Ocular Pharmacology-I

Learning Objectives

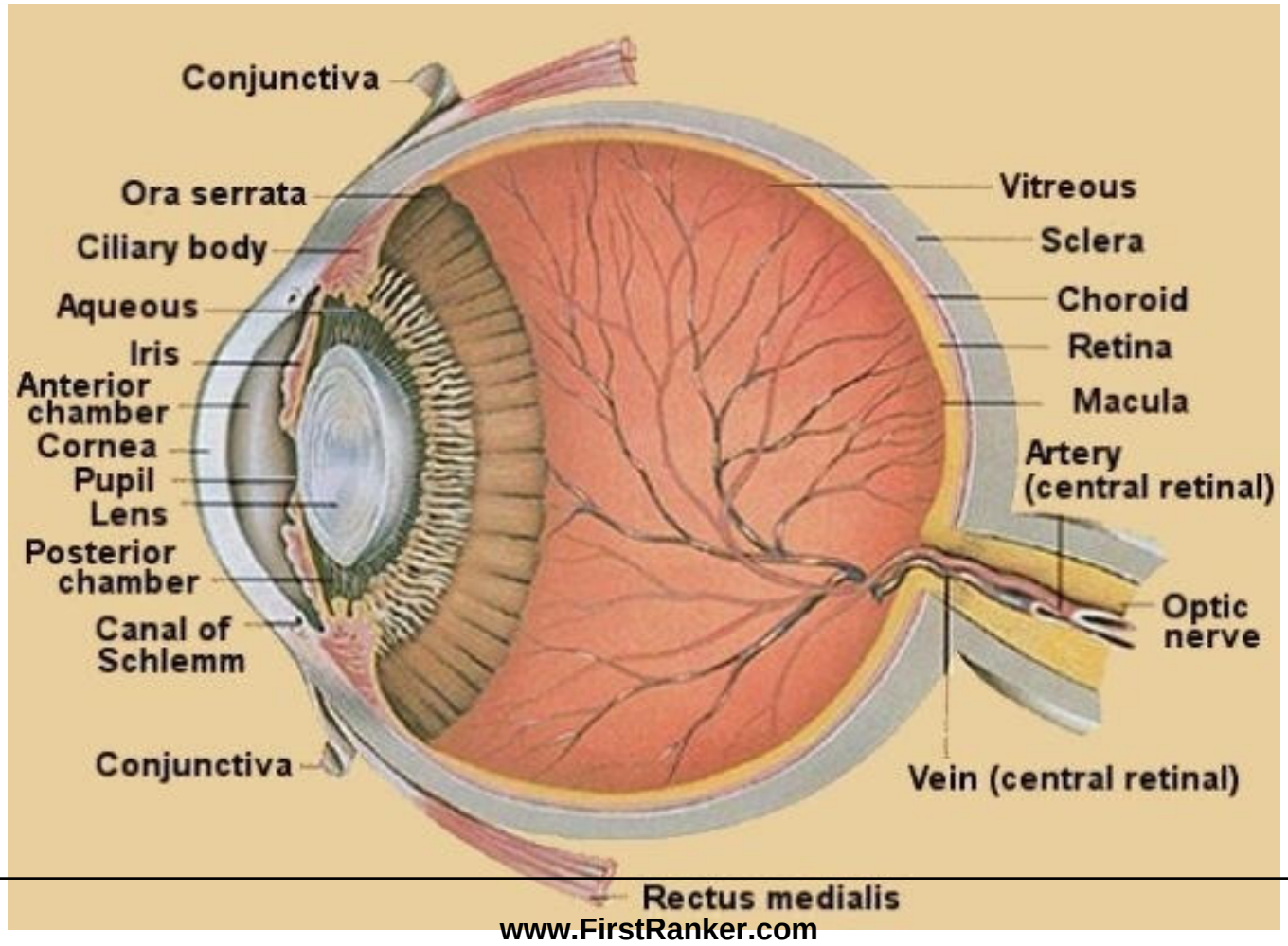
At the end of this class students shall have a basic understanding of :

- pharmacokinetics and pharmacodynamics of ocular drugs
- Ocular routes of drug administration
- Topical antibiotic and cycloplegic agents

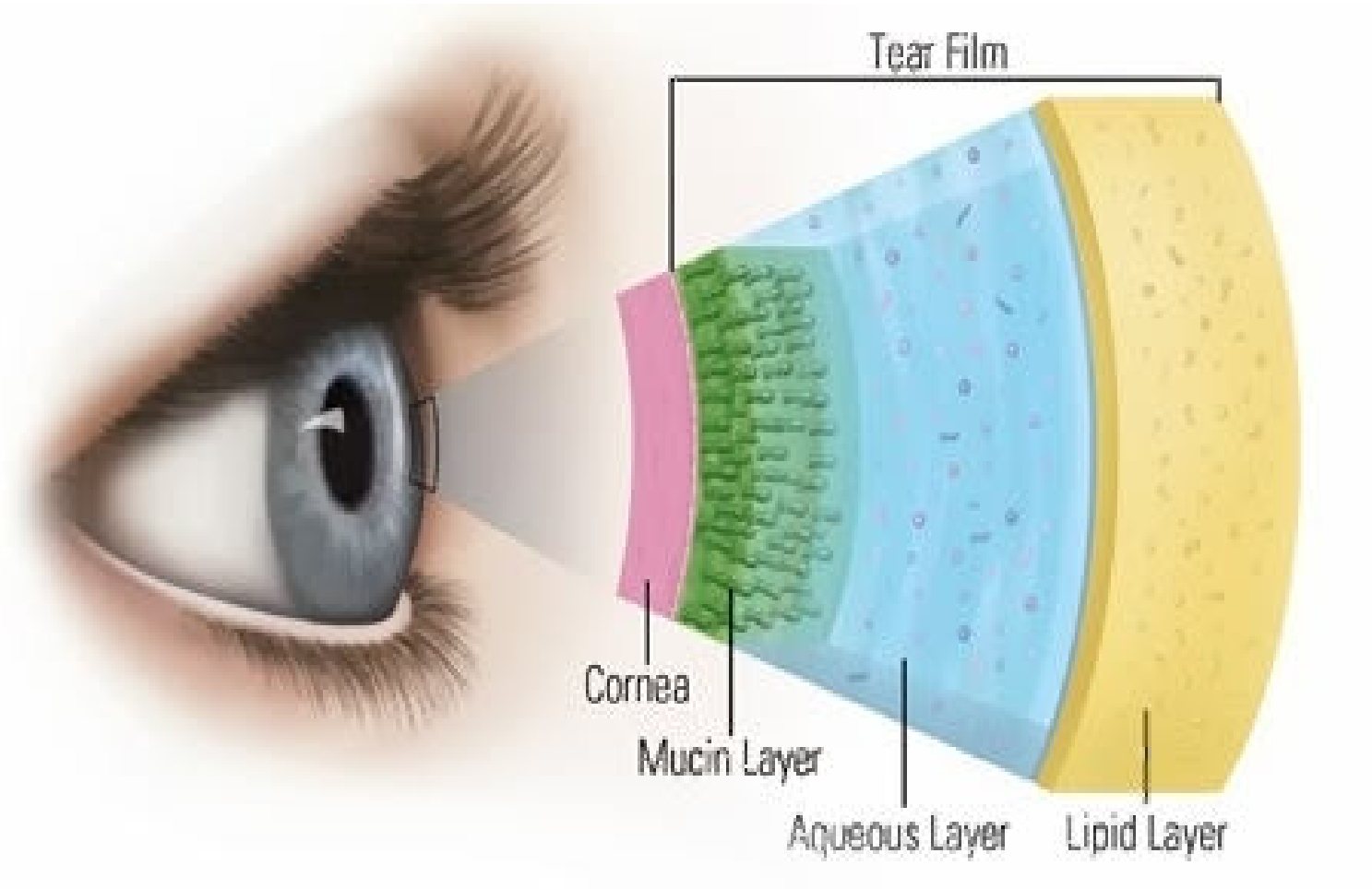
Overview

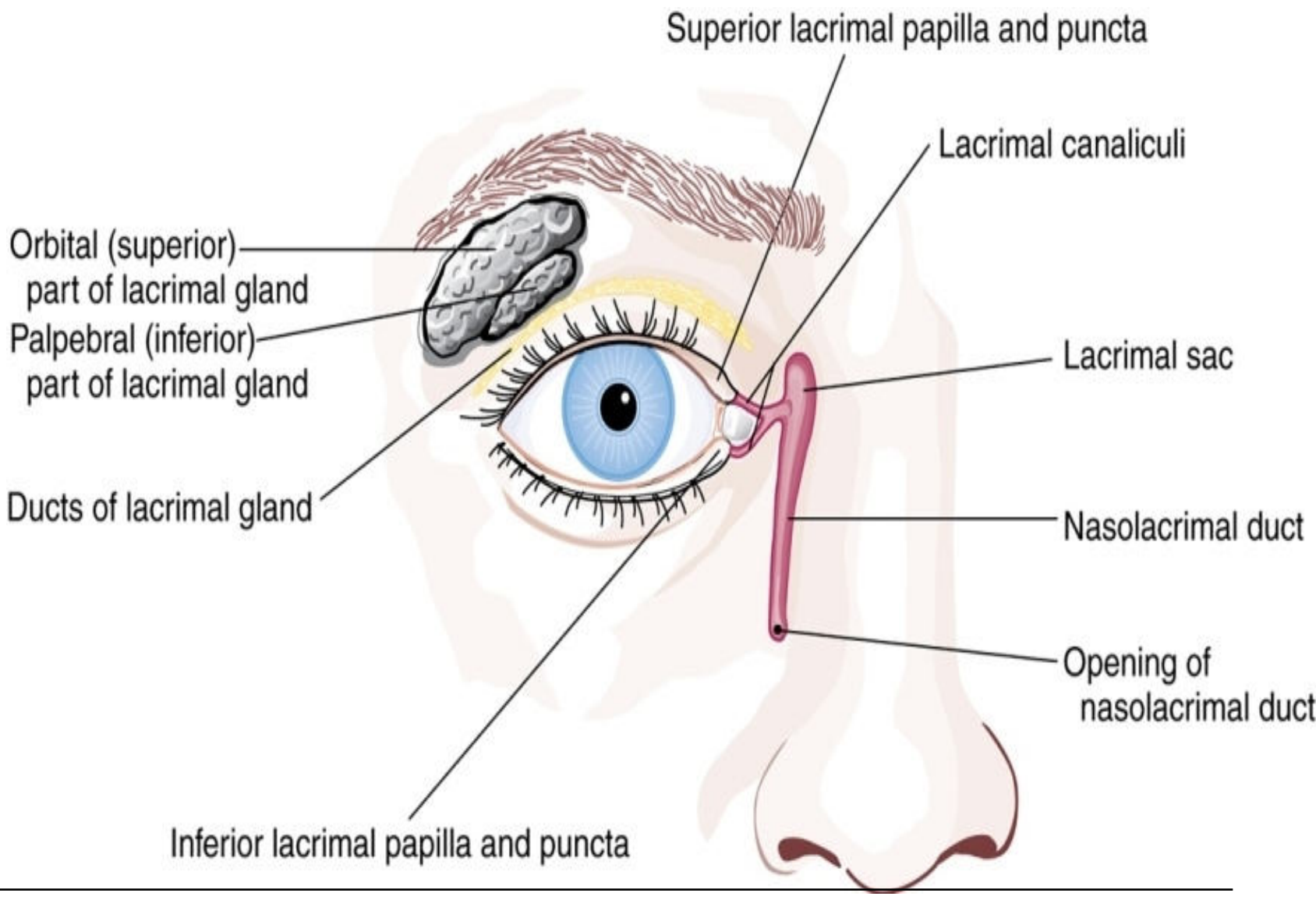
- Overview of ocular anatomy & physiology
- Pharmacodynamics and Pharmacokinetics of ocular therapeutic agents
- Ocular Routes of Drug Administration
- Therapeutic & Diagnostic applications of Drugs in Ophthalmology
- Ophthalmic Effects of Selected Vitamin Deficiencies & Zinc Deficiency
- Systemic Agents with Ocular Side Effects
- Conclusion

Anatomy of Eye



Tear Film





Pharmacodynamics

- It is the biological and therapeutic effect of the drug (mechanism of action)
- Most drugs act by binding to regulatory macromolecules, usually neurotransmitters or hormone receptors or enzymes
- If the drug is working at the receptor level, it can be agonist or antagonist
- If the drug is working at the enzyme level, it can be activator or inhibitor

Pharmacokinetics

- It is the absorption, distribution, metabolism, and excretion of the drug
- A drug can be delivered to ocular tissue as:
  - Locally:
    - Eye drop
    - Ointment
    - Periocular injection
    - Intraocular injection
  - Systemically:
    - Orally
    - IV

Pharmacokinetics of Ocular Drugs

- Classical pharmacokinetic theory based on systemically administered drugs does not fully apply to all ophthalmic drugs

- Topical route – most commonly used

Absorption

Rate & extent of absorption of topically instilled drugs depends upon –

"*Drug penetration into the eye is approximately linearly related to its concentration in the tear film.*"

1. **Time the drug remains in the cul-de-sac & precorneal tear film**
2. **Elimination by nasolacrimal drainage**
3. **Drug binding to tear proteins**
4. **Drug metabolism by tear & tissue proteins**
5. **Diffusion across cornea & conjunctiva**

Distribution

Transcorneal absorption

↓

Accumulation in aqueous humor

↓

Distribution to intraocular structures

↓

Trabecular meshwork pathway

↓

Distribution to systemic circulation

Distribution

➢Melanin binding of certain drugs –

- Eg:

1. Mydriatic effect of alpha adrenergic agonists slower in onset - darkly pigmented irides compared to those with lightly pigmented irides

2. Atropine's mydriatic effect – long lasting in non-albino rabbits than in albino rabbits

3. Accumulation of chloroquine in retinal pigment epithelium – Bull's eye maculopathy

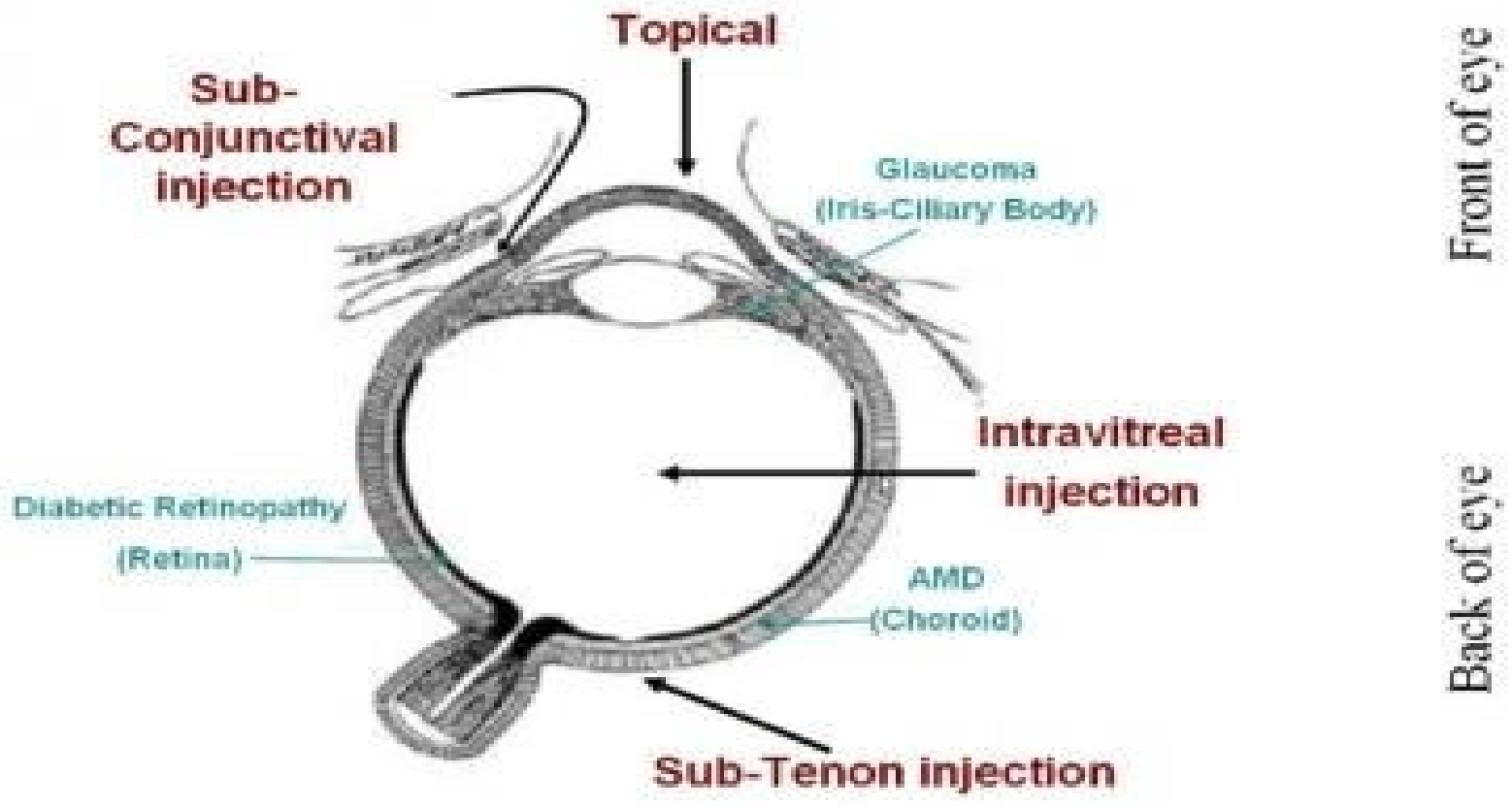
Metabolism

- Enzymatic biotransformation of ocular drugs - significant
- Esterases – particular interest

Eg: Development of prodrugs for enhanced ocular permeability

1. Dipivefrin hydrochloride
2. Latanoprost

Routes of Ocular Delivery



Drug Delivery in Eyes

Topical	Periocular	Intraocular	Systemic
drop	Subconjunctival	Intracameral	Oral
ointment	Subtenon	Intravitreal	intravenous
gel	Peribulbar		Intramuscular
Soft contact lens	Retrobulbar		

Ocular Routes of Drug Administration

Sr.No	Route	Special Utility	Limitations & Precautions
1.	Topical	--Convenient -- Economical --Relatively safe	--Compliance --Corneal & conjunctival toxicity --Nasal mucosal toxicity --Systemic side effects from nasolacrimal absorption
2.	Subconjunctival, sub-Tenon's & Retrobulbar injections	-Anterior segment infections -Posterior uveitis -Cystoid Macular Edema (CME)	-Local Toxicity -Globe perforation -Optic nerve trauma -Central retinal artery or vein occlusion
3.	Intraocular Injections	Anterior segment surgery or infections	-Corneal toxicity -Relatively short duration of action
4.	Intravitreal Injection	Immediate local effect	Retinal toxicity

Factors influencing local drug penetration into ocular tissue

- **Drug concentration and solubility**:
  higher concentration -- better penetration
  e.g pilocarpine 1-4% but limited by reflex tearing

- **Viscosity:** addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing contact time with cornea and altering corneal epithelium

- **Lipid solubility**: higher lipid solubility- more penetration

Factors influencing local drug penetration into ocular tissue

- **Surfactants**: preservatives alter cell membrane in cornea and increase drug permeability e.g. benzylkonium and thiomersal

- **pH**: the normal tear pH is 7.4
  If drug pH is much different, this will cause reflex tearing

- **Drug tonicity**: when an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration

- **Molecular weight and size**

TOPICAL

Drop (Gutta)- simplest and most convenient
mainly for day time use

1 drop=50 microlitre

Conjuctival sac capacity=7-13 micro liter

so, even 1 drop is more than enough

Method

hold the skin below the lower eye lid
↓
pull it forward slightly
↓
INSTILL 1 drop

- **measures to increase drop absorption**:
  -wait 5-10 minutes between drops
  -compress lacrimal sac
  -keep lids closed for 5 minutes after instillation

Ointments

- Increase the contact time of ocular medication to ocular surface, thus better effect

- It has the disadvantage of blurring vision
- The drug has to be highly lipid soluble with some water solubility to have maximum effect as ointment

Peri-ocular injections

- They reach behind iris-lens diaphragm better than topical application
- E.g. subconjunctival, subtenon, peribulbar, or retrobulbar
- This route bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillins)
- Also steroids and local anesthetics can be applied this way

Periocular

Subconjunctival - To achieve higher concentration
Drugs which cannot penetrate cornea due to large size
Penetrate via sclera

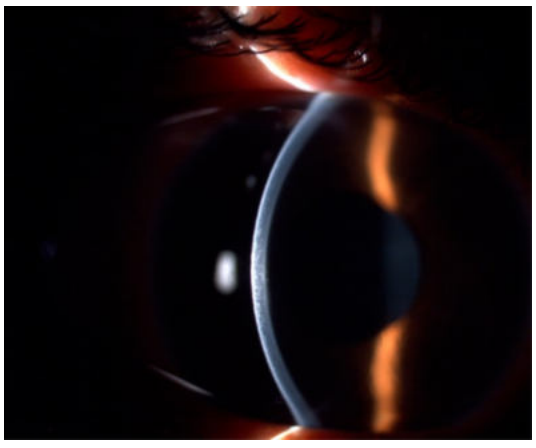
Subtenon—Ant. Subtenon– diseases anterior to the lens
Post. Subtenon– disease posterior to the lens

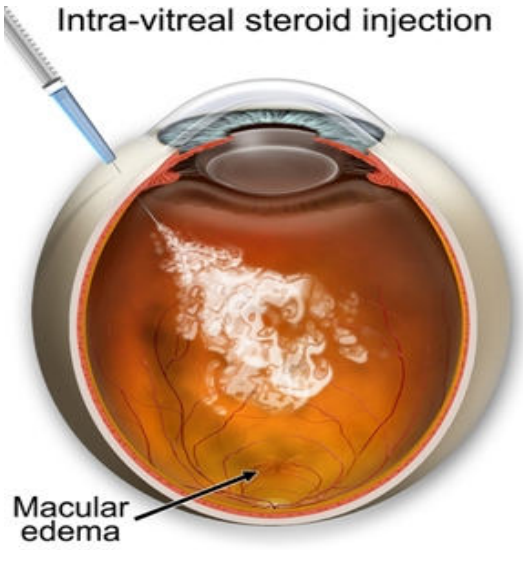
Retrobulbar- Optic neuritis
Papillitis
Posterior uveitis
Anesthesia

Peribulbar-- anesthesia

Intraocular injections

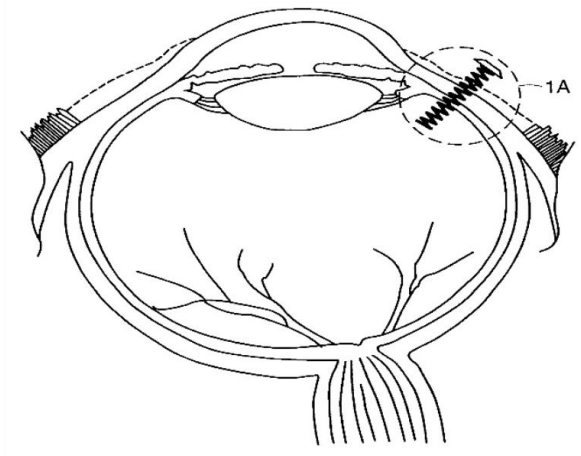
- Intracameral or intravitreal
- E.g.
  - Intracameral acetylcholine (miochol) during cataract surgery
  - Intravitreal antibiotics in cases of endophthalmitis
  - Intravitreal steroids in macular edema
  - Intravitreal Anti-VEGF for DR



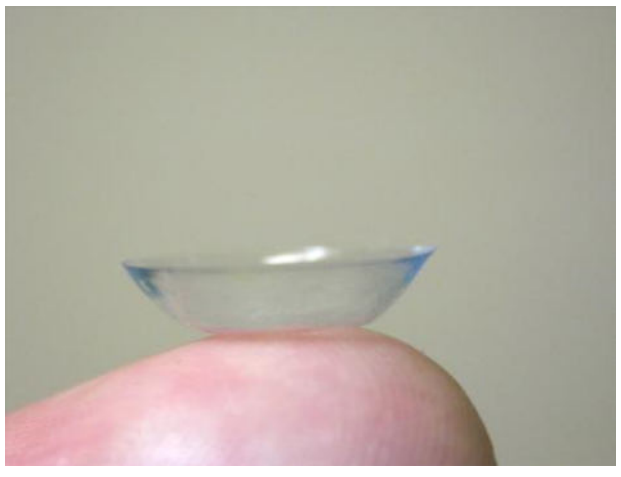


Sustained-release devices

- These are devices that deliver an adequate supply of medication at a steady-state level



- E.g.
  - Ocusert delivering pilocarpine
  - Timoptic XE delivering timolol
  - Ganciclovir sustained-release intraocular device
  - Collagen shields



Systemic drugs

- Oral or IV
- Factor influencing systemic drug penetration into ocular tissue:
  - lipid solubility of the drug: more penetration with high lipid solubility
  - Protein binding: more effect with low protein binding
  - Ocular inflammation: more penetration with ocular inflammation

Therapeutic applications of Drugs in Ophthalmology

Common ocular drugs

- Antibacterials (antibiotics)
- Antivirals
- Antifungals
- Mydriatics and cycloplegics
- Antiglaucoma medications
- Anti-inflammatory agents → Corticosteroids, NSAID's
- Ocular Lubricants
- Local anesthetics
- Ocular diagnostic drugs
- Ocular Toxicology

Topical Antibacterial Agents Commercially Available for Ophthalmic Use

Generic Name	Formulation	Toxicity	Indication for Use
Azithromycin	1% solution	H	Conjunctivitis
Ciprofloxacin hydrochloride	0.3% solution; 0.3% ointment	H D-RCD	-Conjunctivitis -Keratitis -Keratoconjunctivitis -Corneal Ulcers -Blepharitis -Dacryocystitis
Erythromycin	0.5% ointment	H	-Superficial Ocular Infections involving cornea or conjunctiva
Gatifloxacin	0.3% solution	H	Conjunctivitis

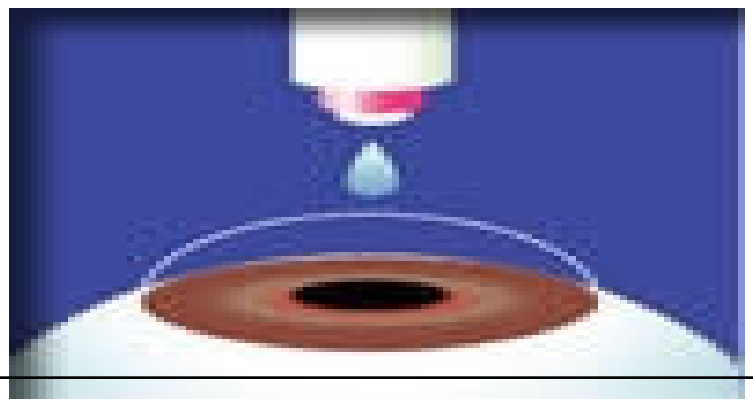
H- Hypersensitivity ; D-RCD – Drug Related Corneal Deposits

Topical Antibacterial Agents Commercially Available for Ophthalmic Use…..

Generic Name	Formulation	Toxicity	Indication for Use
Gentamicin sulfate	0.3% solution	H	Conjunctivitis, Keratitis
Levofloxacin	0.5%	H	Conjunctivitis
Levofloxacin	1.5%	H	Corneal Ulcers
Moxifloxacin	0.5% solution	H	Conjunctivitis
Ofloxacin	0.3% solution	H	Conjunctivitis Corneal Ulcers
Tobramycin sulfate	0.3% solution 0.3% ointment	H	External infections of the eye

Antibacterials(antibiotics)

- Penicillins
- Cephalosporins
- Sulfonamides
- Tetracyclines
- Chloramphenicol
- Aminoglycosides
- Fluoroquinolones
- Vancomycin
- Macrolides



Antibiotics

- Used topically in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.
- Used orally for the treatment of preseptal cellulitis

  e.g. amoxycillin with clavulanate, cefaclor
- Used intravenously for the treatment of orbital cellulitis

  e.g. gentamicin, cephalosporin, vancomycin,
- Can be injected intravitrally for the treatment of endophthalmitis

- Specific antibiotic for almost each organisms
- **Sulfonamides**- Chlamydial infections like TRACHOMA
  INCLUSION CONJUNCTIVITIS
  TOXOPLAMOSIS

Bacterial cell wall synthesis inhibitors-

Penicillin

Cephalosporins

I) First generation- Gram + cocci eg cephazoline

ii) Second generation —Gram – ve and antistaphylococcal— cefuroxime

iii) Third generation– Gram –ve bacilli --ceftriaxones

- **Side effects-** allergic reaction
  neutropenia
  thrombocytopenia

Amino glycosides

Mainly against gram negative bacilli

Bacterial protein synthesis inhibitors

Gentamycin- 0.3% eye drops

Tobramycin- 0.3% eye drop

Neomycin— 0.3-0.5% eye drops

Amikacin ----- 1% eye drops

Tetracycline

Inhibit protein synthesis

active against both gram+ and gram -ve, some fungi and Chlamydia

Chloramphenicol

Broad spectrum ,bacteriostatic,

gram+/gram-ve, Chlamydia

0.5% Eye drops, ointment

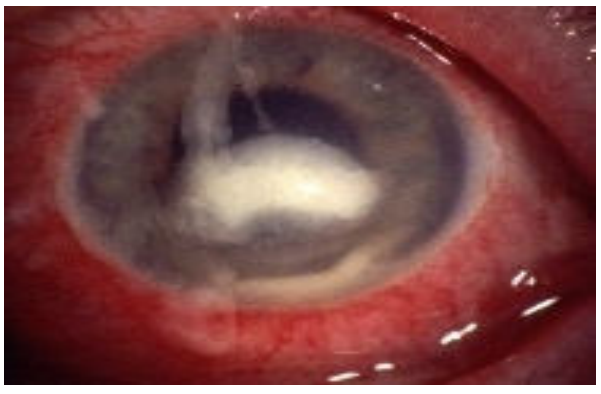
Fluoroqinolones

- Most frequently used topical broad spectrum antibiotics
- Ciprofloxacin – 0.3% eye drops
- Ofloxacin - 0.3% eye drops
- Moxifloxacin - 0.5 % eye drops
- Levofloxacin and Besifloxacin eye drops

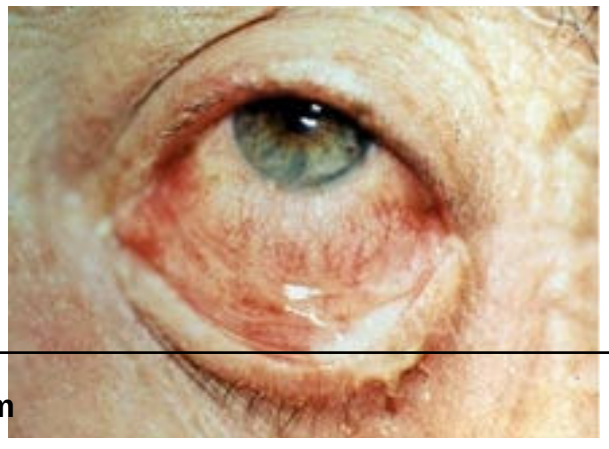
Antibiotics

- **Trachoma** can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin.

- **Bacterial keratitis** (bacterial corneal ulcers) can be treated by topical fortified cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones.



- **Bacterial conjunctivitis** is usually self limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used



Dacryocystitis - Infection of the lacrimal sac

Hordeolum/ Stye – Infection of the meibomian, Zeis or Moll gland

Conjunctivitis – Inflammatory process of the conjunctiva

Blepharitis – Bilateral inflammatory process of the eyelids

Antiviral Agents for Ophthalmic Use

GENERIC NAME	ROUTE OF ADMINISTRATION	OCULAR TOXICITY	INDICATIONS FOR USE
Trifluridine	Topical (1% solution)	PK, H	-Herpes simplex keratitis - Keratoconjuctivitis
Acyclovir	Oral (200 mg capsules, 800 mg tablets) Intravenous		-Herpes zoster ophthalmicus - Herpes simplex iridocyclitis
Valacyclovir	Oral (500- & 1000 mg)		-Herpes simplex keratitis -Herpes zoster ophthalmicus
Famciclovir	Oral (125-,250 mg tablets)		-Herpes simplex keratitis -Herpes zoster ophthalmicus

PK – Punctate Keratopathy ; H - Hypersensitivity

Antiviral Agents for Ophthalmic Use…

GENERIC NAME	ROUTE OF ADMINISTRATION	OCULAR TOXICITY	INDICATIONS FOR USE
Foscarnet	Intravenous Intravitreal	-----	Cytomegalovirus Retinitis
Ganciclovir	Intravenous, Oral Intravitreal implant	-----	Cytomegalovirus Retinitis
Valganciclovir	Oral	-------	Cytomegalovirus Retinitis
Cidofovir	Intravenous	------	Cytomegalovirus Retinitis

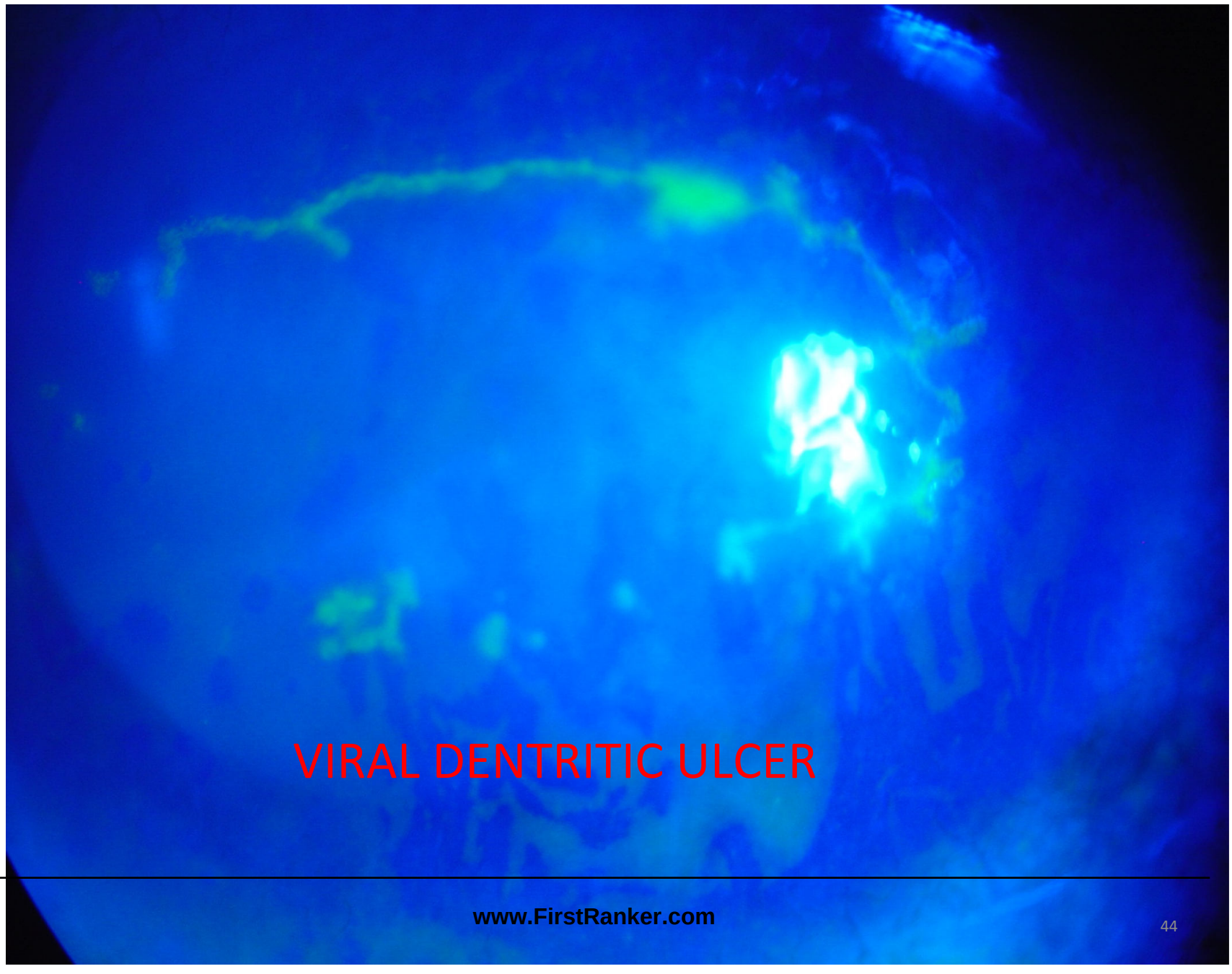
Antivirals

- Acyclovir- Most commonly used anti-viral
  3% ointment 5 times-10-14 days
  800mg oral 5 times 10-14 days
  Intravenous for Herpes zoster retinitis

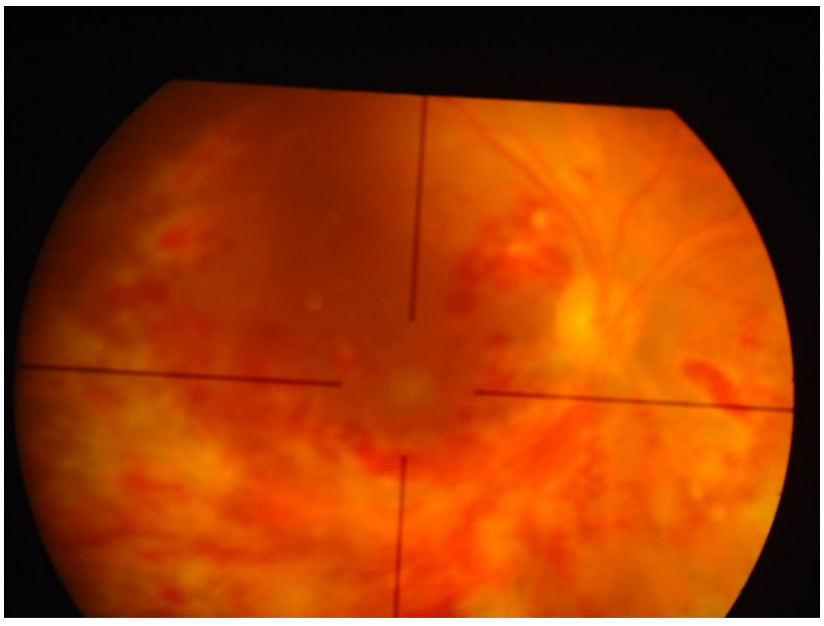
Others

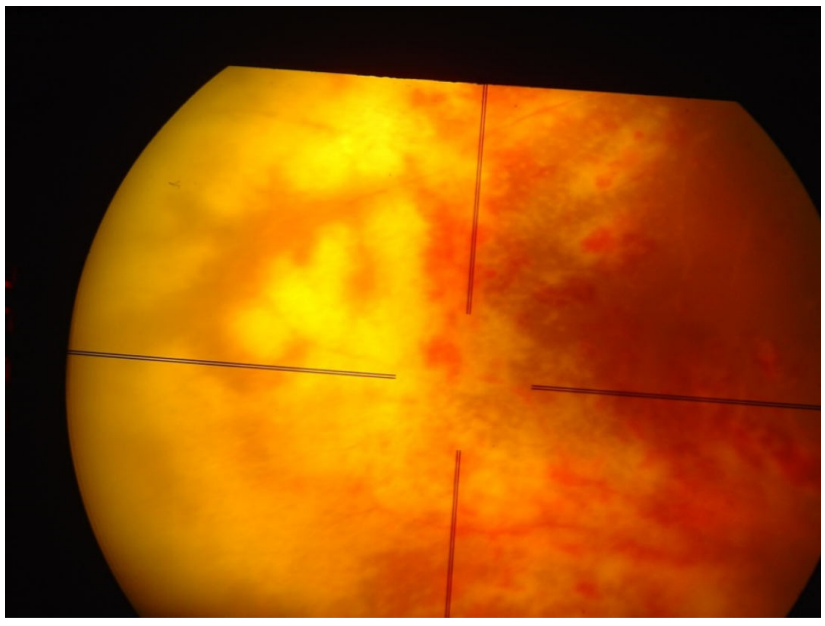
Idoxuridine
Vidarabine
Cytarabine
Triflurothymidine
Gancyclovir

INDICATIONS
HZ keratitis
Viral uveitis



CMV Retinitis





Antifungal Agents for Ophthalmic Use

Drug	Method of Administration	Indications for Use
Amphotericin B	0.1-0.5% solution 0.8-1 mg Subconjunctival 5 microgram intravitreal injection	Yeast & fungal keratitis & endophthalmitis - Yeast & fungal endophthalmitis - Yeast & fungal endophthalmitis - Yeast & fungal endophthalmitis
Natamycin	5% topical suspension	-Yeast & fungal blepharitis -Conjunctivitis ; keratitis
Fluconazole	Topical, Oral & Intravenous	Yeast keratitis & endophthalmitis
Itraconazole	Topical ,Oral	Yeast & fungal keratitis & endophthalmitis
Ketoconazole	Oral	Yeast keratitis & endophthalmitis
Miconazole	1% topical solution	Yeast & fungal keratitis

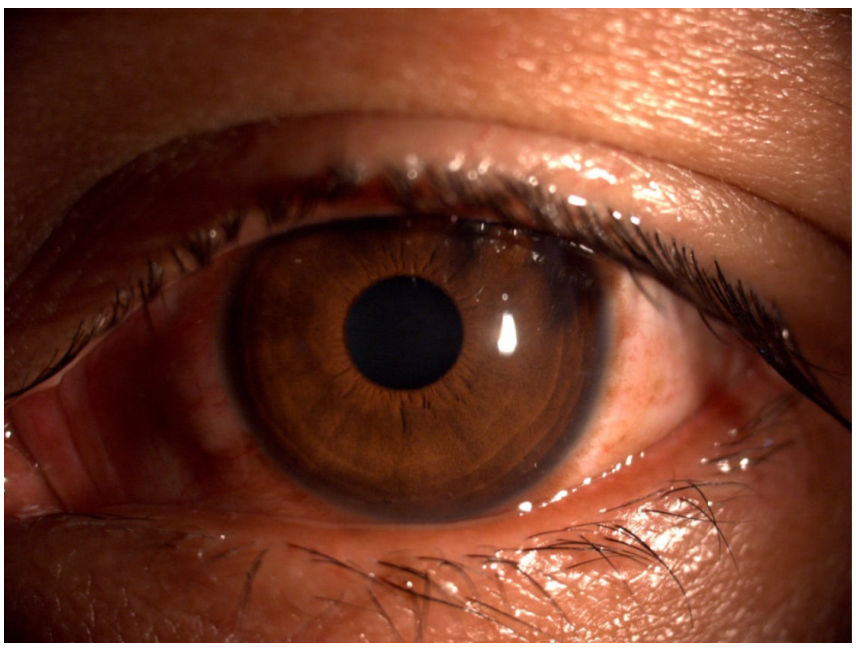
ANTIFUNGAL
INDICATIONS

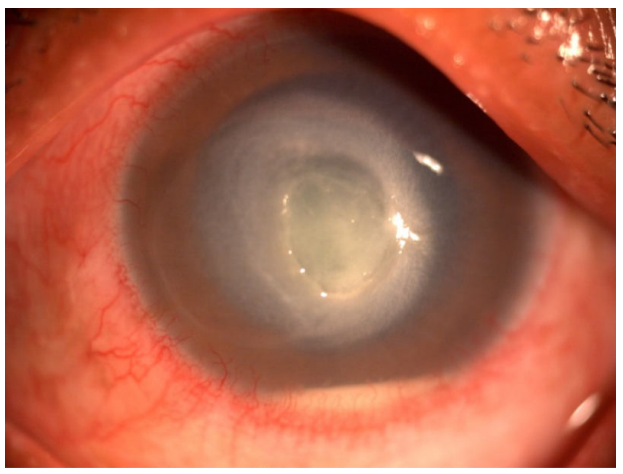
Fungal corneal ulcer

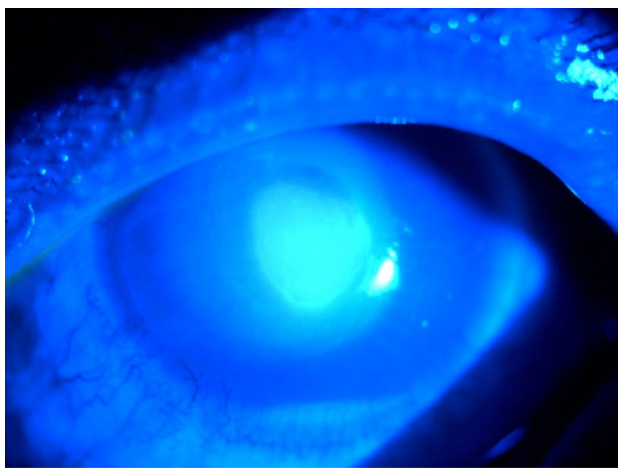
Fungal retinitis/ Endophthalmitis

Commonly used drugs are

- **Polyenes**
  - damage cell membrane of susceptible fungi
  - e.g. amphotericin B, natamycin, nystatin
  - side effect: nephrotoxicity
- **Imidazoles**
  - increase fungal cell membrane permeability
  - e.g. miconazole, ketoconazole,fluconazole
- **Flucytocine**
  - act by inhibiting DNA synthesis







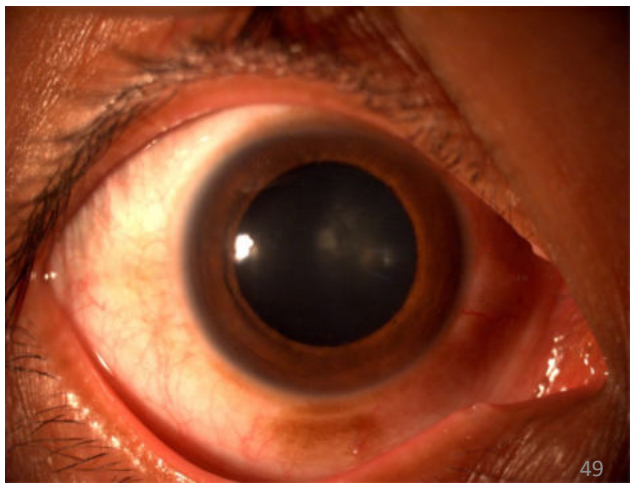
Mydriatics and cycloplegics

- Dilate the pupil, ciliary muscle paralysis
- **CLASSIFICATION**

Short acting- Tropicamide (4-6 hours)
Intermediate- homatropine (24 hours)
Long acting- atropine (2 weeks)

Indications

corneal ulcer
uveitis
cycloplegic refraction



SR. NO.	DRUG	FORMULATION	INDICATIONS FOR USE	OCULAR SIDE EFFECTS
1	Atropine	0.5%, 1% & 2% solution; 1% ointment	-Cycloplegia -Mydriasis -Cycloplegic retinoscopy -Dilated fundoscopic Exam	-Photosensitivity -Blurred vision
2	Scopolamine	0.25% solution	Cycloplegia -Mydriasis	Photosensitivity -Blurred vision
3	Homatropine	2% & 5% solution	Cycloplegia -Mydriasis	Photosensitivity -Blurred vision
4	Cyclopentolate	0.5% 1% solution	Cycloplegia -Mydriasis	Photosensitivity -Blurred vision
5	Tropicamide	0.5% & 1% solution	Cycloplegia -Mydriasis	Photosensitivity -Blurred vision

Thank you