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Sunday, August 11, 2019

(Room 4)

8:30 - 9:25 WS #150: Ophthalmology Update

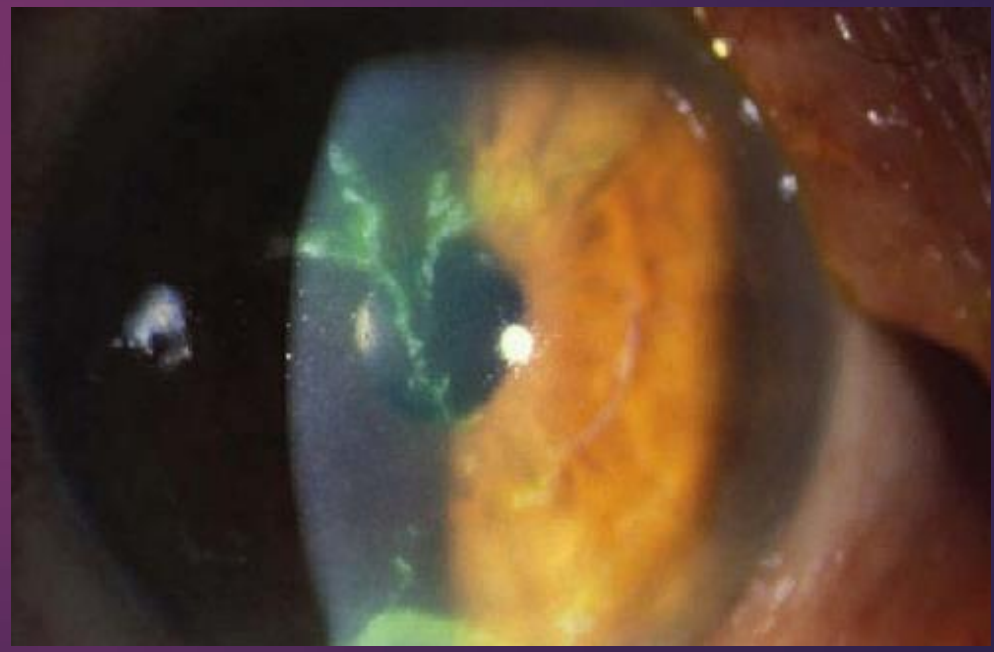
9:35 - 10:30 WS #160: Ophthalmology Update (Repeated)

Herpes Simplex Virus and the Cornea – Current Management

JOHN RAWSTRON

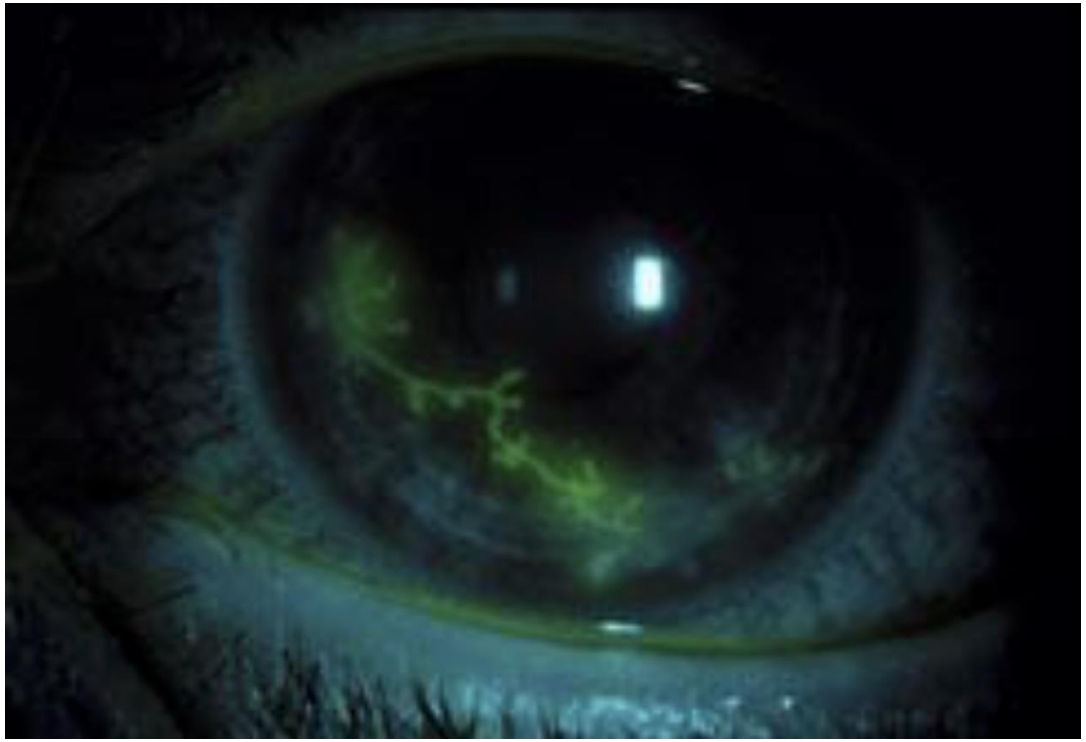
GPCME CHRISTCHURCH

2019



introduction

- Common – most common infectious cause for corneal blindness in developed nations. Approx 750 new/yr in nz and more recurrent.
- Variation in treatment/new paradigm
- Best practice?
- Poor practice?
- Drug resistance



Corneal Anatomy

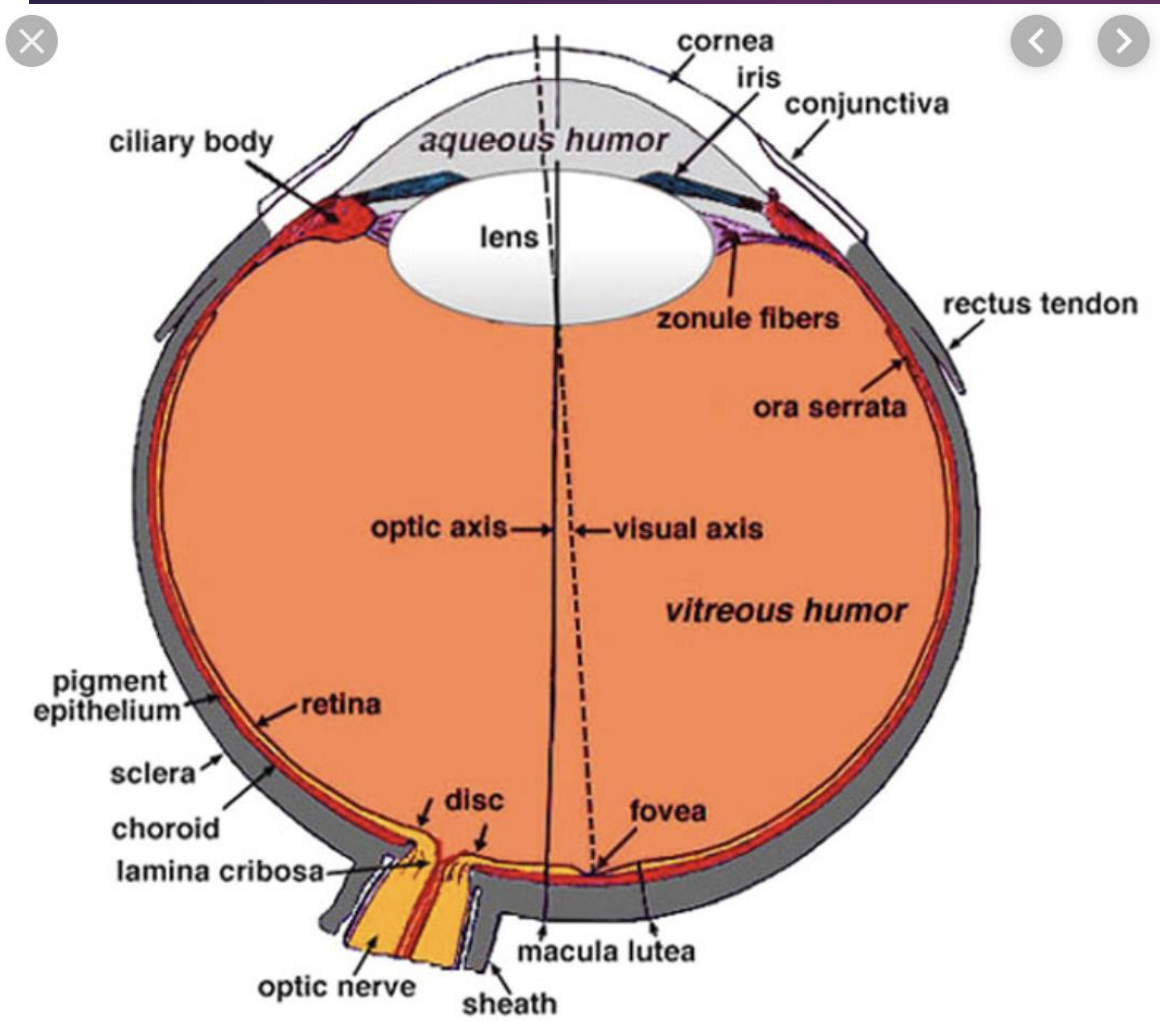
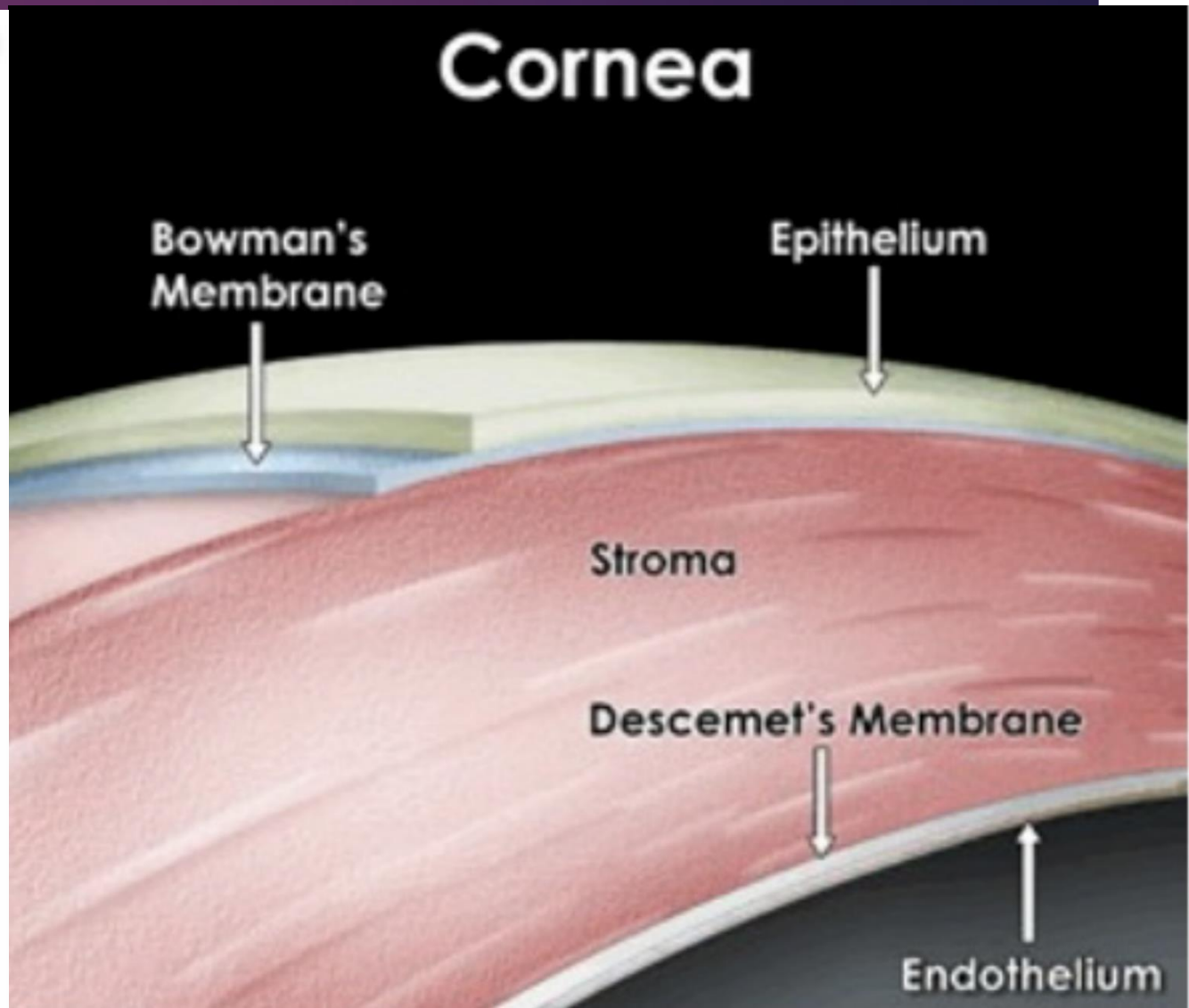
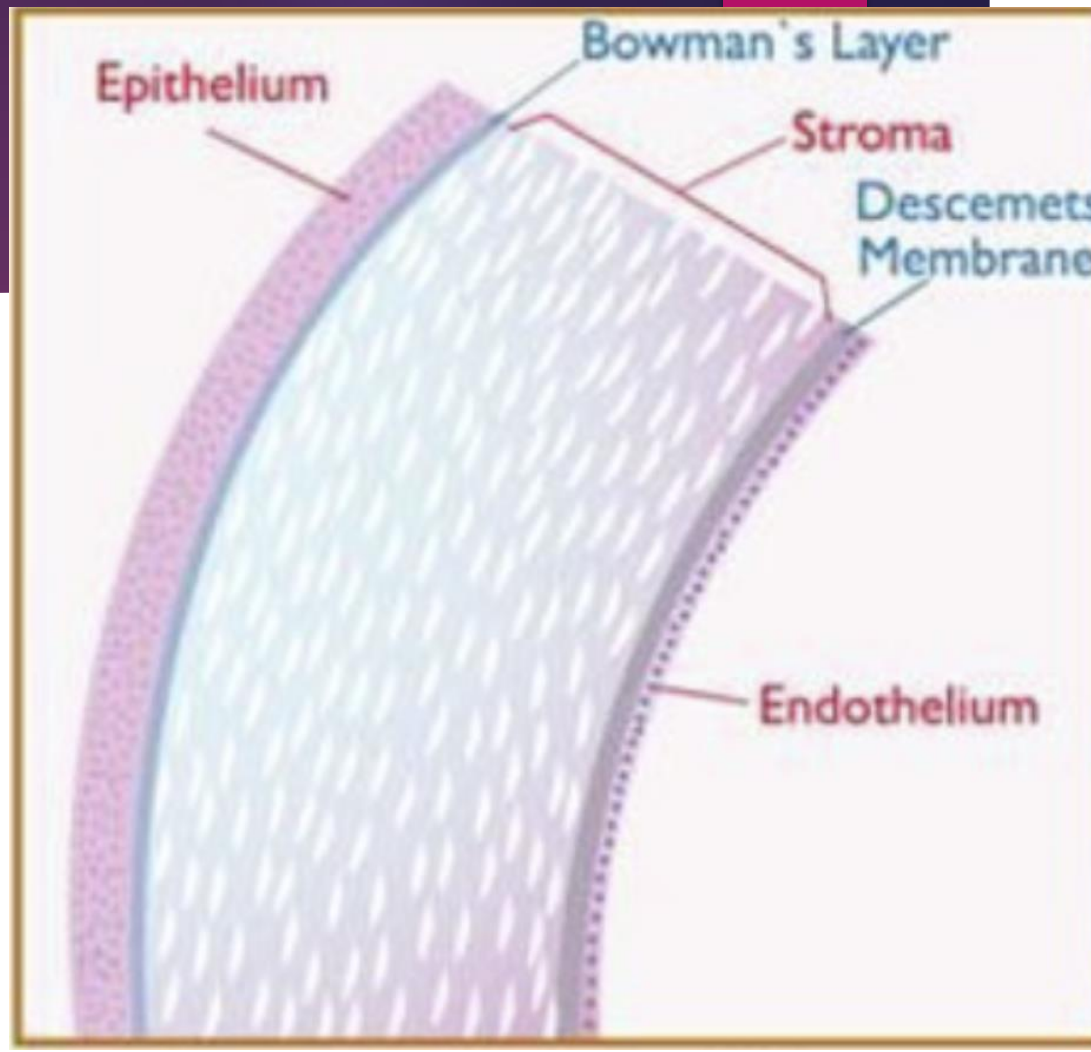


Fig. 2. Sagittal horizontal section of the adult human eye.



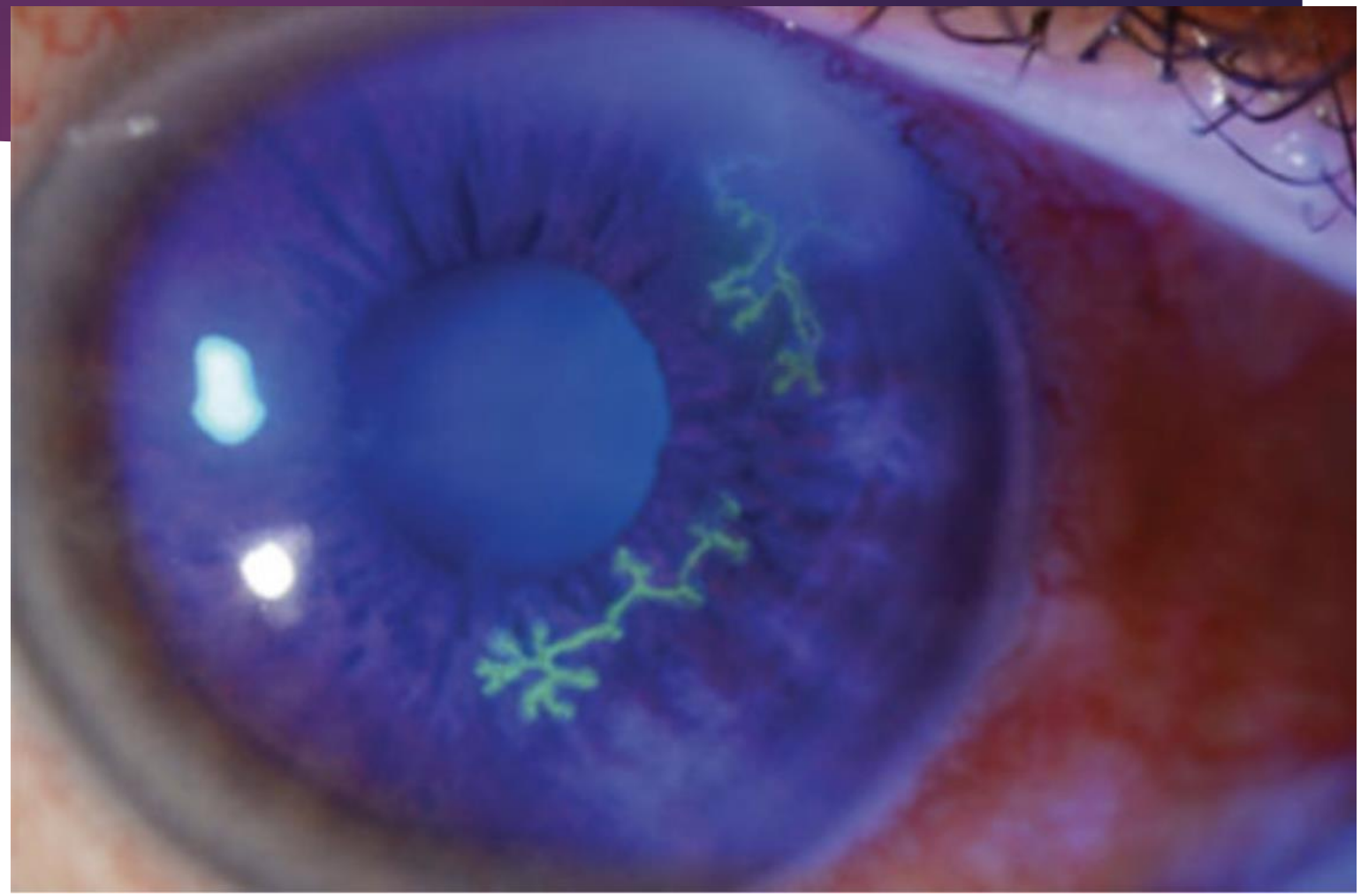
Definitions

- Epithelial HSV = active surface infection/ulcer
- Stromal – immune response, affecting the deeper, main body of the cornea. Causes scarring.
- Endothelial – inflammation of the inner corneal layer, with oedema
- Keratouveitis
- Trabeculitis



Dendritic ulcer

- =epithelial HSV keratitis
- Diagnosis?
- Treatment?



Diagnosis of dendritic ulcer - epithelial HSV keratitis

- FLUORESCEIN
- Blue light from slit lamp
- Blue light from ophthalmoscope
- Magnification – any

- LOWER LID SWAB FOR PCR will confirm

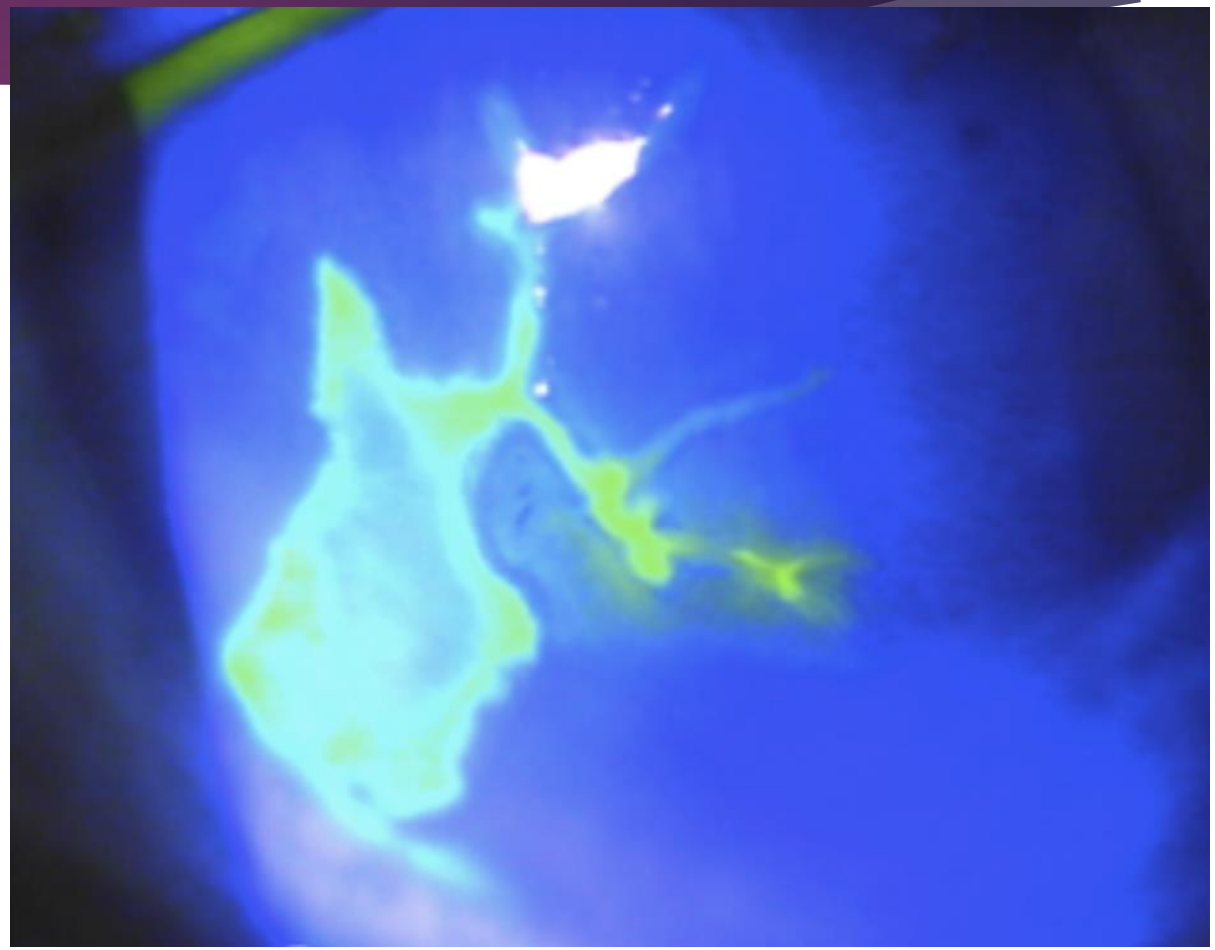
Treatment of dendritic ulcer - epithelial HSV keratitis

- ORAL TREATMENT IS *AS EFFEECTIVE* AS TOPICAL (multiple studies)
- Aciclovir ointment 5x per day for 7-10 days
- Ganciclovir gel 5x per day for 7-10 days
- Valaciclovir tabs 500mg PO bd or tds for 7-10 days
- Aciclovir 400mg tabs PO 5x per day for 7-10 days

- DON'T TREAT FOR WEEKS ON END WITH TOPICAL ANTIVIRALS DUE TO EPITHELIAL TOXICITY

Geographic ulcer

- = epithelial HSV
- More extensive and severe than dentritic ulcer
- Treatment?

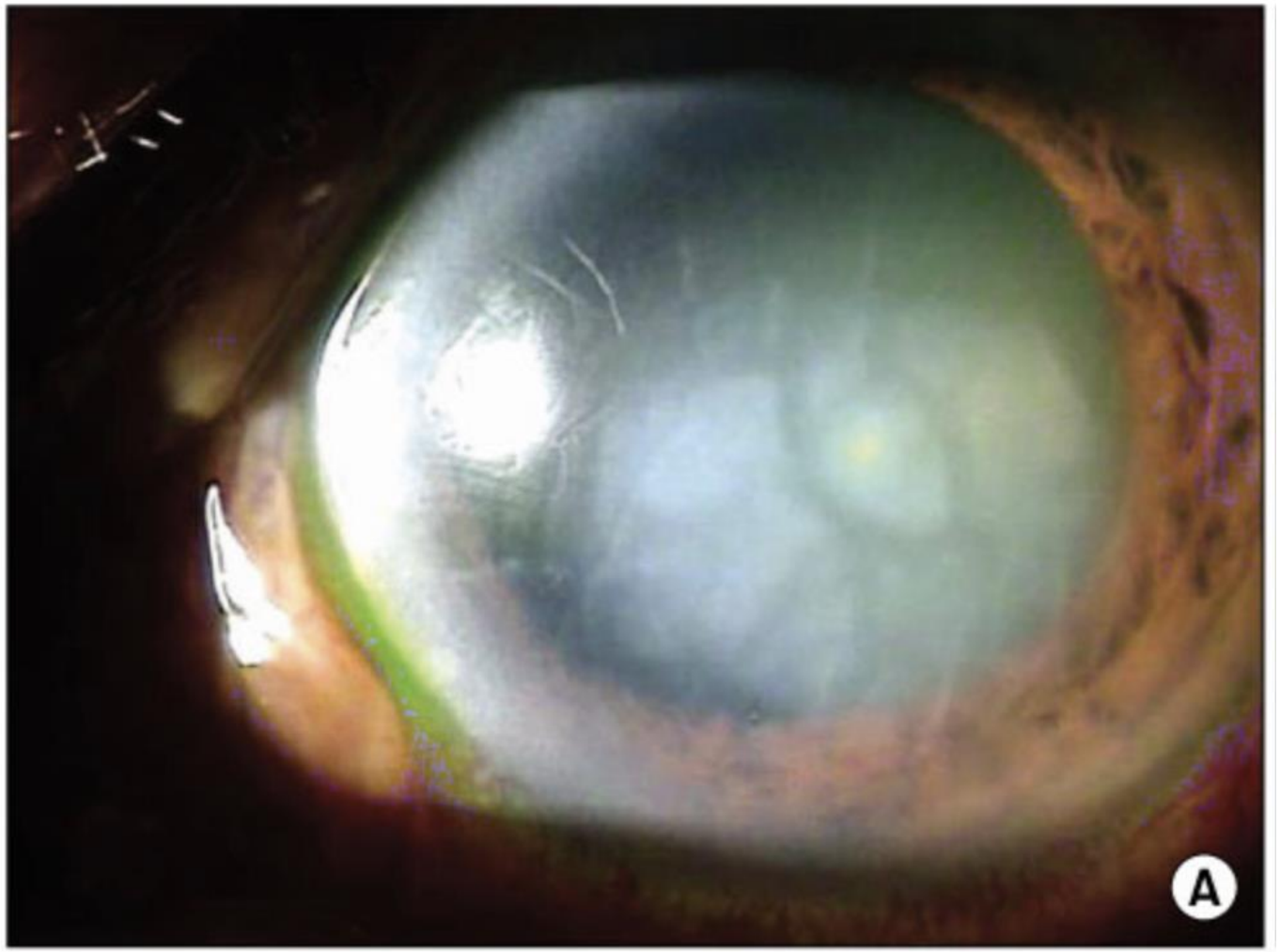


Treatment of geographic ulcer – ‘higher grade’ epithelial HSV

- Higher dose/longer
- Oral Valaciclovir 500mg to 1g PO tds for 7-10 days
- Aciclovir eye ointment 5x per day for 7 days then review

Stromal keratitis

- Immune response to HSV
- Treatment?



Treatment of stromal HSV keratitis

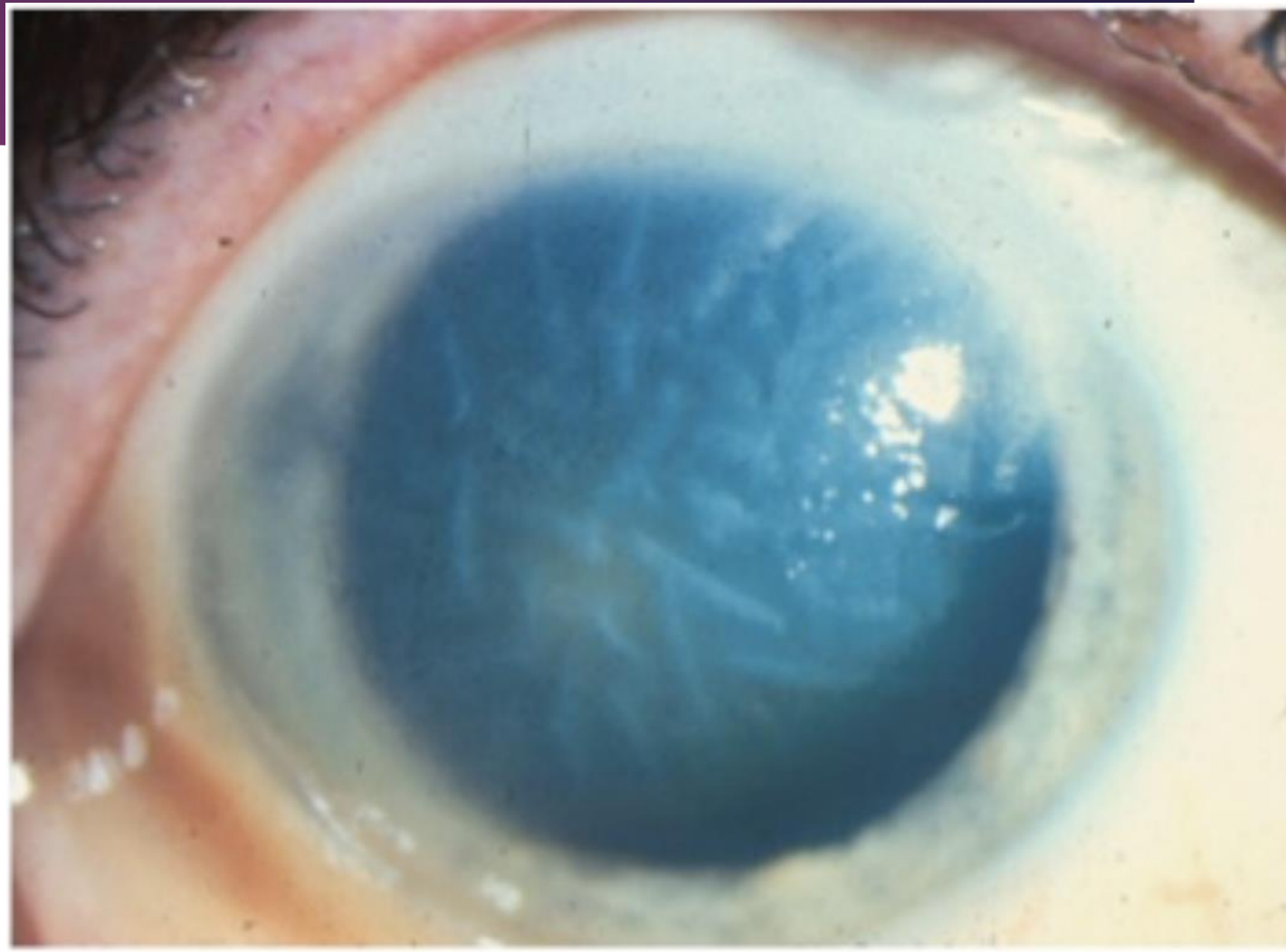
- STEROID treatment for AT LEAST 10 WEEKS
- AND prophylactic antiviral

- Eg dexamethasone eye drops qid, taper over 3 months
- Valaciclovir 500mg PO daily prophylaxis against viral reactivation

- OPHTHALMOLOGY MONITORING
  - Side effects of steroid (pressure, reinfection)
  - Corneal melting
  - Corneal scarring

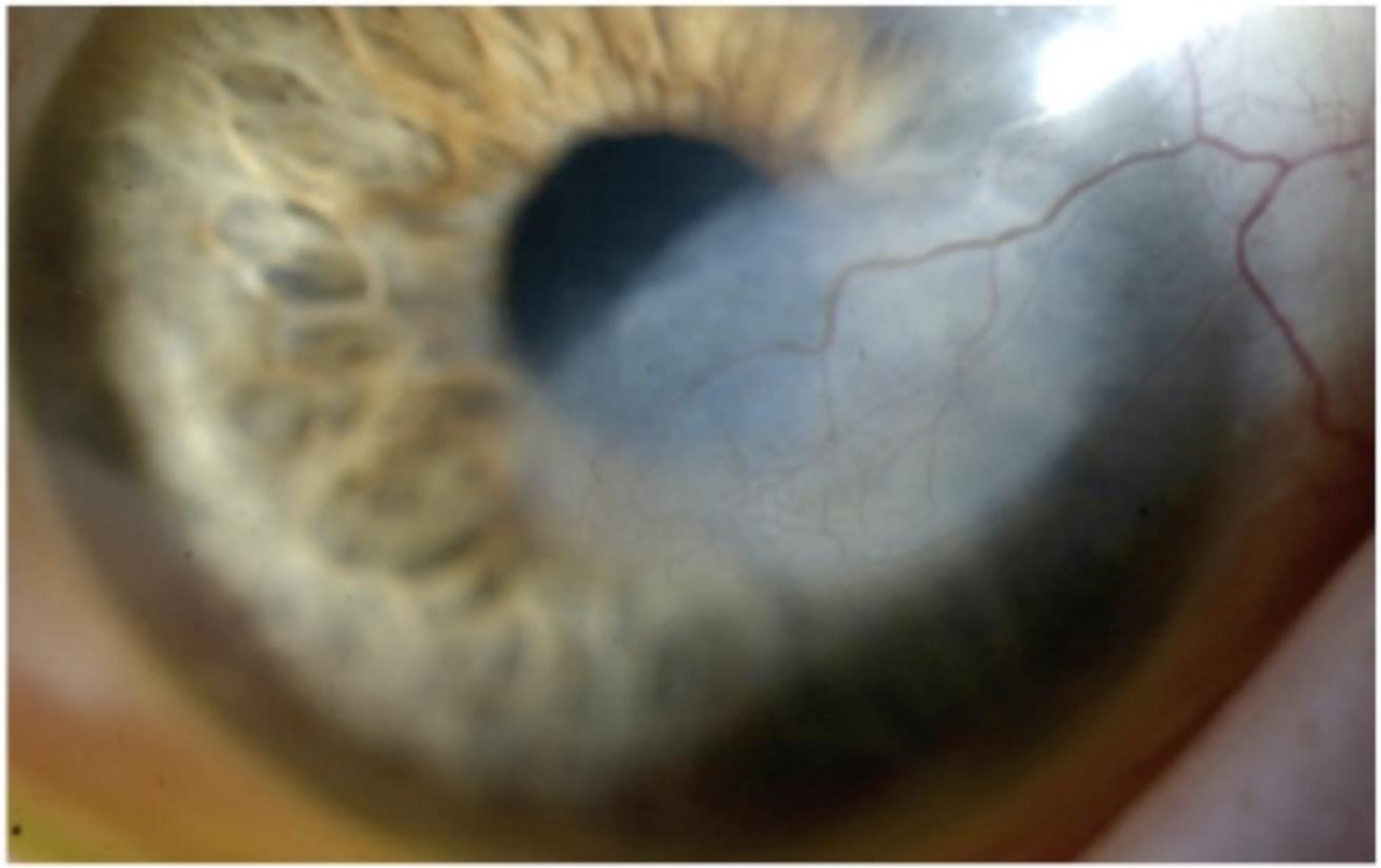
Disciform keratitis

- = endothelial HSV
- Treatment?
- As per stromal
- May have raised IOP



Vascularised Scar

- Corneal stromal scarring
- Treatment?
- Subconjunctival anti-VEGF
- Surgery (corneal transplant)
- Maintenance steroid and antiviral prophylaxis



Current Best Practice in Rx HSV[1]

- Dendritic ulcers:
  - 7-10 days of topical OR oral Rx 500mg bd or 400mg 5x
  - Oral and topical shown to be equivalent
  - Don't use topical antivirals for weeks on end, cause epithelial toxicity
- Geographic ulcers
  - Treat longer and stronger – 14-21 days (if oral 800mg 5x /1g tds)
- Stromal keratitis
  - Oral antivirals and topical steroid and taper for longer than 10 weeks
- Disciform keratitis
  - As per stromal

1. White and chodosh, Harvard/Mass Eye and Ear/ AAO guidelines 2014

Aciclovir resistant HSV

- 0.1-0.6% of HSV in immunocompetent patients
- 3.5 – 10% in immunocompromised
- 30% reported in allogeneic BMT recipients[1]

- Can result in mucosal disease and visceral dissemination in immunocompromised patients
- Usually result of viral Thymidine kinase mutation

Jiang et al, Int J Oral Sci, 2016

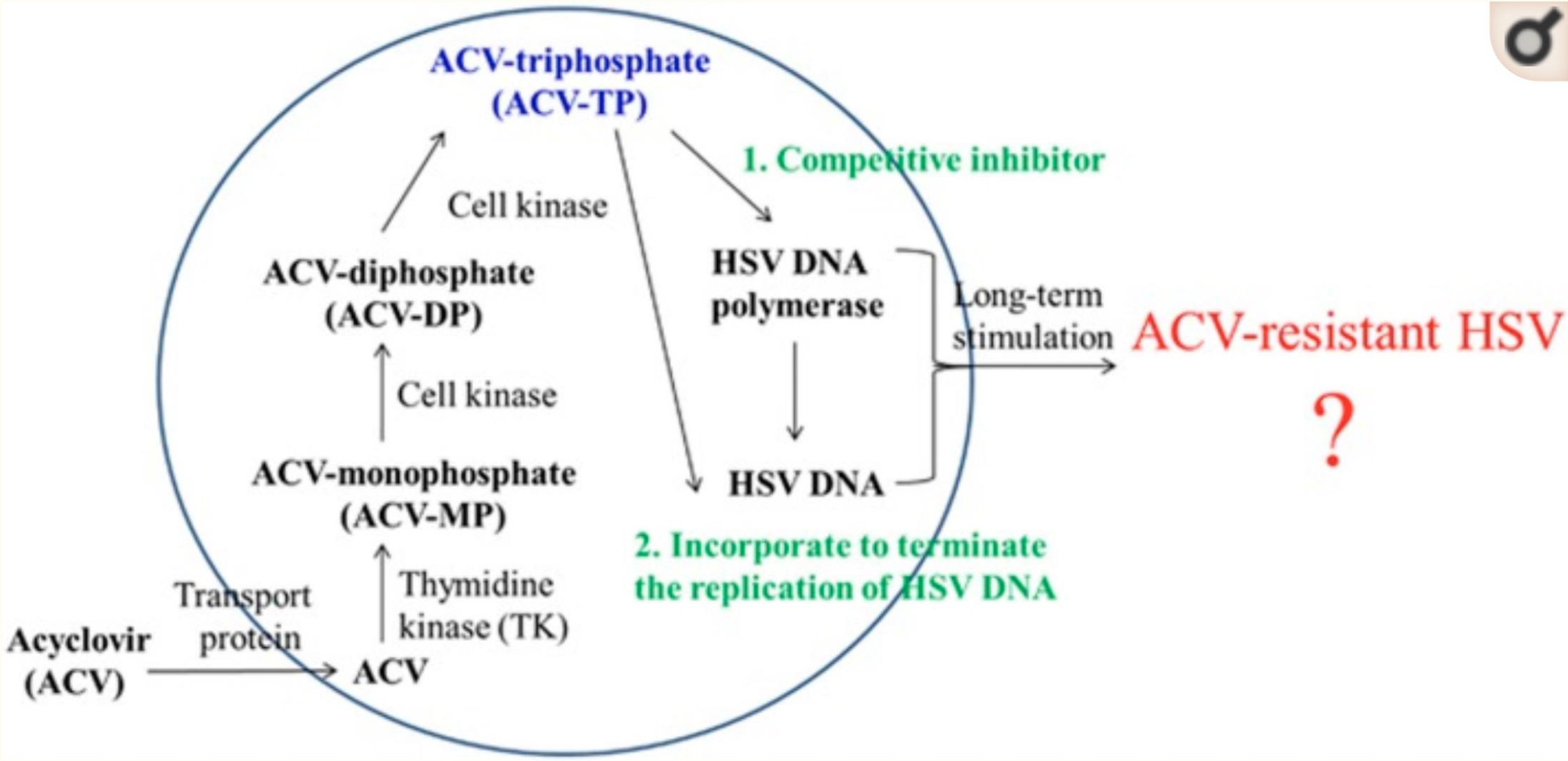


Figure 1

The anti-HSV mechanism of ACV. ACV, acyclovir; HSV, herpes simplex virus.

Antiherpetic drugs

- Purine analogues
  - Guanosine analogues – ACV, GCV, FCV, PCV, VACV, VGCV
  - Adenosine analogues – vidarabine
- Pyrimidine analogues
  - Trifluridine, idoxuridine
- Nucleotide analogues
  - Cidofovir, adefovir
- Pyrophosphate analogues
  - foscarnet

Topical Povidone Iodine as an antiviral

- Good evidence for efficacy against other viruses
- Oct 2018 AJO India Pepose et al
- Adenoviral conjunctivitis
- Povidone Iodine 0.6% plus dexamethasone 0.1% qid for 5 days
- reduces symptoms, duration, and improves viral clearance
- Better with dex than without for symptoms, similar clearance

- Thankyou!

Detected mutations in Thymidin Kinase gene of sample 17AI0123K:

Nucleotide	Amino Acid	Effect	Drug susceptibility testing (plaque reduction assay)					Reference
			ACV	BVDU	PCV	FOS	CDV	
A68G	N23S	Natural polymorphism						Sauerbrei, 2015
A106G	K36E	Natural polymorphism						Sauerbrei, 2015
G181A	G61R	Probable resistance as G61A mentioned to confer ACV	R	R	R	S	S	Sauerbrei, 2015
G266A	R89Q	Natural polymorphism						Sauerbrei, 2015
C278T	A93V	ACV resistant PCV sensitive FOS sensitive CDV sensitive	R EC_{50} > 40 µM	Not tested	S EC_{50} 9.7 µM	S EC_{50} 92.1 µM	S EC_{50} 2.8 µM	Sauerbrei, 2015
G793A	A265T	Natural polymorphism						Sauerbrei, 2015

ACV: Acyclovir
BVDU: Brivudin
PCV: Penciclovir
FOS: Foscarnet
CDV: Cidofovir

Case points

- Aciclovir resistance
- Alternative treatments for HSV – foscarnet, trifluridine, iodine
- Current best practice for treatment of HSV keratitis

APPENDIX I: Antiviral Agents Effective Against Herpes Simplex Virus

Formulation	Antiviral Agent	Available in the United States	FDA Approved for HSV-1 Infection	FDA Approved for HSV Keratitis	Limitations
Topical					
	Trifluridine Solution	Yes	Yes	Yes	
	Ganciclovir Gel	Yes	Yes	Yes	
	Acyclovir Ointment	No	Widely used in Europe		
	Idoxuridine	No longer manufactured			
	Vidarabine	No longer manufactured			
	Brivudine	No longer manufactured			
Oral					
	Acyclovir	Yes	Yes	No	
	Valacyclovir	Yes	Yes	No	
	Famciclovir	Yes	Yes	No	
	Brivudine	No	No	No	
	Valganciclovir	Yes	No	No	Safety*
Intravenous					
	Acyclovir	Yes	Yes	No	
	Foscarnet	Yes	Yes	No	Safety*
	Cidofovir	Yes	No	No	Safety*
	Ganciclovir	Yes	No	No	Safety*

* Please see manufacturers' prescribing information for details.

Current Best Practice in Rx HSV[1]

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1. White and chodosh, Harvard/Mass Eye and Ear/ AAO guidelines 2014

Epithelial toxicity of acyclovir/ganciclovir

- Punctate epitheliopathy becomes more common after ten days
- In already neurotrophic corneas may prolong or stop healing
- In already dry corneas may prolong or stop healing
- Use only as required
- Oral antivirals are valid alternatives

Valacyclovir vs Acyclovir

- Fully funded 1 March 2016 by Pharmac
- Dose as low as 500mg PO bd for 7/7 effective for epithelial dendrites (I would use more usually)
- Prodrug
- 3-5x plasma levels of acyclovir for same dose (first pass and hepatic conversion to acyclovir)
- Valtrex available for many years in US/Australia and not expensive
- For Shingles 1000mg PO tds
  - Pain reduced 25% faster cf acyclovir

trifluridine

- Pyrimidine nucleoside analogue
- ?does not require viral thymidine kinase for phosphorylation
- Much higher systemic toxicity than acyclovir

Trifluridine

- Indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2
- 1 gtt onto cornea q2hr while awake until reepithelialization (not to exceed 9 gtt/day), THEN
- 1 gtt q4hr (minimum 5 gtt/day) x7 days
- Not to exceed treatment beyond 21 days

Trifluridine corneal toxicity

- Punctate keratopathy
- Stromal oedema
- Toxicity may become severe if used > 2 weeks (C Rapuano, Wills)

- Note trifluridine EXTREMELY WIDELY USED in USA, as FDA approval for ganciclovir only in 2010!. Acyclovir still not FDA approved in US.
- Prior to 2010 Valtrex bd PO widely used as first line

Foscarnet

- Inhibits viral DNA polymerase
- Not activated by viral kinases therefore mutant thymidine kinase does not confer resistance
- Resistance can be conferred by mutant dna polymerase
- Dose 2.4mg/0.1mL (can use 0.05mL of this) intravitreal injection
- Twice weekly treatment, once weekly maintenance
- Effective against CMV, HSV