

# Clinical Grand Rounds:

## Herpes:

“Everything you wanted to know, but  
were afraid to ask”

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# What is a virus?

- \* Small infectious (100 times smaller than bacteria) agent that can only replicate inside the living cells of organisms
- \* Latin = “to poison”
- \* "obligate intracellular parasites"

# Herpes Virus Family

- \* HSV 1 - Cold sores and ophthalmic infections
- \* HSV 2 - Genital
- \* HSV 3 - Varicella-Zoster (chicken pox and shingles)
- \* HSV 4 - Epstein-Barr (mononucleosis)
- \* HSV 5 - Cytomegalovirus
- \* HSV 6/7 - exanthum subitum / roseola infantum
- \* HSV 8 - Kaposi's Sarcoma

# Herpes Virus 1

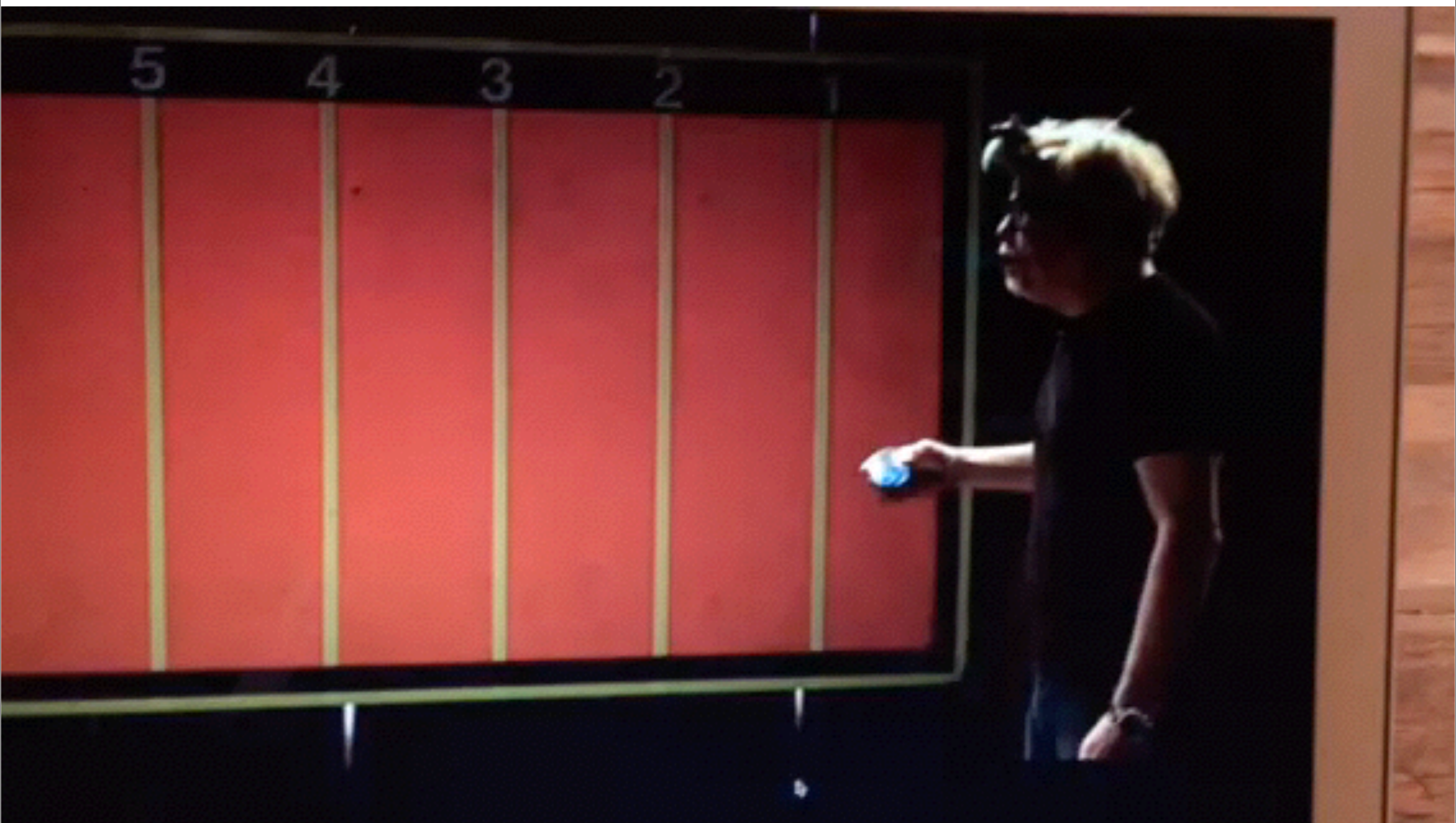
- \* “ubiquitous human pathogen”
- \* causes both **asymptomatic** and **symptomatic** infection
- \* both **HSV 1 & 2** can infect the eye, although typically HSV 1 is much more common
  - \* exception: in neonates, 75% HSV 2
- \* different viral strains may produce different patterns of ocular disease

# HSV Epidemiology

- \* Patients ask: **How did I get it?**
- \* Humans are the only natural reservoir of HSV
- \* close personal contact (mucous membranes and external skin)
- \* primary infection **usually** asymptomatic and is followed by latency in sensory ganglia (trigeminal ganglia)
  - \* primary infection manifests only 1-6% of the time
- \* clinical appearance of an infection may represent reactivation of an earlier primary infection at a different end organ





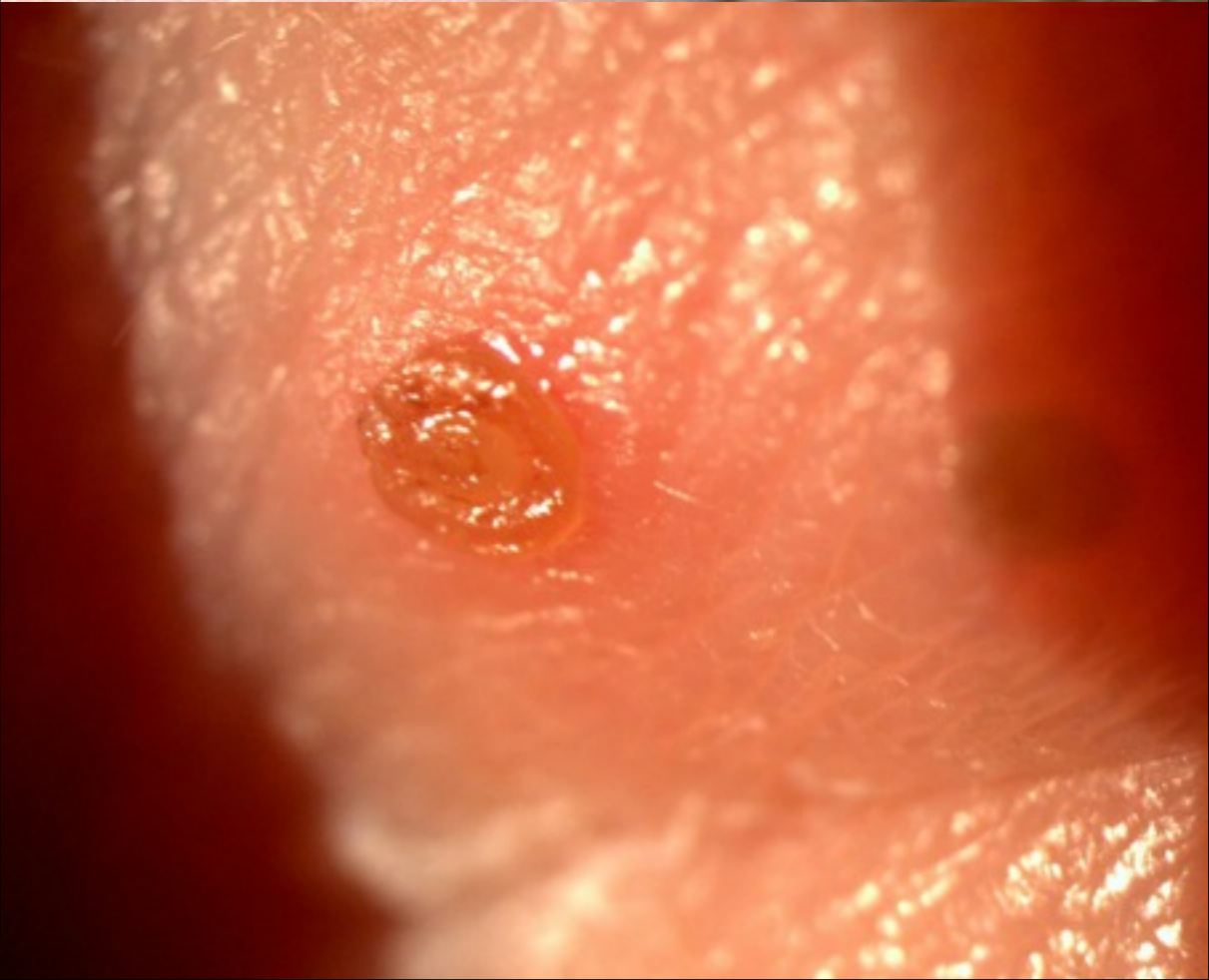
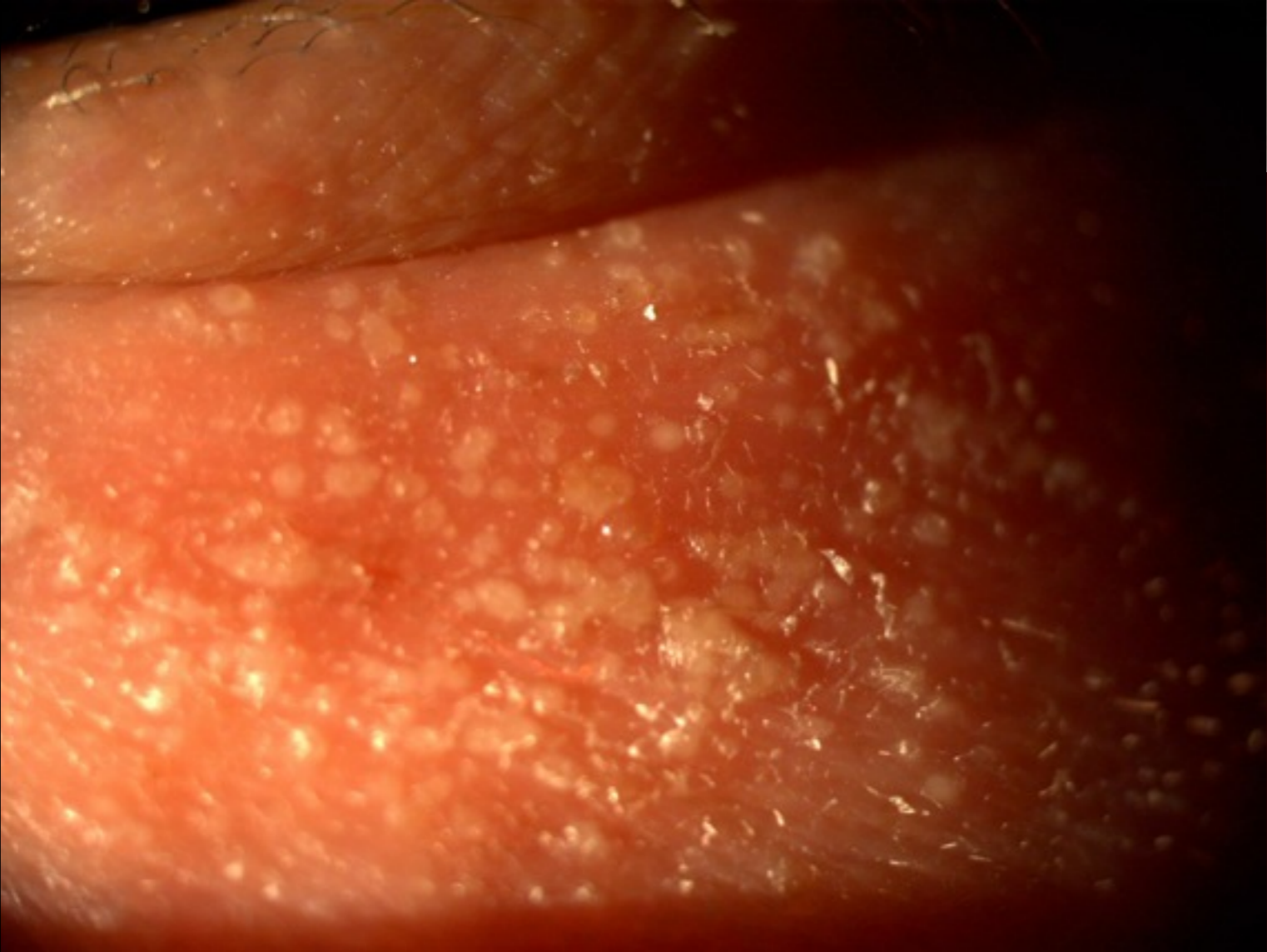


# Clinical Manifestations

- \* Congenital -rare
- \* Neonatal:
  - \* usually HSV 2 passed on from mother
  - \* 1500-2000 cases per year
- \* Historically by the age of 5, 60% of the population has been infected with HSV although this is trending down due to pediatric vaccination

# Herpetic Blepharitis

- \* **focal vesicular lesions** on the eyelid with surrounding erythema (similar to that of a cold sore around the mouth)
- \* will progress to **ulceration and crusting**
- \* frequently seen along with conjunctivitis

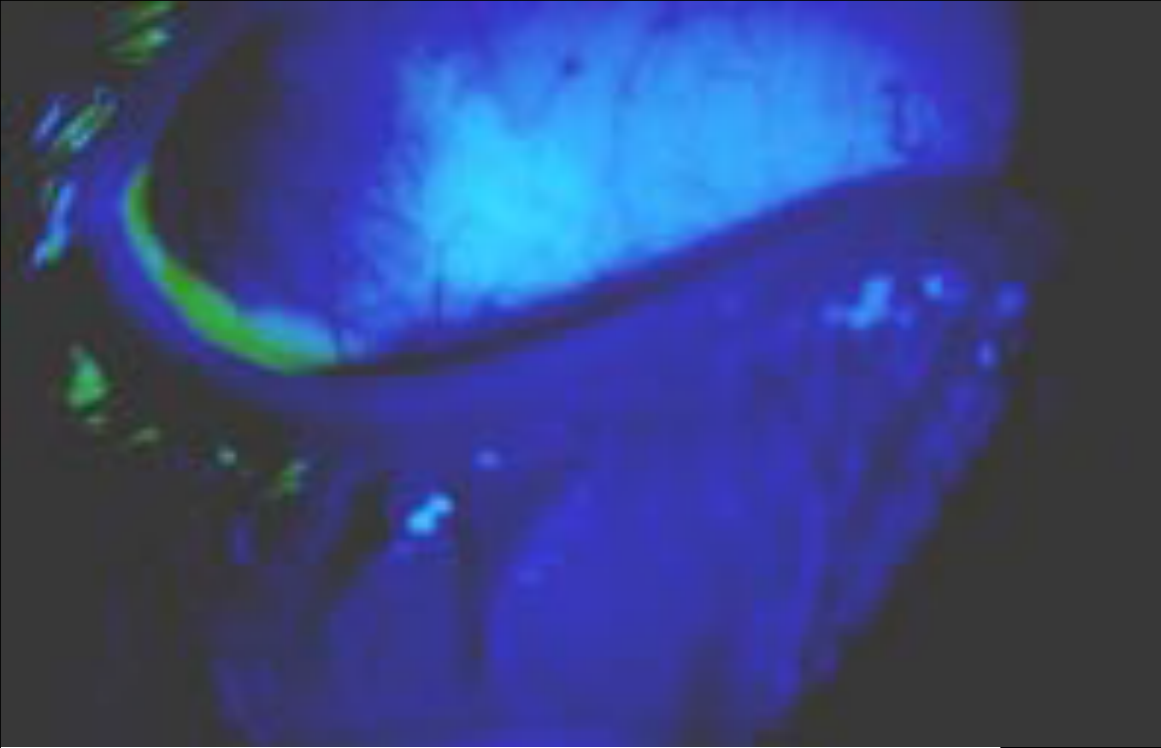


# Herpetic Blepharitis

- \* Treatment:
  - \* Oral antivirals x 7-10 days
  - \* Topical antivirals? - no data to support
  - \* If misdiagnosed as normal blepharitis, antibiotic/steroid combination will make HSV blepharitis worse
  - \* Take home = if you see ulcerative blepharitis, think HSV

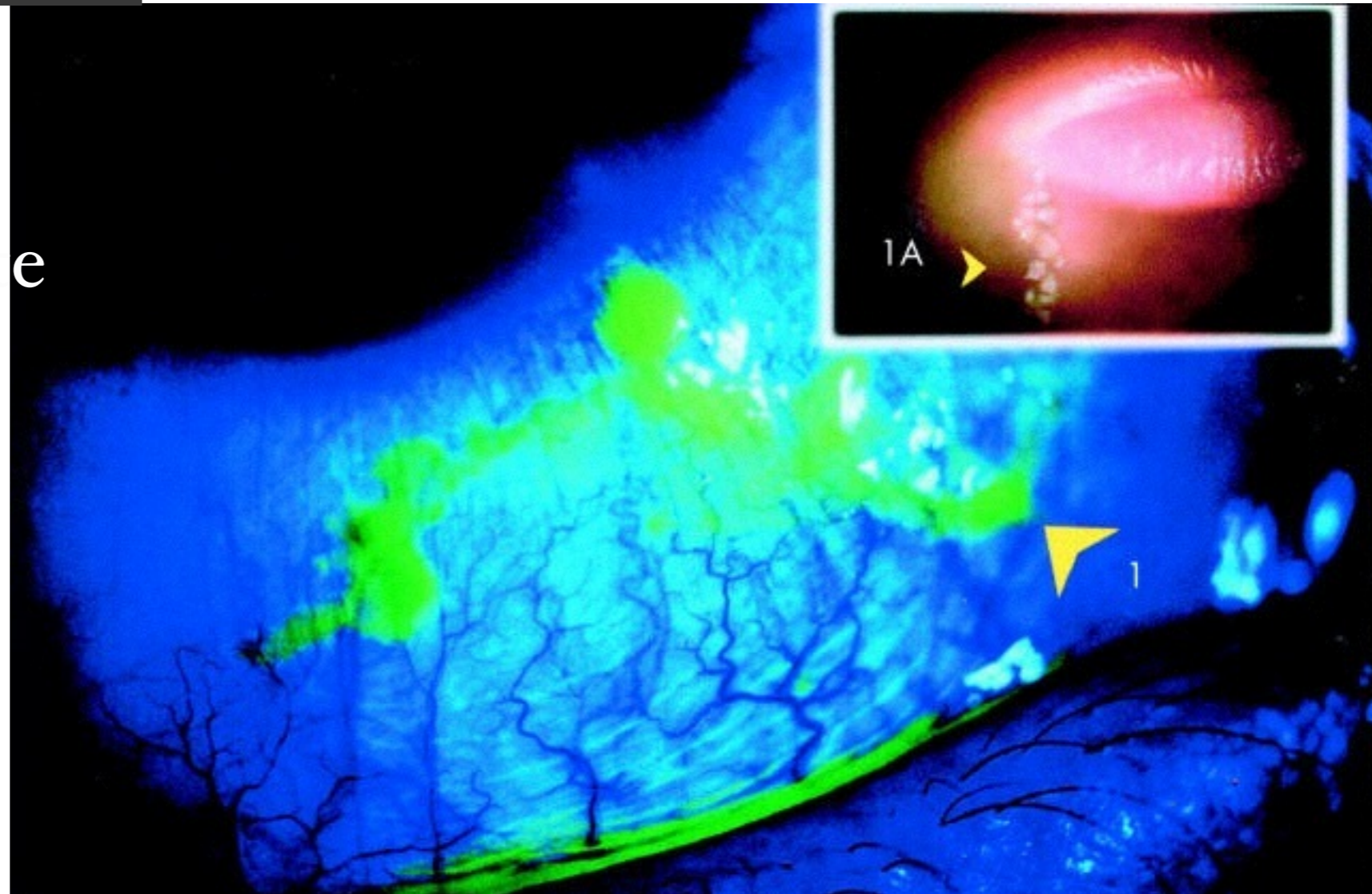
# Herpetic Conjunctivitis

- \* primary HSV can present as **follicular conjunctivitis**
- \* may be responsible for up to **23% of all cases**
- \* often self limiting, BUT can go on to subsequent keratitis
- \* can see conjunctival dendritic ulcers with stain



\* Geographic conjunctival dendrite

\* Conjunctival dendrite



# HSV Conjunctivitis

- \* Treatment:

- \* Oral antivirals 7-10 days

- \* Topical antivirals? - with consideration of expense, may be more than you need

- \* If treated with the Gold Standard for all conjunctivitis i.e. Tobradex, you will see worsening

- \* **Take home =**

- \* **1. Conjunctivitis can be from HSV**

- \* **2. Stain all conjunctivitis to look for dendrites on conj or cornea**

- \* **3. Followup conjunctivitis pts and warn if they worsen to RTC**



# HSV Keratitis

- \* World Health Organization (WHO)
- \* Corneal Scarring/Blindness is 4th most common reason for visual loss on the planet
- \* “one of the most challenging entities confronting the clinician”

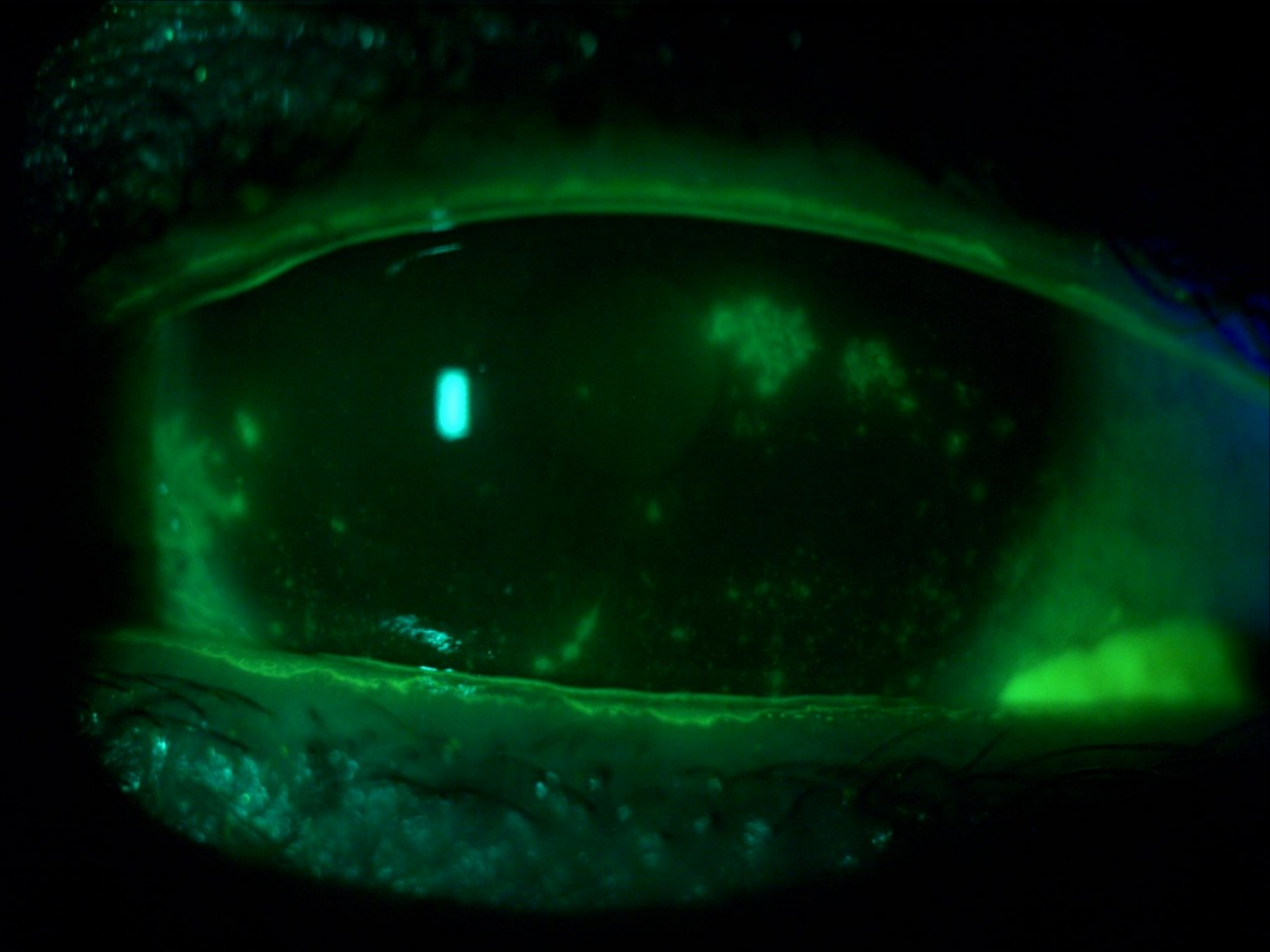
# Classification of HSV Keratitis

1. Infectious Epithelial Keratitis
2. Stromal Keratitis
3. Endothelialiitis
4. Neurotrophic Keratopathy

# Infectious epithelial keratitis

## I. **Corneal Vesicles**

- \* earliest epithelial lesion
- \* minute, raised, clear vesicles
- \* with time coalesce to form a raised, dendritic lesion
- \* eventually becomes dendritic ulcer



A high-magnification electron micrograph showing a Herpes Simplex Virus (HSV) dendrite. The dendrite is a long, thin, and highly branched structure with numerous small, bulbous terminal ends. It is surrounded by a network of fine, dark lines representing cytoplasmic filaments. The overall structure is complex and tree-like, characteristic of viral dendrites.

\* HSV Dendrite

- terminal bulbs

- swollen epithelium at end bulbs

- ulcerated lesion

# Infectious epithelial keratitis

## 2. Dendritic ulcer:

- \* most common presentation
- \* “dendron” = tree
- \* branching, linear lesion with terminal bulbs and swollen epithelial borders that contain live virus
- \* true “ulcer” = loss of tissue extending through the basement membrane
- \* differentiate between:
  - \* healing epithelium / recurrent corneal erosion
  - \* herpes zoster pseudodendrites

# Infectious epithelial keratitis

## Dendritic ulcer:

- \* staining patterns:

- \* NaFl will stain ulcerated base, but not terminal bulbs

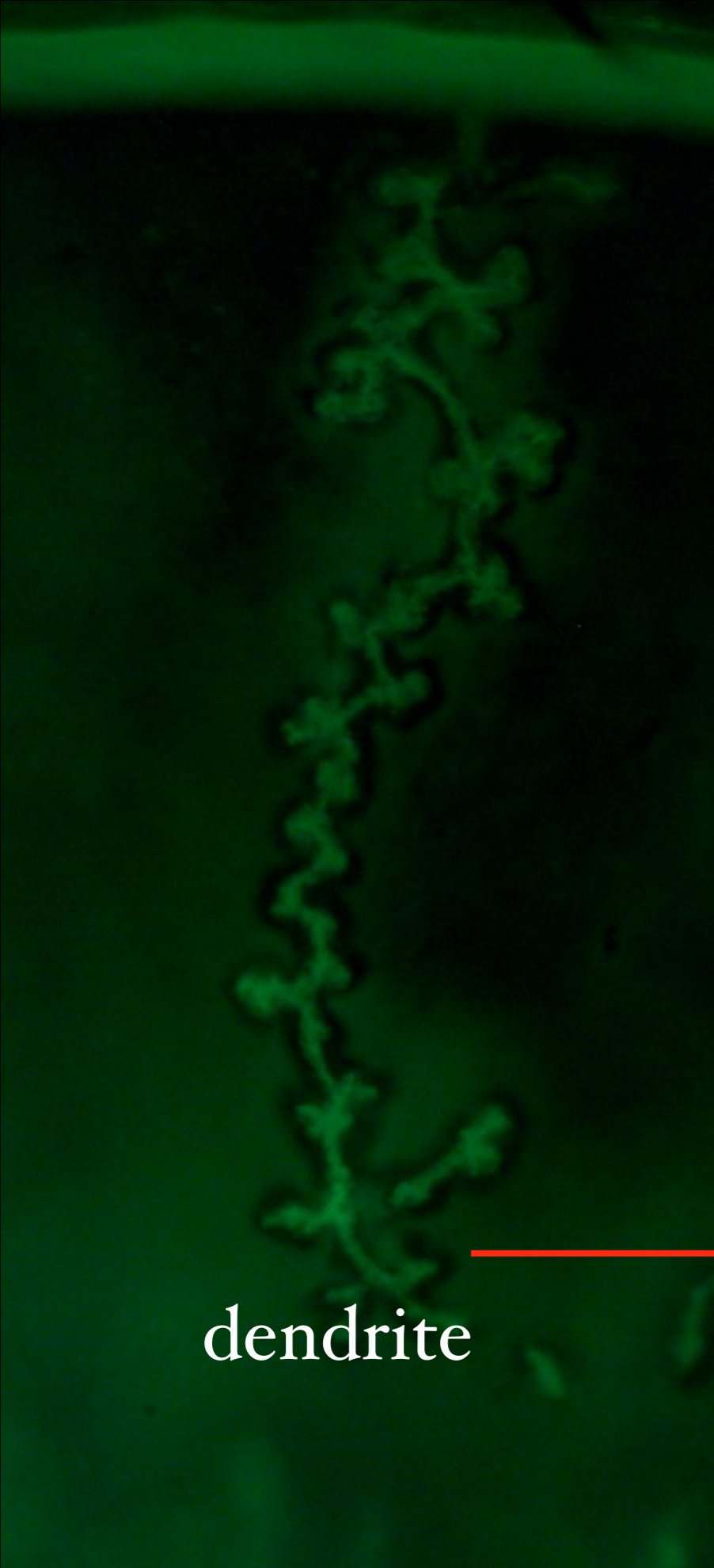
- \* Rose bengal will stain swollen epithelial cells at the borders

- \* rose bengal is toxic to HSV, therefore do not use Rose bengal until after culturing

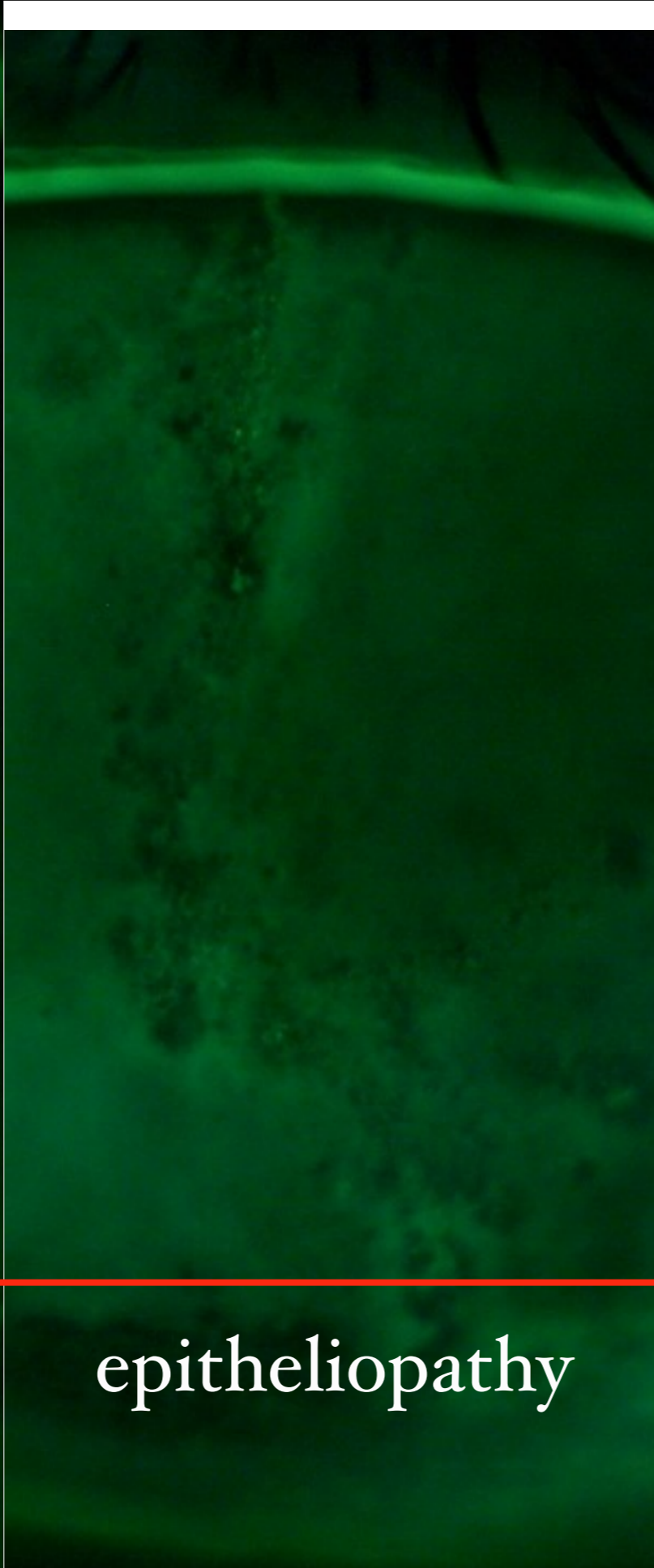
# Infectious epithelial keratitis

- \* Dendritic ulcer:
  - \* following resolution of the dendritic ulcer, epithelium will be abnormal for several weeks
  - \* dendritic epitheliopathy, HSV footprinting

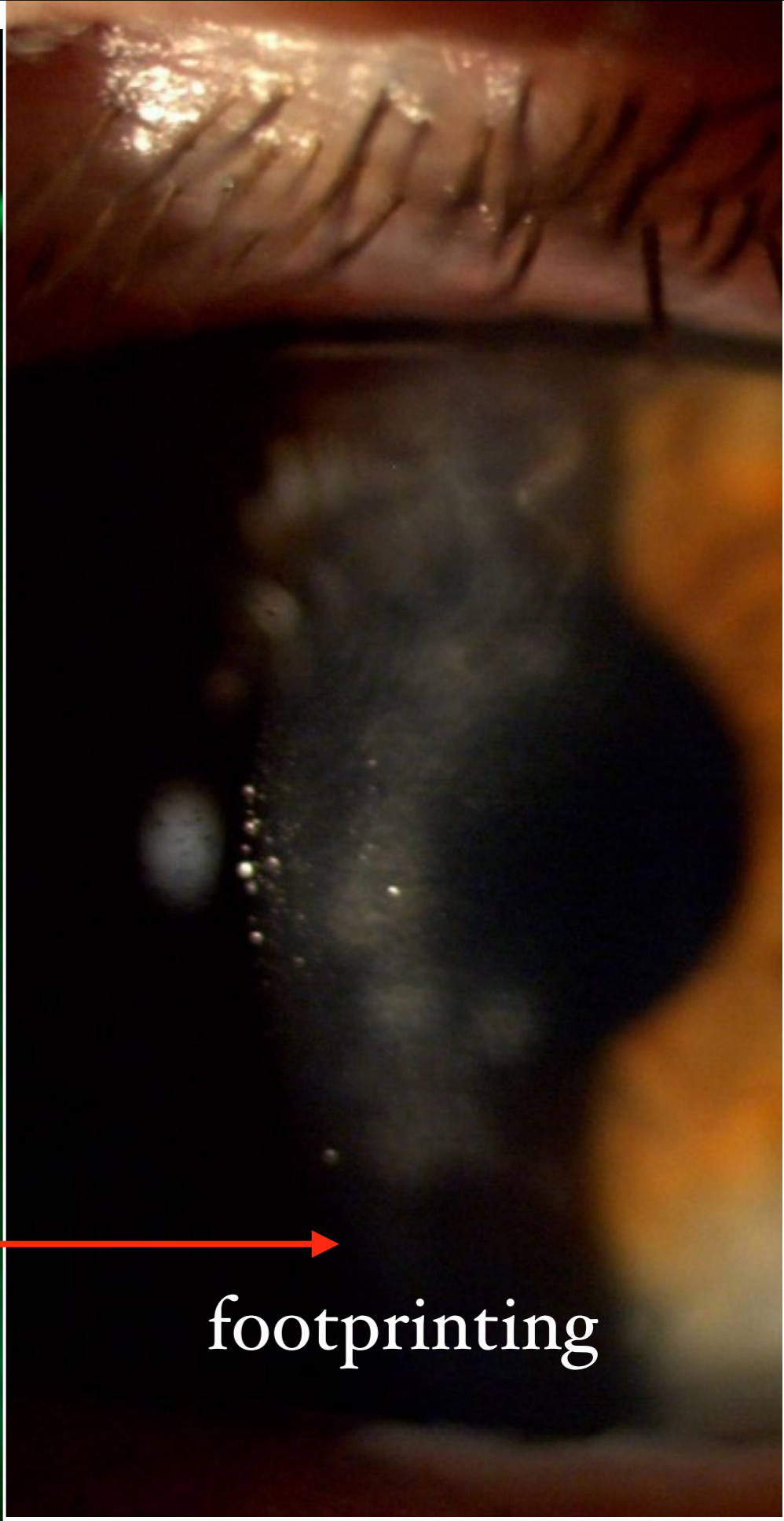




dendrite



epitheliopathy



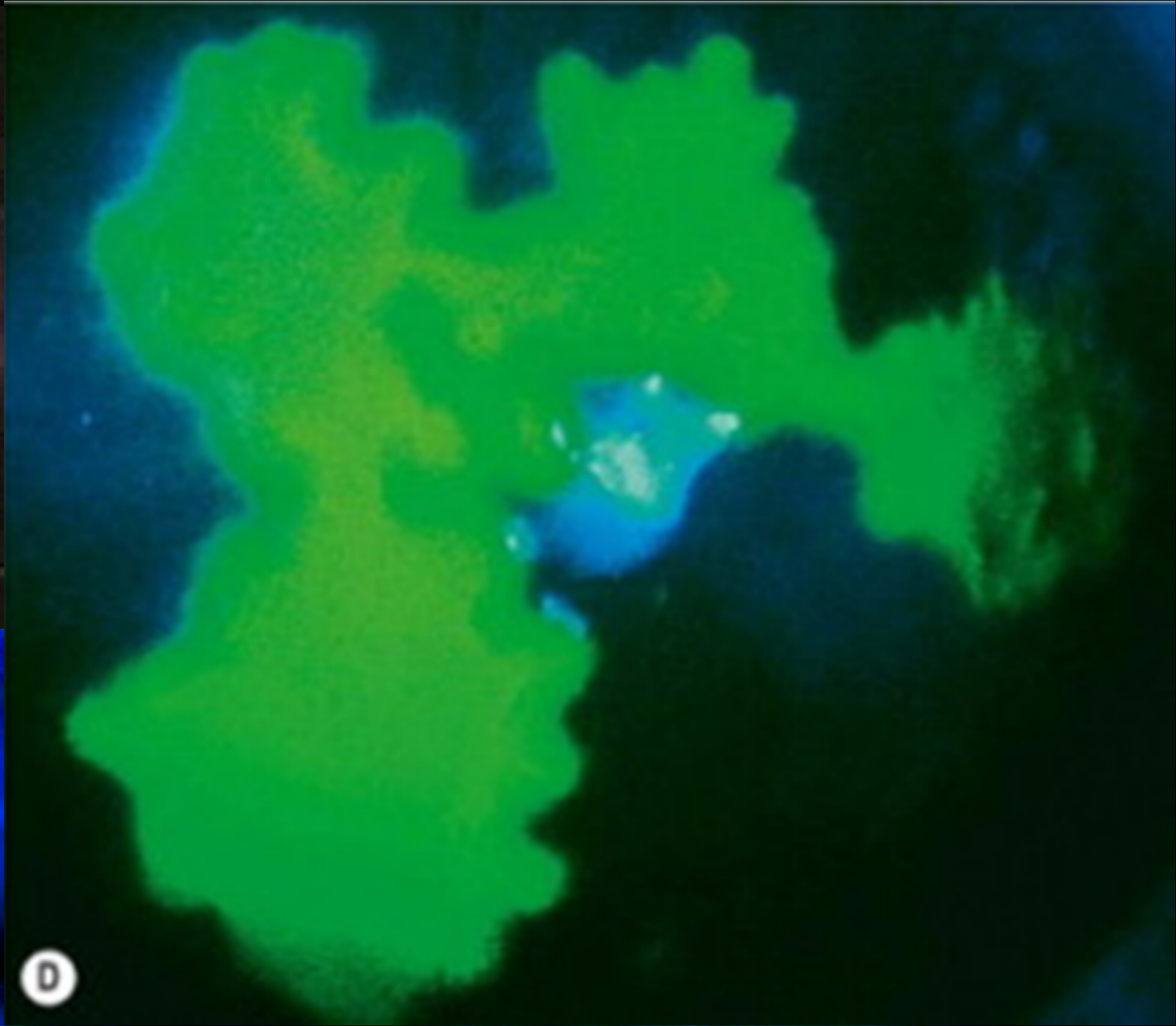
footprinting



# Infectious epithelial keratitis

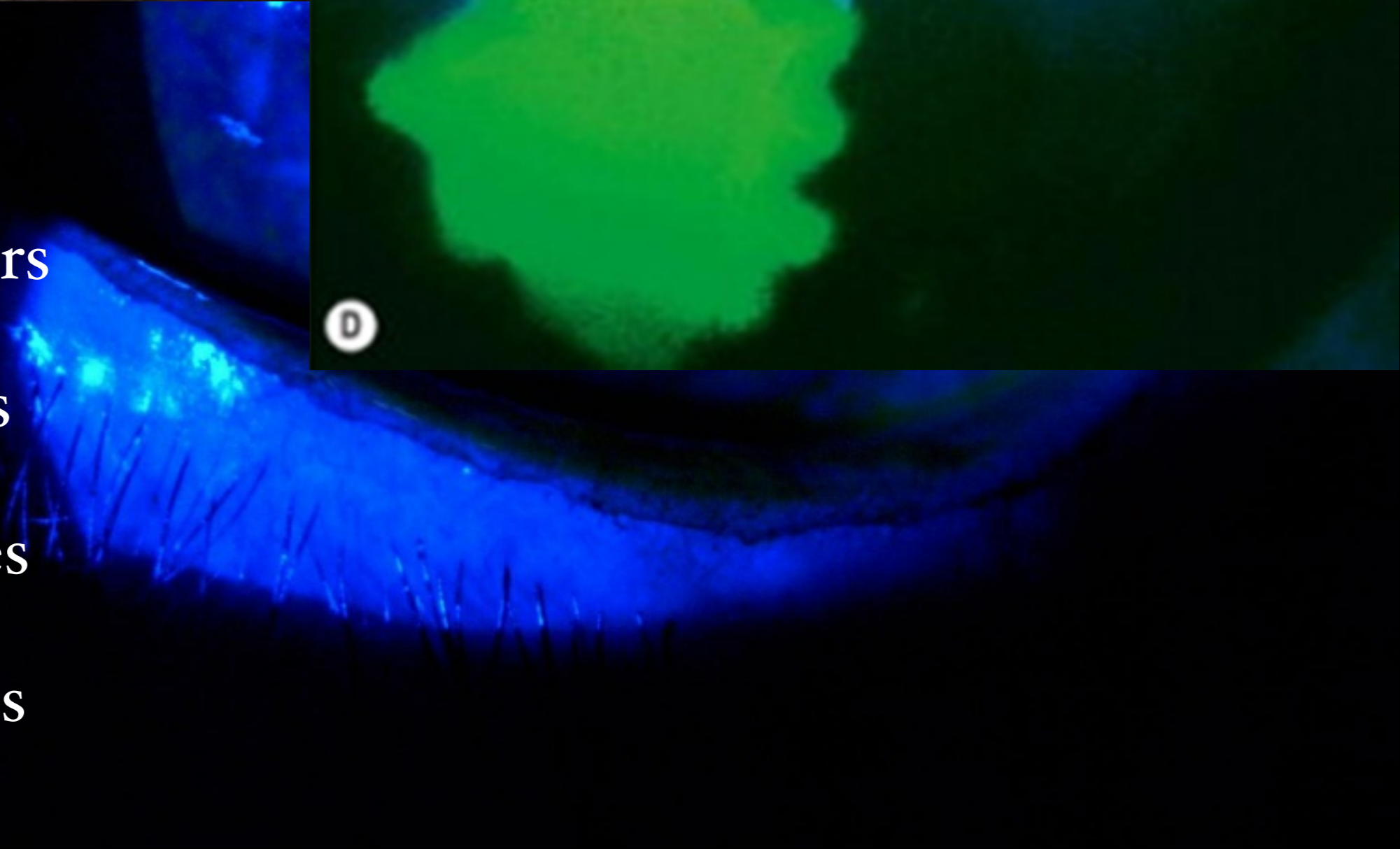
## 3. **Geographic ulcer:**

- \* enlarged dendritic ulcer that is no longer linear
- \* scalloped edges with swollen epithelial borders
- \* differentiate between:
  - \* epithelial defect
  - \* neurotrophic ulcer
- \* can be the result of steroid use on a dendritic ulcer



## Geographic ulcers

- large dendrites
- scalloped edges
- dendritic edges



# Infectious epithelial keratitis

## 4. **Marginal ulcer:**

- \* dendritic ulcers found near the peripheral cornea
- \* tend to be more painful and symptomatic
- \* more inflammation due to proximity of limbal vessels
- \* can be harder to treat due to excessive inflammation
- \* differentiate between:
  - \* staph marginal ulcer

## Marginal HSV

vs.

## Staph Marginal Infiltrate

- \* infectious, with secondary immune reaction
- \* epithelial defect
- \* vascularization
- \* progresses centrally

- \* immune response to staphylococcal antigen
- \* does not start with epithelial defect
- \* no vascularization
- \* progresses circumferentially

A slit lamp photograph of a human cornea showing a marginal infiltrate. The infiltrate is a pale, oval-shaped area located near the periphery of the cornea. A red curved line is drawn below the infiltrate, indicating its spread along the limbus. The surrounding corneal tissue appears normal.

# Staph Marginal Infiltrate

no vascularization

no epithelial defect

spreads along limbus

# Infectious epithelial keratitis

- \* Treatment options:

- \* 1. Debridement:

- \* will resolve in 2-3 days

- \* 2. Topical antivirals:

- \* will resolve in 7-10 days

- \* 3. Oral antivirals:

- \* will resolve in 7-10 days

# Management: Topical Antivirals

| Drug                    | Dosing         | Cost per day |
|-------------------------|----------------|--------------|
| Trifluridine (Viroptic) | q2hr then qid  | \$10         |
| Ganciclovir (Zirgan)    | 5x/day then 3x | \$16         |



# Management: Oral Antivirals

| Drug         | Dosing                 | Cost per day |
|--------------|------------------------|--------------|
| Acyclovir    | 400mg 5 times per day  | \$2          |
| Valacyclovir | 500 mg 3 times per day | \$7          |
| Famciclovir  | 500mg 3 times per day  | \$7          |

# Treatment for Infectious Epithelial Disease?

## Debridement

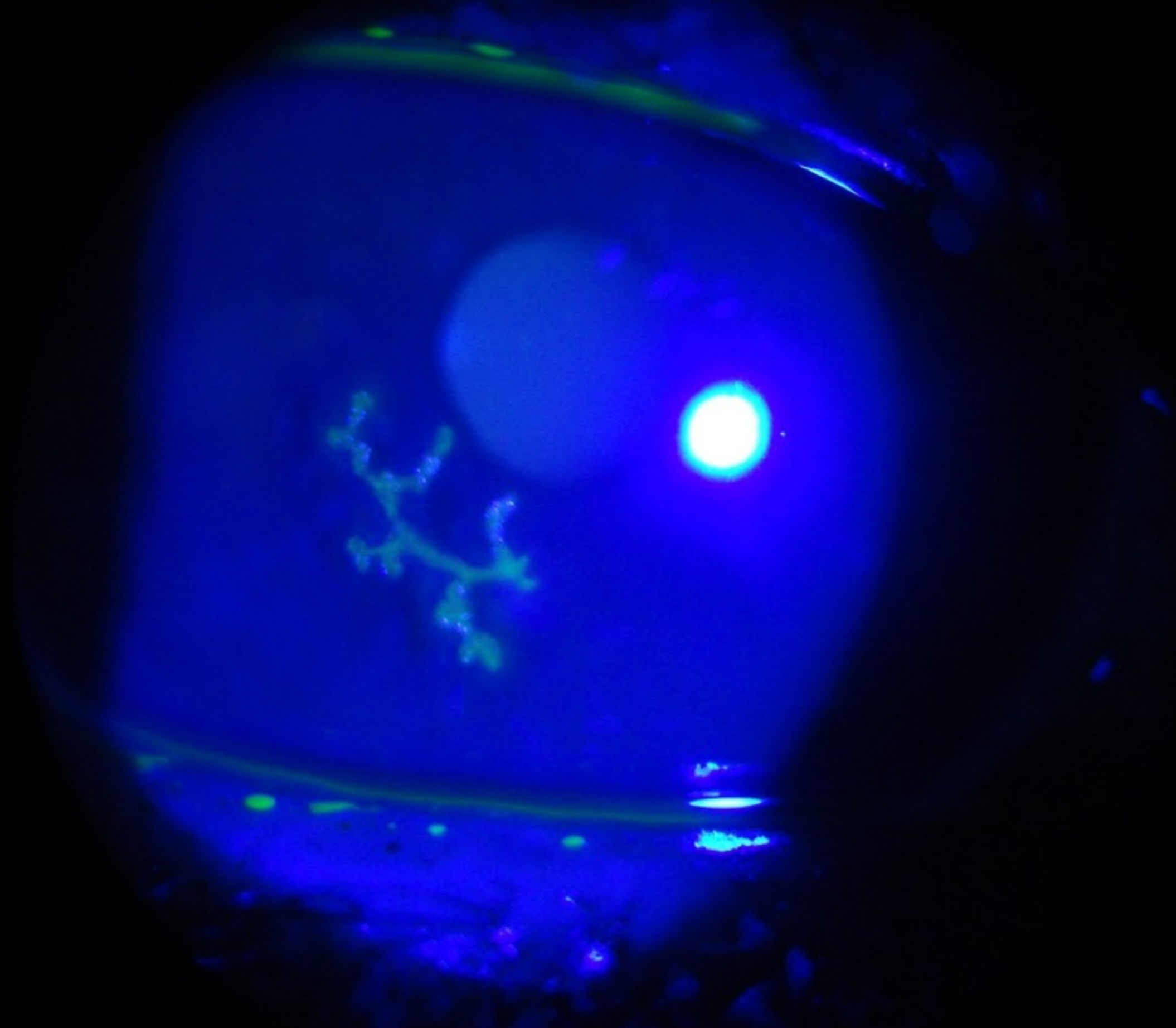
- effective
- cheap
- no toxicity

## Topical Antivirals

- effective
- expensive
- toxicity

## Oral Antivirals

- effective
- cheap
- safe



# Oral Antiviral Prophylaxis

- \* Discuss option of prophylaxis with every patient
- \* Shown to reduce recurrence by at least 50% and more current studies have indicated maybe 75%
- \* Acyclovir 400mg BID po or Valtrex 500mg QD po
- \* Who needs this?
  - \* atopic patients?
  - \* immunosuppressed patients?

# HSV Stromal Keratitis

- \* Accounts for only 2% of initial episodes, BUT 20-48% of recurrent HSV disease
- \* commonly confused and poorly categorized
- \* goal in treatment is to limit stromal scarring

# HSV Stromal Keratitis

- \* chronic, recurrent inflammation due to retained viral antigen within the stroma
- \* stromal inflammation with (almost always) intact epithelium
- \* may be focal, multifocal or diffuse in pattern
- \* depending on the strain of virus, can lead to permanent stromal scarring
  - \* leads to need for penetrating keratoplasty

# HSV Stromal Keratitis

- \* Neovascularization

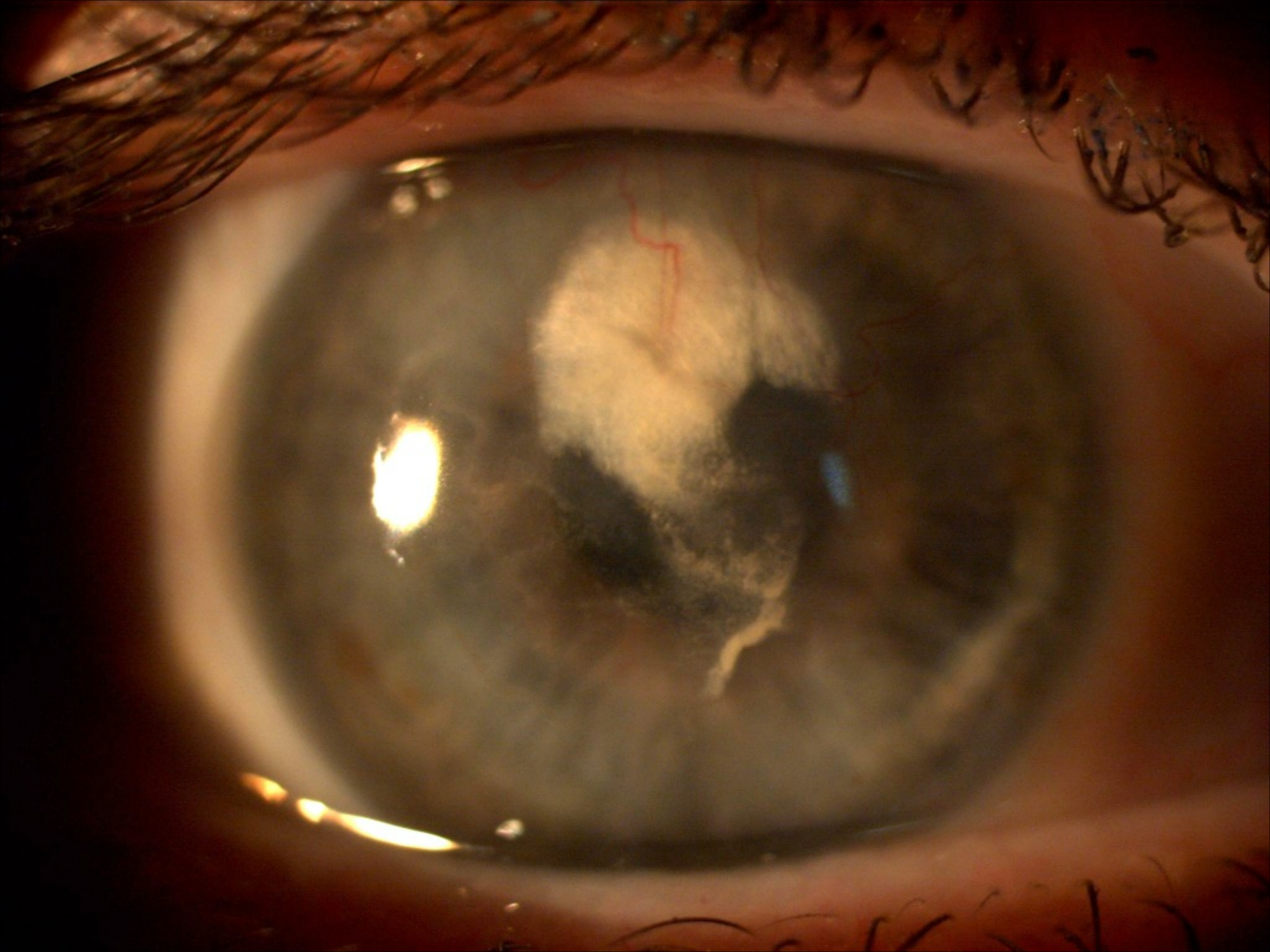
- \* can occur at any level of the stroma with varying degrees of inflammation

- \* lipid deposition can follow with subsequent scarring and loss of vision

# HSV Stromal Keratitis

- \* can present days to years after initial infectious episode
- \* clinical course is chronic, recurrent inflammation that can persist for years
- \* long term topical steroids may be required to suppress inflammatory reaction and prevent significant vision loss





# Treatment for HSV Stromal Keratitis?

- \* Topical steroids

- \* How often? - depends of severity of stromal inflammation

- \* Taper? - Critical to taper slowly, and some patients may require permanent topical steroids to control inflammation

- \* Permanent steroids = must monitor IOP and cataract formation

- \* Antivirals?

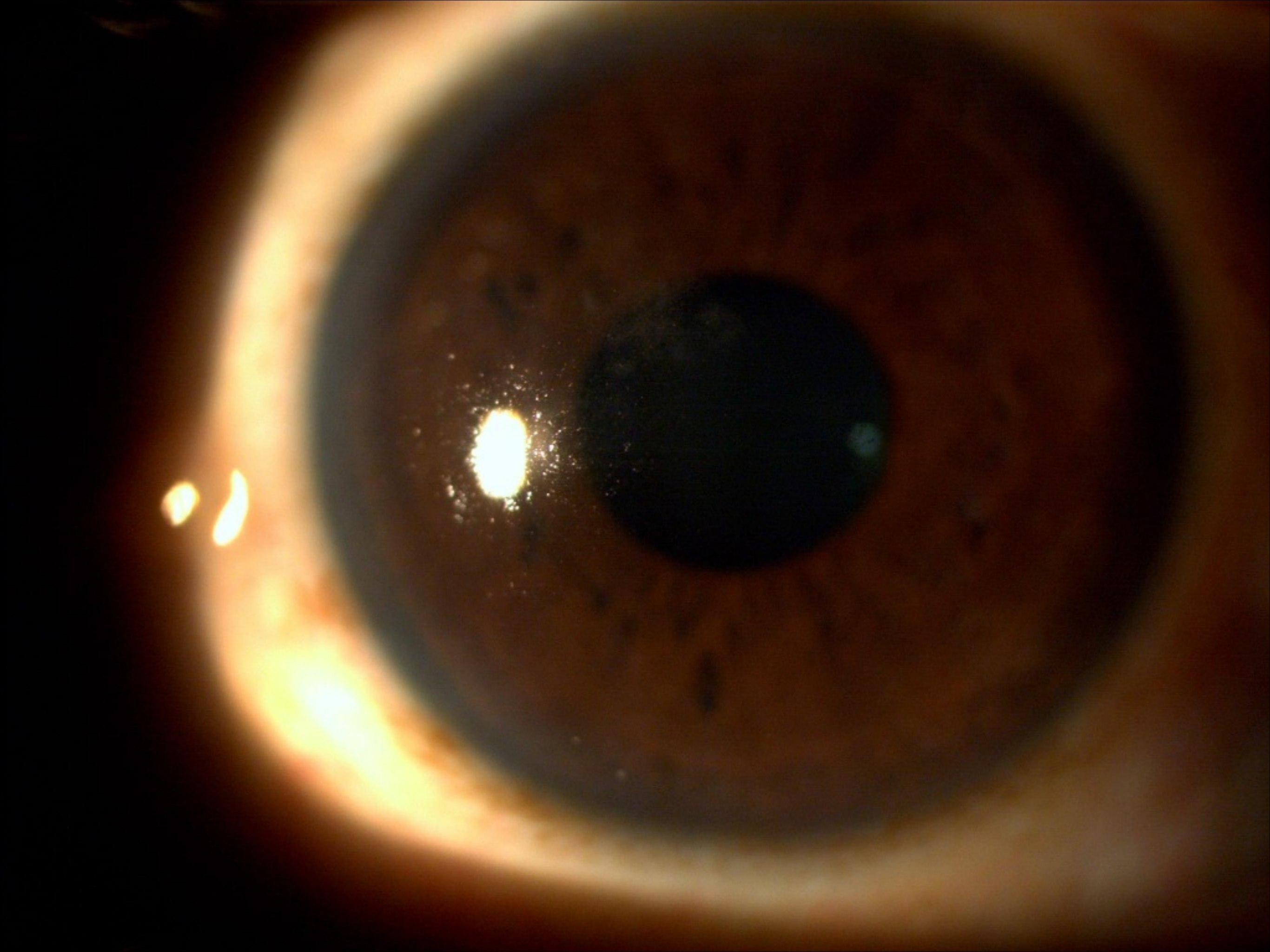
- \* topical vs. oral

- \* topical for up to 2 weeks

- \* oral for prolonged or prophylactic treatment

# Endotheliitis

- \* inflammatory reaction at the level of the endothelium
- \* epithelial edema, stromal edema, underlying keratic precipitates and iritis
- \* absence of stromal infiltrate or neovascularization
- \* can have endothelial cell loss with resulting corneal edema
- \* thought to be immunologic reaction and responds with topical steroids



# Treatment HSV endotheliitis?

- \* Topical steroids

- \* How often? - depends of severity of stromal inflammation

- \* Taper? - Critical to taper slowly, and some patients may require permanent topical steroids to control inflammation

- \* Permanent steroids = must monitor IOP and cataract formation

- \* Antivirals?

- \* topical vs. oral

- \* topical for up to 2 weeks

- \* oral for prolonged or prophylactic treatment

# Neurotrophic keratopathy

- \* patients who have had herpes keratitis are at risk to develop neurotrophic keratopathy
- \* neither immune nor infectious
- \* impaired corneal innervation in combination with decreased tear secretion

# How to check corneal sensation?



# Neurotrophic keratopathy

- \* irregularity of the corneal surface
- \* loss of corneal epithelial clarity
- \* punctate erosions that develop into persistent epithelial defects
  - \* **oval epithelial defect** with smooth borders
  - \* epithelium at edge of defect will become **gray-white** with **rolled/thickened edges**
- \* continuation of the epithelial defect will lead to stromal ulceration  
= loss of tissue



A circular microscopic view of a corneal epithelial defect. The image shows a central area of grayish-white epithelium, a surrounding area of yellowish epithelium, and a dark area of epithelial breakdown. The text labels these features: 'epithelial breakdown and defect' at the top, 'Gray / White epithelium' on the left, and 'Loss of epithelial clarity' at the bottom.

epithelial breakdown and defect

Gray / White epithelium

Loss of epithelial clarity

# Neurotrophic Keratopathy

- \* Treatment Options:

- \* Lubrication

- \* Punctal plug

- \* Debridement and bandage contact lens

- \* Amniotic membrane

- \* Serum tears



# Iridocyclitis

- \* patients with HSV keratitis may develop a concomitant or subsequent iridocyclitis
- \* can be the primary episode (no history of keratitis)
- \* in addition to typical AC reaction and endothelial KP, often find segmental iris atrophy
- \* HSV has been loosely linked as a possible cause of:
  - \* Iridocorneal endothelial syndrome ICE
  - \* Fuch's heterochromic iridocyclitis
  - \* Posner-Schlossman syndrome

# Iridocyclitis

- \* frequently see IOP spike due to trabeculitis that responds well to topical steroids
- \* chronic inflammation often leads to secondary glaucoma
- \* these patients may respond well to oral antivirals



# Treatment of HSV Iridiocyclus

- \* For most:
  - \* Topical steroids
- \* Some will ALSO need:
  - \* Oral antivirals
- \* Trabeculitis leads to IOP spikes
  - \* may need glaucoma medications, BUT it is the steroid that will decrease trabeculitis and improve IOP

# Diagnosis

- \* relies heavily on ophthalmic examination
- \* viral cell culture:
  - \* early culturing
  - \* may take a week to grow
  - \* yield will be reduced if previous antiviral therapy has been used
  - \* high false negatives



# Diagnosis

- \* Immunologic tests:
  - \* Herpcheck
  - \* Virogenlatex agglutination
  - \* enzyme immunofiltration
  - \* 1-hour enzyme linked immunoassay
- \* studies haven't found any increase in sensitivity with addition of the above tests in addition to clinical examination

# Diagnosis

- \* Polymerase Chain Reaction PCR:
  - \* equally sensitive and maybe more sensitive than cell culture
  - \* 24-48hr results
- \* Serum antibody titers:
  - \* can be used to differentiate primary infection from recurrent disease

# Management

\* Herpetic Eye Disease Study HEDS:

\* multi-center, randomized, placebo-controlled study

\* Address following questions:

1. Topical corticosteroids in treating stromal keratitis already on topical antivirals
2. Oral acyclovir in treating stromal keratitis already on a topical steroid and antiviral
3. Oral acyclovir in treating iridocyclitis already on topical steroid
4. Oral acyclovir in preventing recurrence of epithelial and stromal keratitis
5. Demographic and disease-specific predictors of recurrent HSV keratitis
6. Risk factors for recurrence of ocular HSV

# Topical corticosteroids in treating stromal keratitis already on a topical antiviral

- \* topical corticosteroids helped in the treatment of stromal keratitis
- \* failures related to tapering schedule of topical steroids
  - \* need to slowly taper on a gradual, individualized basis

# Oral acyclovir in treating stromal keratitis already on a topical steroid and antiviral

- \* no benefit to adding oral antiviral when already on topical steroid and antiviral for treatment of stromal keratitis

# Oral acyclovir in treating iridocyclitis already on topical steroid

- \* hard time recruiting these patients and this arm was discontinued with incomplete participation
- \* difficult to notice benefit because patients with stromal keratitis and iridocyclitis were both in the is group
- \* stromal keratitis is thought to be immunologic and wouldn't be expected to benefit from oral antivirals
- \* iridocyclitis is thought to be infectious and would expect to benefit from oral antivirals

# Oral acyclovir in preventing recurrence of epithelial and stromal keratitis

- \* 400mg BID po acyclovir for 1 year
- \* decreased recurrence of ocular HSV by 50%
- \* applied to both epithelial and stromal keratitis
  - \* greater effect with stromal keratitis with history of a prior episode
- \* stromal keratitis more likely to recur compared to epithelial keratitis

# Demographic and risk factors for recurrence

- \* Stress, systemic infection, sunlight exposure, menstruation, contact lens wear and eye injury WERE NOT deemed significant



# So what DID HEDS tell us?

- \* Oral antivirals reduces recurrences of epithelial and stromal keratitis
- \* Topical steroids benefit stromal keratitis
- \* Oral antivirals may help iridocyclitis
- \* Prophylactic oral antivirals help prevent recurrences of herpetic keratitis, particularly in those with repeated stromal keratitis

# Incidence, recurrence and outcomes of herpes simplex virus eye disease in Olmsted county, Minnesota 1976-2007

\* Leading infectious cause of corneal blindness

\* 394 cases initial presentation:

\* **Dendritic epithelial keratitis (59%)**

\* Other keratitis (16%)

\* Blepharoconjunctivitis (20%)

\* Conjunctivitis (4%)

\* Uveitis (0.5%)

\* **Bilateral involvement (4%)**



40.5%

# Incidence, recurrence and outcomes of herpes simplex virus eye disease in Olmsted county, Minnesota 1976-2007

\* Likelihood of recurrence after initial episode:

\* 27% at 1 year

\* 50% at 5 years

\* 63% at 20 years

\* Of those that had a first occurrence (169), (108) had second:

\* 38% at 1 year

\* 67% at 5 years

\* 83% at 20 years

# Incidence, recurrence and outcomes of herpes simplex virus eye disease in Olmsted county, Minnesota 1976-2007

- \* 44% treated with prophylactic (400mg acyclovir bid po):
  - \* Decreased risk of first reoccurrence by 2.9
- \* If not treated prophylactically:
  - \* 9.4x more likely to have epithelial keratitis
  - \* 8.4x more likely to have stromal keratitis
  - \* 34.5x more likely to have blepharitis/conjunctivitis

# Herpes Zoster

- \* varicella-zoster virus = Herpes Virus 3
- \* Causes two distinct conditions:
  - \* Varicella (Chickenpox) - primary infection
  - \* Herpes Zoster (Shingles) - reactivation of latent virus

# Varicella: Epidemiology

- \* serological evidence of prior VZV infection is present in 95% of US
- \* 4 million cases per year before vaccinations beginning in 1995
- \* Since vaccine, 57-90% decrease in varicella

# Zoster: Epidemiology

- \* life time risk 10-30%
- \* 500,000 cases annually
- \* Effect of the zoster vaccine yet to be determined
- \* Increasing age and altered immunity a significant risk factor

# Varicella-Zoster Virus

- \* Humans the only known natural reservoir
- \* *VZV* is among the smallest within the herpes virus family
- \* Remains latent within ganglion cells and neurons
- \* With reactivation, virus spreads to the skin and mucous membranes
- \* Abnormal skin sensations, pain and tenderness followed by the characteristic unilateral dermatomal eruption



# Varicella-Zoster Virus

- \* Involves the lower thoracic and upper lumbar dermatomes in 50%
- \* 13-20% cases involve cranial nerves
  - \* trigeminal nerve most frequently

# Clinical Findings: Varicella

- \* characteristic rash
  - \* small red papules progressing to vesicular lesions
  - \* usually more numerous on face and trunk
  - \* rarely, found on mucosal surfaces

# Ophthalmic Findings: Varicella

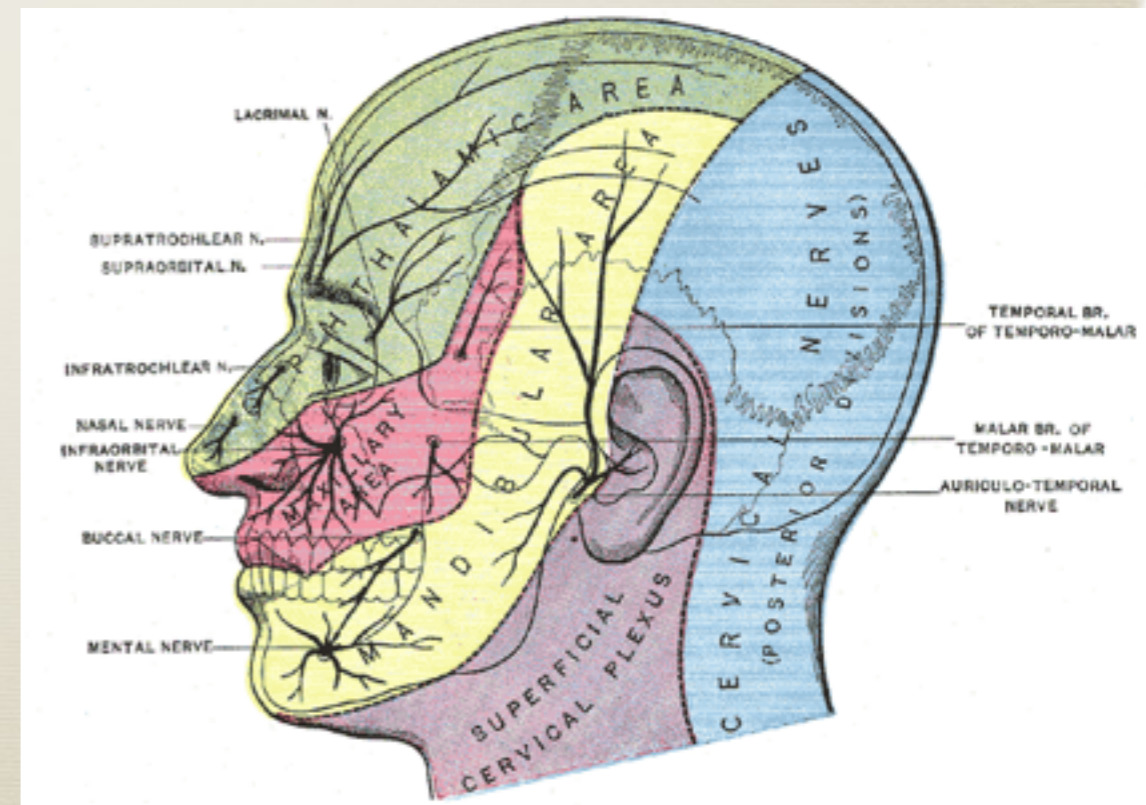
- \* vesicular eruption on periocular skin and eyelids is common
- \* can also involve conjunctiva and cornea
  - \* papillary conjunctivitis
  - \* punctate or dendritic keratitis
  - \* disciform keratitis

# Clinical Findings: Herpes Zoster

- \* 1-4 days of prodromal symptoms:
  - \* fever, malaise, headache, pain, itching, burning, erythema in affected dermatome
- \* Macular rash which becomes papular and then vesicular within 24 hours
- \* Usually involve one dermatome, but can include up to 3 adjacent
- \* Vesicles may continue to develop over 4 days and longer in immunocompromised patients
- \* after 2-3 weeks the acute phase subsides and the rash will crust over with the chance of persistent pain known as post-herpetic neuralgia

# Clinical Findings: Herpes Zoster Ophthalmicus

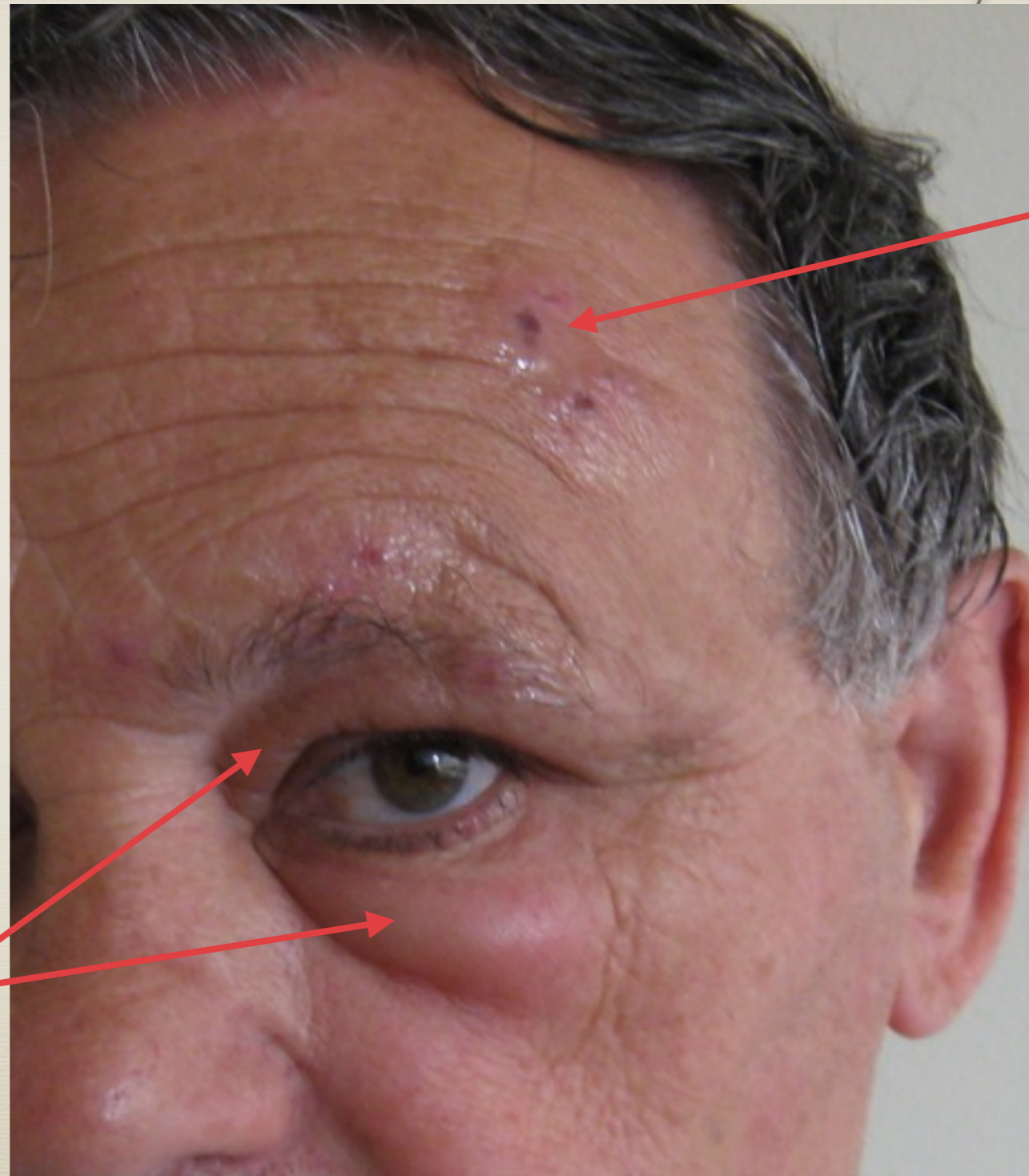
- \* Reactivation from the trigeminal ganglia with ocular involvement
- \* 3 division of the trigeminal nerve (ophthalmic, maxillary and mandibular)
  - \* **ophthalmic most commonly affected (8-56%)**
- \* Ophthalmic divides into
  - \* nasociliary
  - \* **frontal (most commonly affected)**
  - \* lacrimal



# Clinical Findings: Herpes Zoster Ophthalmicus

- \* Nasociliary nerve:
  - \* innervates: anterior and posterior ethmoidal sinuses, the skin of the eyelids, the tip of the nose, conjunctiva, sclera, cornea, iris and choroid
  - \* if nasociliary is involved = 50-75% chance of ocular complications
  - \* Hutchinson's sign

# Ophthalmic Manifestations: Periocular skin and eyelids



Maculopapular  
rash

Lid edema

# Ophthalmic Manifestations: Periocular skin and eyelids

## Vesicular rash

- vesicles can be cultured
- can lead to significant scarring

## Maculopapular rash

## Lid edema

- can be confused with preseptal cellulitis

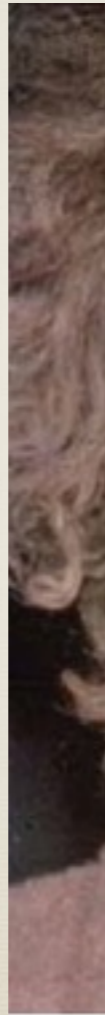




# Ophthalmic Manifestations: Periocular skin and eyelids

## Vesicular rash

- vesicles can be cultured
- can lead to significant scarring



## Maculopapular rash

## Lid edema

- can be confused with preseptal cellulitis

# Ophthalmic Manifestations: Conjunctiva and Sclera



conjunctivitis



episcleritis



scleritis

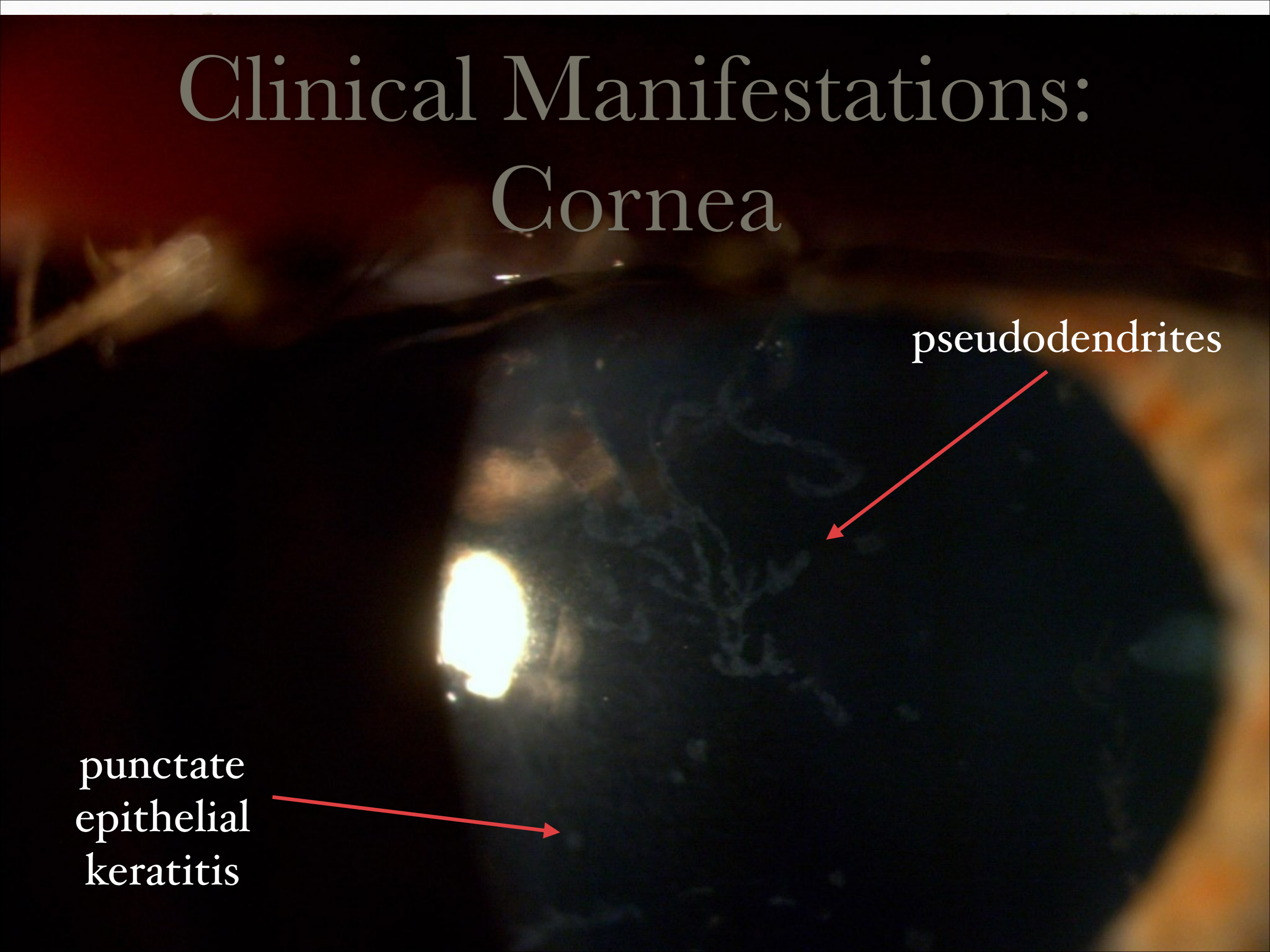
# Clinical Manifestations: Cornea

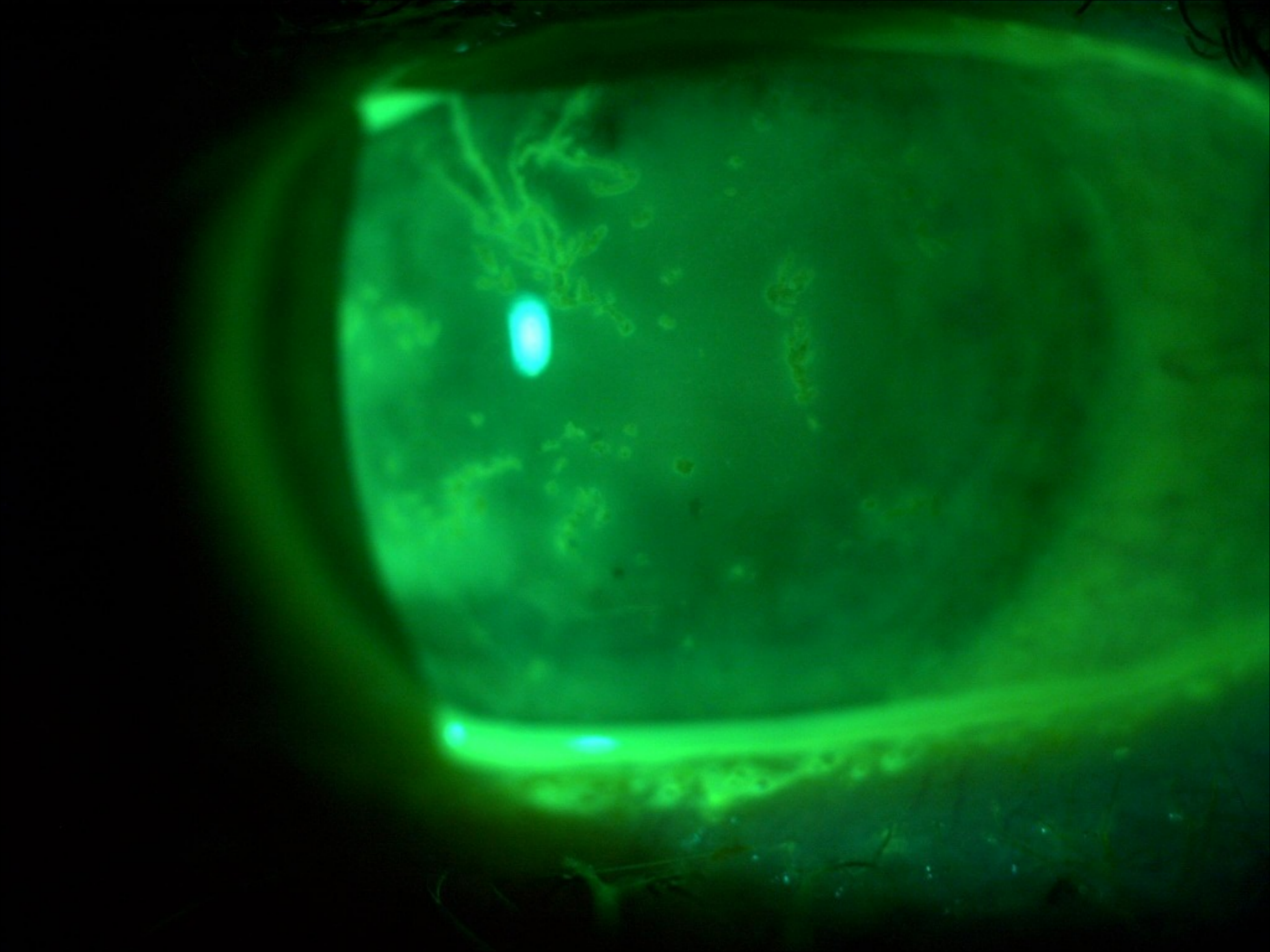
| <b>Corneal Change</b>         | <b>Frequency</b> | <b>Onset</b> |
|-------------------------------|------------------|--------------|
| punctate keratitis            | 50%              | 2 days       |
| pseudodendrites               | 50%              | 4-6 days     |
| anterior stromal keratitis    | 40%              | 10 days      |
| endotheliitis                 | 34%              | 7 days       |
| Serpiginous ulcer             | 7%               | 1 month      |
| Sclerokeratitis               | 1%               | 1 month      |
| Corneal mucous plaques        | 13%              | 2-3 months   |
| Disciform keratitis           | 10%              | 3-4 months   |
| Neurotrophic keratitis        | 25%              | 2 months     |
| Exposure keratopathy          | 11%              | 2-3 months   |
| Interstitial Keratitis/ Lipid | 15%              | 1-2 years    |
| Permanent Corneal Edema       | 5%               | 1-2 years    |

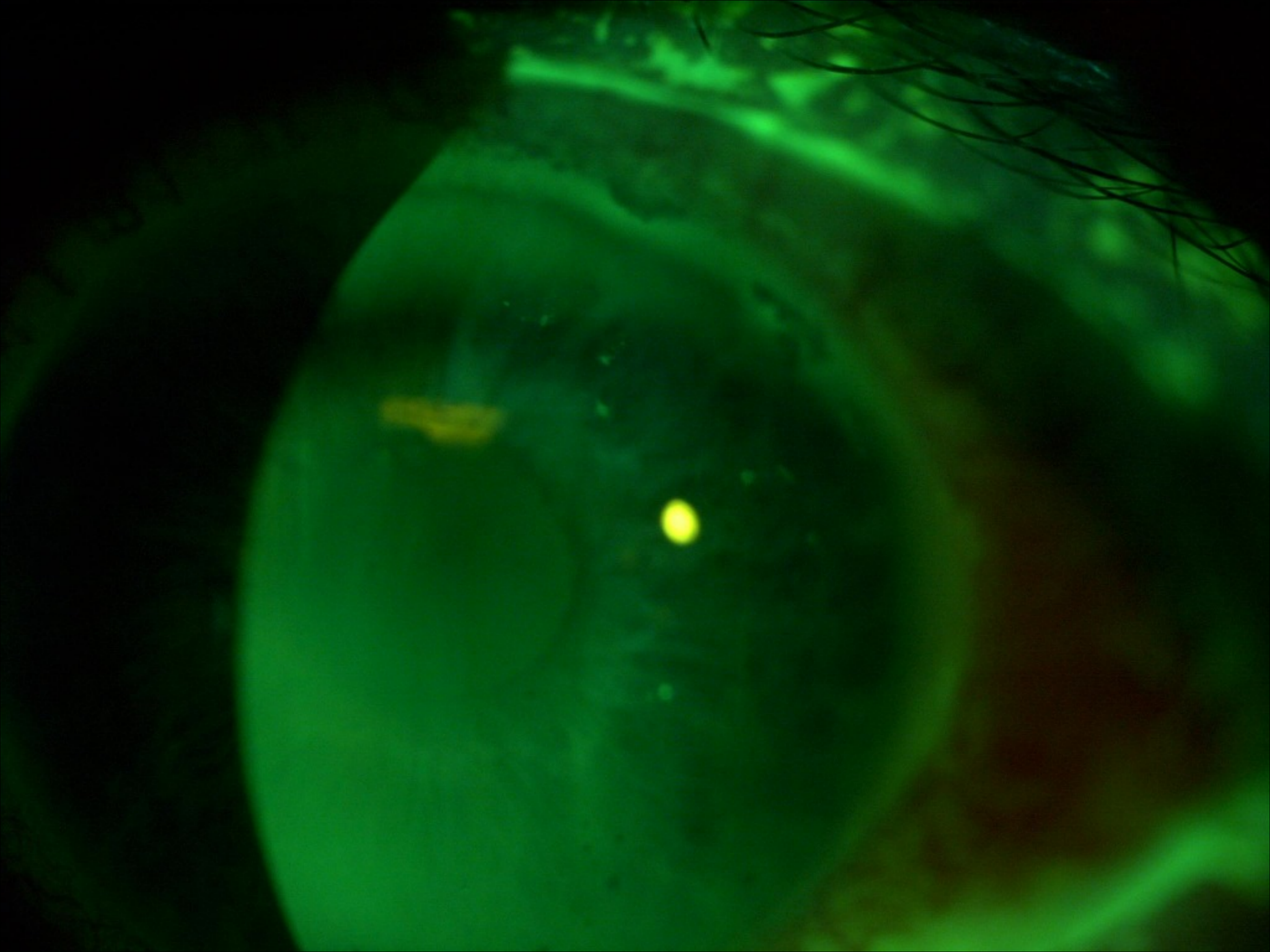
# Clinical Manifestations: Cornea

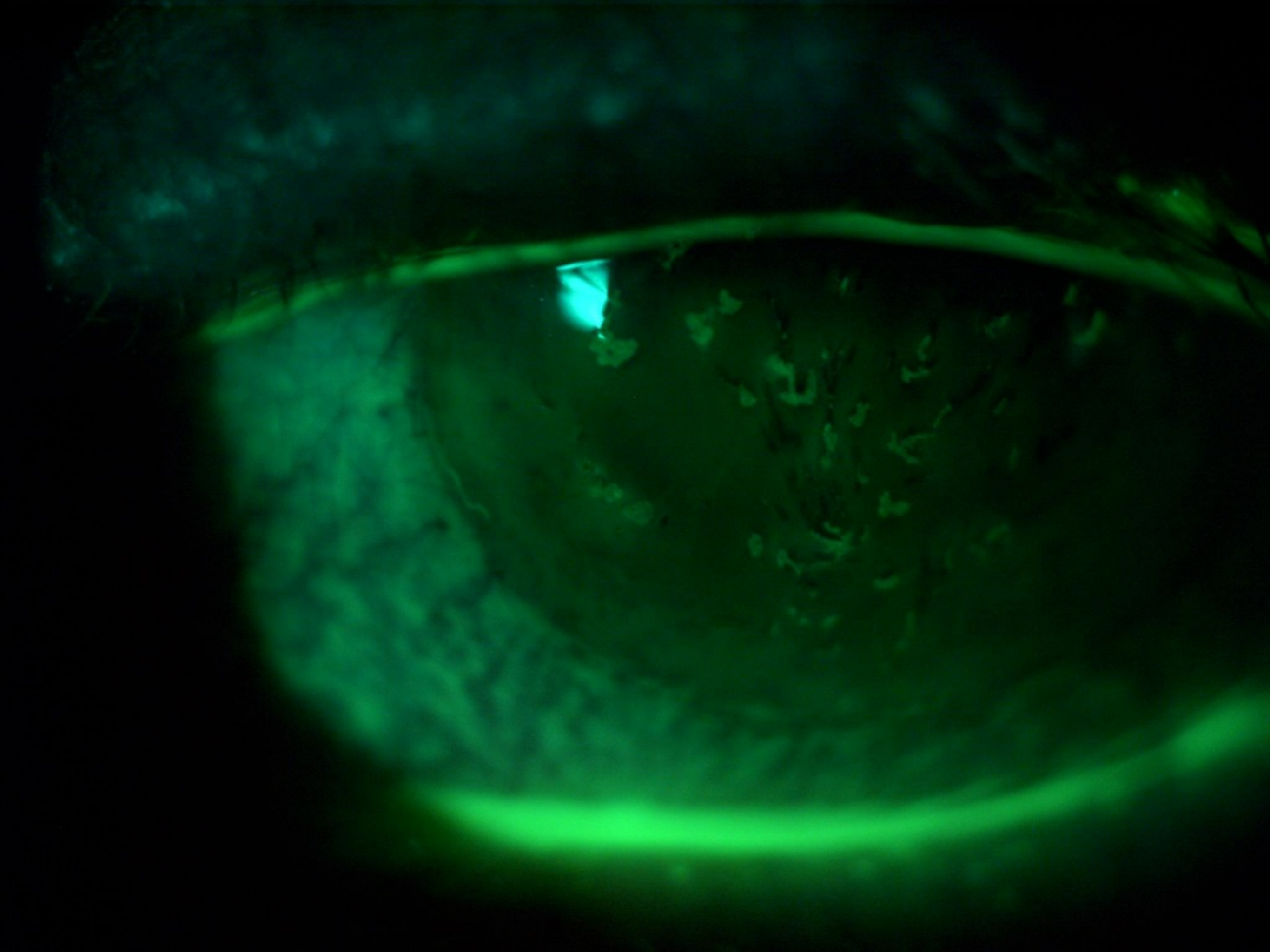
pseudodendrites

punctate  
epithelial  
keratitis









# Early Corneal Findings

- \* Punctate epithelial keratitis:

- \* blotchy, swollen epithelial cells

- \* Pseudodendrites:

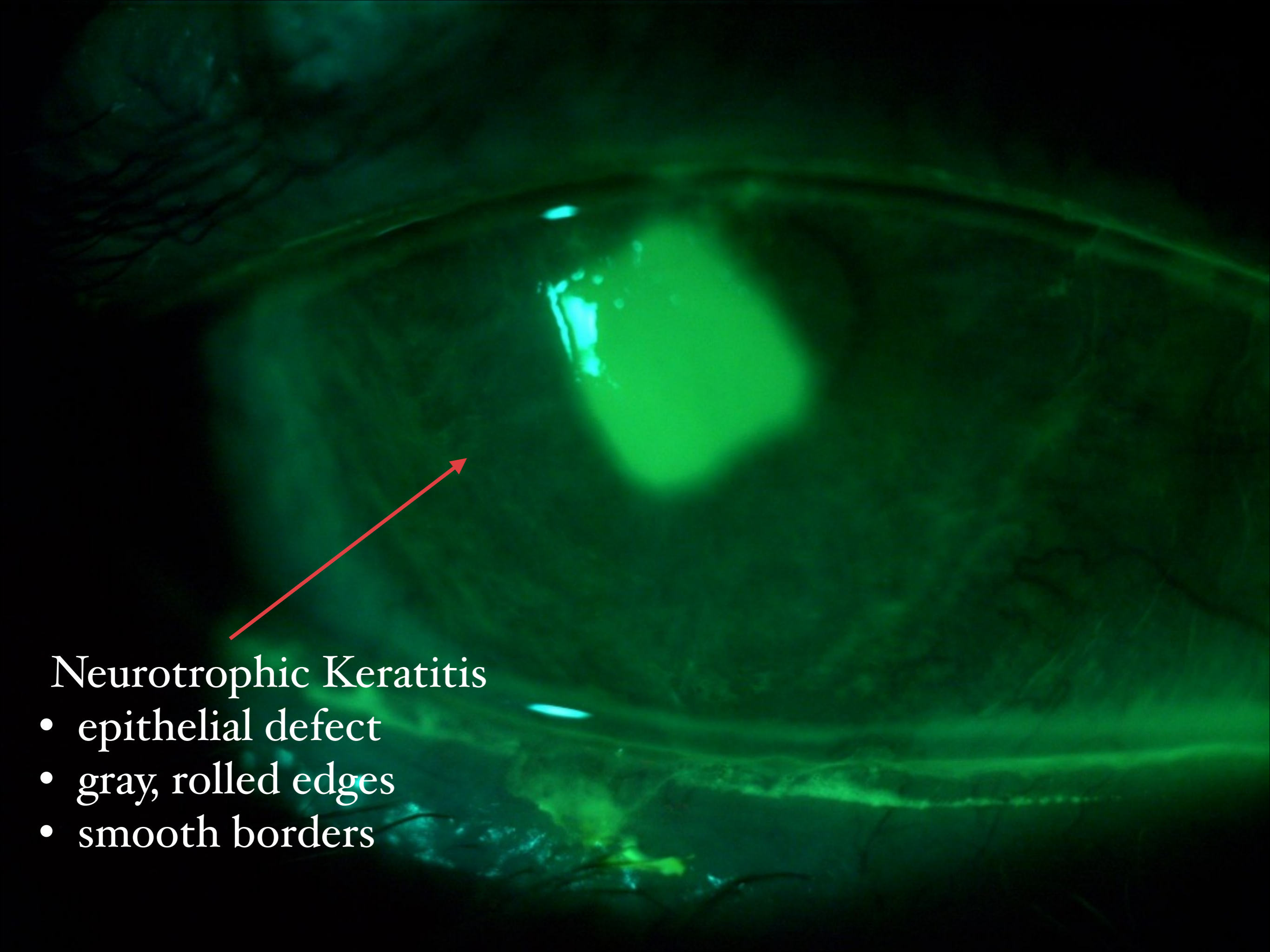
- \* “dendritic” shaped lesions of raised epithelial cells

- \* superficial, with ill defined endings

- \* lack well defined terminal bulbs

- \* no central ulceration





## Neurotrophic Keratitis

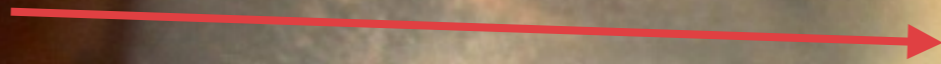
- epithelial defect
- gray, rolled edges
- smooth borders

# Late Corneal Findings

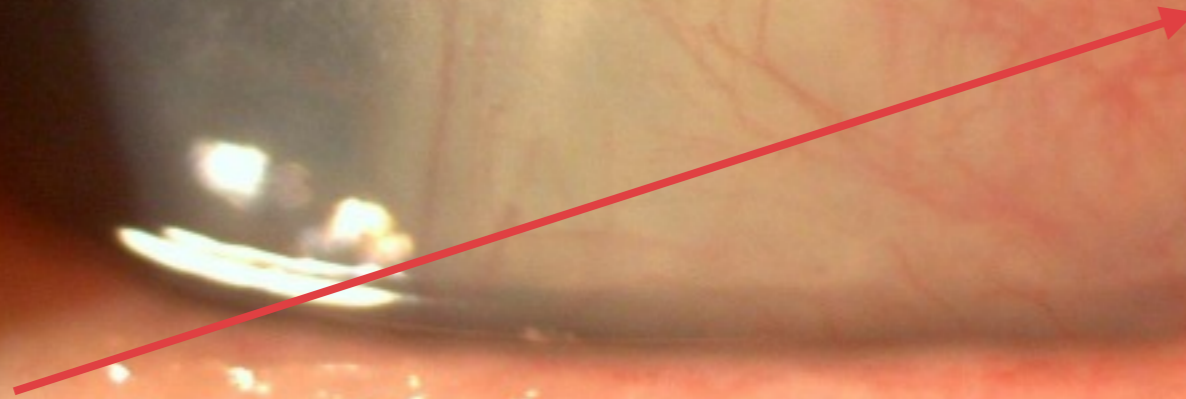
- \* Neurotrophic Keratitis:
  - \* loss of corneal sensation leads to loss of epithelial integrity with subsequent epithelial breakdown
  - \* some people regain normal sensation, some never regain total sensation and others continue to worsen
  - \* 20% will have some loss of corneal sensation

# Late Corneal Findings

Lipid  
Keratopathy



Interstitial  
Keratitis



After weeks of topical  
steroids

Ghost vessels



# Interstitial Keratitis and Lipid Keratopathy

- \* extensive corneal inflammation
- \* new blood vessels grow within corneal stroma
- \* vessels leak inflammatory cells and eventual lipid
- \* can progress to cause permanent corneal opacification

# Keratouveitis

- \* seen in up to 40% of HZO patients
- \* extensive keratic precipitates, corneal edema and posterior synechiae
- \* 56% will have secondary glaucoma



