CMV and HSV resistant to acyclovir and ganciclovir
        - Adverse effects: Nephrotoxicity (50%), neurotoxicity, hypocalcemia
        - Intravitreal injections can be done for CMV retinitis
    - **Cidovudine**
        - Cytidine nucleoside analog
        - Approved for CMV retinitis
        - Prolonged intracellular half-life
            - Weekly injections during induction, then every 2 weeks
        - Intravitreal injection with average time to progression ~2 months
        - Ocular adverse effects: Hypotony and uveitis

        - Systemic adverse effects: Nephrotoxicity
    - **Zidovudine (Retrovir)**
        - Nucleoside reverse transcriptase inhibitor (NRTI) which has activity against HIV
        - Thymidine nucleoside analog
        - Triphosphate form competes against viral reverse transcriptase
        - Has azido group that prevents DNA chain elongation

XXIV. Acanthamoeba Medications

- Acanthamoeba is ubiquitous and can be found in soil, water, and air
- Contact lens use increased incidence of corneal infections
- Exists and trophozoits and double wall cysts
- No single drug is effective in treating all cases and combination therapy is usually needed
- **Polyhexamethylene (0.02%; PHMB)**
    - Disinfectant
    - First-line agent due to lowest amoebicidal concentration
- **Chlorhexidine, neomycin, polymyxin B-neomycin-gramicidin, natamycin, miconazole, propamidine isethionate, dibromopropamidine, etc.**

XXV. Neurotoxin Complex

- **Botulinum Toxin Type A (Botox)**
    - Produced from cultures of Clostridium botulinum
    - Blocks neuromuscular conduction by blocking receptor sites on motor nerve terminals
        - Inhibits release of acetylcholine
    - Blocks excessive/abnormal contractions
        - Blepharospasm
        - Hemifacial spam
    - Cosmetic use
    - Strabismus
        - Atrophic lengthening of injected extraocular muscle

XXVI. Hyperosmolar agents

- **Sodium chloride 2%, 5% (Muro)**
    - Treats corneal edema from Fuch's dystrophy, post-operative corneal edema, and other endotherlial dysfunctions
    - Used for recurrent erosion syndrome

XXVII. Diagnostic agents

- External ocular diseases
    - **Fluorescein 2% and Lissamine Green 1%**
        - Outlines defects in the corneal and conjunctival epithelium
    - **Rose Bengal**
        - Stains abnormal devitalized epithelial cells

        - Has anti-viral properties → Do not use prior to getting viral cultures
    - Retinal and choroidal disease
        - **Fluorescein 5, 10, 25%**
            - Injected intravenously to diagnose various vascular disorders of the retina
            - Adverse effect
                - Nausea (10%), localized skin reaction, anaphylaxis
        - **Indocyanine green (ICG)**
            - Useful is delineating choroidal vasculature
            - Can be used for anterior scleritis
            - Adverse effect
                - Skin reaction, sore throat, hot flushes
                - Cases of anaphylaxis, hypotension, tachycardia, urticaria reported
    - Anterior capsule staining during cataract surgery
        - **Trypan Blue Dye and ICG**
    - Staining of the internal limiting membrane during retinal surgery
        - **Brilliant Blue G, Trypan Blue and ICG**
            - ICG stains better than trypan but may be toxic to retina and RPE cells
                - Limit prolonged exposure with ICG

XXVIII. Ophthalmic Viscosurgical Devices (OVDs)

- Protect ocular tissues during surgery
- Helps maintain intraocular space and facilitate tissue manipulation
- Compounds include:
    - Sodium hyaluronate, chondroitin sulfate, hydroxypropyl methylcellulose, and polyacrylamide
- Dispersive vs. Cohesive
    - Dispersive OVDs have a lower molecular weight and surface tension and tend to coat intraocular structures
    - Cohesive OVDs have higher molecular weight and surface tension and tends to cohere to itself

XXIX. Fibrinolytic Agents

- **Tissue Plasminogen Activator (tPA), urokinase and streptokinase**
    - tPA is a naturally occurring serine protease → less toxic than other agents
    - Present in higher concentrations in the aqueous compared blood
    - Is used to dissolves fibrin clots after intraocular surgery (off-label)

XXX. Thrombin

- Controls hemorrhage from small vessels such as capillaries and venules
- Use during intraocular surgery is off-label
    - Can be put in vitrectomy infusate (100U/mL) to shorten intraocular bleeding time
- Adverse effects

    - Ultrastructural corneal endothelial at high concentrations (1000U/mL)
- **Fibrin Sealant**
    - Biological tissue adhesive prepared from human plasma
    - Fibrinogen is activated by thrombin and imitates the final stages of the coagulation cascade
    - Used in ophthalmic surgeries
        - Substitute for suturing for conjunctival closures
        - Closing or preventing corneal perforations
        - Amniotic membrane transplantations

XXXI. Antifibrinolytic agents

- These medications inhibit the activation of plasminogen
- Used in ophthalmology to prevent recurrent traumatic hyphemas
- Contraindicated in presence of active intravascular clotting (i.e. DIC)
    - Increased risk of thrombosis
- **Aminocaproic acid**
    - Dose: 50-100mg/kg Q4H for 5-6 days
    - Adverse reaction: Nausea, vomiting, muscle cramps, conjunctival suffusion, nasal congestion, headache, rash, pruritis, dyspnea, confusion, cardiac arrhythmias, hypotension
- **Tranexamic acid**
    - 10 times more potent
    - 25 mg/kg TID for 3-5 days

XXXII. Interferon

- Naturally occurring defense against viruses
- Topical interferon not effective against EKC or HSV alone
- Few studies have shown improved healing time when combined with acyclovir
- **Interferon alpha-2b** can be used (off-label) for conjunctival intraepithelial neoplasia and invasive squamous cell carcinoma
- Intralesional injection is effective for Kaposi sarcoma (HHV-8)

XXXIII. Anti-VEGF

- Vascular endothelial growth factor (VEGF)
- Expressed in proliferating blood vessels and an important clinical target in retinal neovascular diseases
- Several isoforms exist – $VEGF_{165}$ is the most abundant isoform in the eye
- Newer medications and delivery methods focus on reducing injection burden
- **Pegatanib (Macugen)**
    - First approved drug for choroidal neovascularization (CNV)
    - Aptamer (synthetic oligonucleotide)
    - Intravitreal injections every 6 weeks
    - Replaced by newer (more effective) options
- **Bevacizumab (Avastin)**
    - Whole humanized mouse-derived antibody

    - $VEGF\text{-}A_{165}$
    - FDA approved for systemic carcinomas
    - Off-label for ophthalmology
    - CATT trial showed it was non-inferior to Ranibizumab
- **Ranibizumab (Lucentis)**
    - Monoclonal antibody fragment of bevacizumab
    - All isoforms of VEGF-A
    - FDA-approved for ophthalmic use
- **Aflibercept (Eylea)**
    - Human recombinant fusion protein
    - IgG backbone with fused receptor sequences against VEGFR1 and VEGFR2
    - More durable than predecessors
        - Monthly injections for 3 months then every 2 months
    - All isoforms of VEGF-A, VEGF-B, and PlGF (Placental growth factor)
- **Brolucizumab (Beovu)**
    - Humanized single-chain Ab
    - Smallest monoclonal Ab ever (26kDa)
    - All isoforms of VEGF-A
    - Longest durability q8-12 weeks
    - Adverse effects
        - Retinal arterial occlusion related to ocular inflammation (1%)
        - Ocular inflammation (4%)