First things first: What does HSV stand for in this context?
Anterior HSV Disease

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There are two--HSV-1, and HSV-2
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Which bodypart(s) does each have a predilection for? -- HSV-1 \( \rightarrow \) ? -- HSV-2
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How many ‘types’ of the HSV are there, and what are they named?
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Which bodypart(s) does each have a predilection for?
--HSV-1→‘Above the waist’: The eyes, and perioral area (ie, ‘cold sores’)
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--HSV-1 → ‘Above the waist’: The eyes, and perioral area (ie, ‘cold sores’)
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Predilections aside, can HSV-1 cause genital herpes, and HSV-2 cause ocular/perioral infection?
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Yes and yes
Anterior HSV Disease

1) Usually a unilateral blepharoconjunctivitis
--Presents with lid margin vesicles/ulcers and bulbar conjunctivitis

2) A fundamental way to organize anterior HSV eye dz
Anterior HSV Disease

1) Primary ocular disease

2) Recurrent ocular disease

A fundamental way to organize anterior HSV eye dz
Anterior HSV Disease

1) Primary ocular disease
--Usually a *unilateral* disease

2) Recurrent ocular disease
Anterior HSV Disease

1) Primary ocular disease
   --Usually a *unilateral* blepharconjunctivitis

2) Recurrent ocular disease
Anterior HSV Disease

1) Primary ocular disease
   --Usually a *unilateral* **blepharoconjunctivitis**
   --Presents with lid margin **sign 1** and bulbar **sign 2**

2) Recurrent ocular disease
1) Primary ocular disease
   --Usually a unilateral blepharoconjunctivitis
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*In what percent of cases does primary HSV present bilaterally?*
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*In what percent of cases does primary HSV present bilaterally? ~10%*
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   *Does ‘recurrence’ mean the pt gets re-infected?*
1) Primary ocular disease
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2) Recurrent ocular disease

*Does ‘recurrence’ mean the pt gets re-infected?*

No! Remember, herpes virus infection is never cleared--rather, it becomes latent within the host. Thus, recurrence means the virus is *reactivated*, not re-acquired.
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Where in the body do herpesviruses establish their latency?
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Different members of the herpesvirus family take up residence in different cell types. Of particular interest at present, HSV-1 and HSV-2 hole up in sensory neural ganglia.
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Which sensory ganglion harbors the virions responsible for recurrent ocular dz?
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Which sensory ganglion harbors the virions responsible for recurrent ocular dz?
The trigeminal (CN5; ‘stellate’) ganglion
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--Presents with lid margin vesicles/ulcers and bulbar conj ulcers

2) Recurrent ocular disease
a) ?
b) ?
c) ?
d) ?

Four distinct ocular manifestations (think broadly, and anatomically)
1) Primary ocular disease
--Usually a unilateral **blepharoconjunctivitis**
--Presents with lid margin vesicles/ulcers and bulbar conj ulcers

2) Recurrent ocular disease
a) **Blepharoconjunctivitis**
b) **Keratitis**
c) **Iridocyclitis**
d) **Trabeculitis**

Four distinct ocular manifestations
(think broadly, and anatomically)
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a) *Blepharoconjunctivitis*: Looks like... two words
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      **Does recurrent blepharoconjunctivitis require aggressive treatment?**

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   *Does recurrent blepharoconjunctivitis require aggressive treatment?*
   Not generally—it tends to be self-limited

c) *Iridocyclitis*

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   Not generally—it tends to be self-limited
Under what not ‘generally’ conditions does it not tend to be self-limited, and therefore would require aggressive tx?
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   Does recurrent blepharoconjunctivitis require aggressive treatment?
   Not generally—it tends to be self-limited
   Under what not ‘generally’ conditions does it not tend to be self-limited, and therefore would require aggressive tx?
   If/when the pt is immunocompromised
c) Iridocyclitis
   Can be granulomatous or non-granulomatous
   Classic sign: patchy iris transillumination defects
d) Trabeculitis
Anterior HSV Disease

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  --?
  --?
  --?
  Three specific and distinct keratitis subtypes
  c) *Iridocyclitis*
d) *Trabeculitis*
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2) Recurrent ocular disease
a) **Blepharoconjunctivitis**: Looks like primary disease
b) **Keratitis**
   --Epithelial
   --Stromal
   --Endotheliitis

  *Three specific and distinct keratitis subtypes*

c) **Iridocyclitis**

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Anterior HSV Disease

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--Usually a unilateral blepharoconjunctivitis
--Presents with lid margin vesicles/ulcers and bulbar conj ulcers

2) Recurrent ocular disease
a) Blepharoconjunctivitis: Looks like primary disease
b) Keratitis
   --Epithelial: c/o three words. Classic sign:
   --Stromal
   --Endotheliitis
c) Iridocyclitis
d) Trabeculitis
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   --Usually a unilateral **blepharoconjunctivitis**
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   a) **Blepharoconjunctivitis**: Looks like primary disease
   b) **Keratitis**
      --Epithelial: c/o **foreign body sensation**. Classic sign: **Dendrites**
      --Stromal

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How do HSV dendrites stain with fluorescein and rose bengal?
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   d) Trabeculitis
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   --Necrotizing: looks like an *ulcer*: suppurative, with an overlying epithelial defect
   --Endotheliitis (aka disciform keratitis): Presents as disc-shaped edematous area with KP

c) *Iridocyclitis*
   --Can be granulomatous or non-granulomatous
   --Classic sign: patchy iris transillumination defects

d) *Trabeculitis*
   --Presents with unilateral elevated IOP

What is the typical treatment for HSV infectious epitheliopathy?

Viroptic 9x/day x 2 weeks, then stop

What disaster will befall the patient if you fail to prescribe Viroptic?

Nothing. HSV epitheliopathy is self-limiting; treatment shortens the course

Why must you stop Viroptic after 2 weeks?

It is quite toxic to healthy and/or healing epithelium

What alternative antiviral treatment bypasses the risk of epithelial toxicity entirely?

PO ACA—it is as effective as topical Viroptic
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Other than its less-onerous dosing schedule, does Zirgan have any advantages over Viroptic?
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Are there other topical treatments besides Viroptic and Zirgan?
Yes--it is probably less toxic to the corneal epithelium

What is the typical treatment for HSV infectious epitheliopathy?
Viroptic 9x/day x 2 weeks, then stop

Are there other topical treatments besides Viroptic and Zirgan?
Acyclovir ointment is available in Europe, but not the US

Anything coming down the therapeutic pipeline?
Far up the pipeline is a class of meds called helicase primase inhibitors
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Are there other topical treatments available?
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Two subtypes of stromal keratitis
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        --Necrotizing: Looks like an ulcer: Suppurative, with an overlying epithelial defect
      --Endotheliitis
   c) Iridocyclitis
   d) Trabeculitis
Anterior HSV Disease

1) Primary ocular disease
--Usually a unilateral blepharoconjunctivitis
  --Presents with lid margin vesicles/ulcers and bulbar conj ulcers

2) Recurrent ocular disease
a) Blepharoconjunctivitis: Looks like primary disease
b) Keratitis
  --Epithelial: c/o foreign body sensation. Classic sign: Dendrites
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     --Interstitial: Looks like a scar: hazy, with no overlying epithelial defect
     --Necrotizing: Looks like an ulcer: Suppurative, with an overlying epithelial defect
   --Endotheliitis (aka two words): Presents as -shaped edematous area with

   c) Iridocyclitis

   d) Trabeculitis
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--Usually a unilateral **blepharoconjunctivitis**
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    --**Endotheliitis** (aka **disciform keratitis**): Presents as disc-shaped edematous area with **KP**
c) **Iridocyclitis**
d) **Trabeculitis**
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c) *Iridocyclitis*
   What are the three main complications/sequelae of HSV corneal disease?
   --

d) *Trabeculitis*
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      --Endotheliitis (aka disciform keratitis): Presents as disc-shaped edematous area with KP
   c) Iridocyclitis
      What are the three main complications/sequelae of HSV corneal disease?
      --Toxic epitheliopathy 2° to Viroptic
   d) Trabeculitis
      ulcer
      ulcer
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   c) Iridocyclitis
   d) Trabeculitis

What are the three main complications/sequelae of HSV corneal disease?
   --Toxic epitheliopathy 2° to Viroptic
   --Neurotrophic ulcer
   --Metaherpetic ulcer
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**What are the three main complications/sequelae of HSV corneal disease?**
--Toxic epitheliopathy 2o to Viroptic
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**What does this mean?**
Keratopathy 2o to decreased sensation
Anterior HSV Disease

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What does this mean?
Interstitial keratitis with chronic overlying epi defect
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How can these be differentiated from infectious epitheliopathy?

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      The edges of infectious HSV ulcers stain with rose bengal; neurotrophic and metaherpetic ulcers do not.
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   --Presents with unilateral elevated IOP

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How can these be differentiated from infectious epitheliopathy?
The edges of infectious HSV ulcers stain with rose bengal; neurotrophic and metaherpetic ulcers do not.

Why not?
Recall that rose bengal stains dead and/or devitalized epithium, as happens when cells are infected. Cells at the edges of a neurotrophic or metaherpetic ulcer are healthy, so they don’t take the stain.
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When performing penetrating keratoplasty for HSV-related corneal disease, is it prudent to use antiviral prophylaxis?
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When performing penetrating keratoplasty for HSV-related corneal disease, is it prudent to use antiviral prophylaxis?

Topical or PO, and why?
PO. Viroptic will tear up the already-compromised epithelium of the graft.
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c) Iridocyclitis
  --Can be Granulomatous? Nongranulomatous? Neither? Both?
   
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d) *Trabeculitis*

*In contrast, what one word describes the appearance of iris transillumination defects after a bout of VZV iridocyclitis?*
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‘Sectoral’
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d) Trabeculitis
  --Presents with key exam finding
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Anterior HSV Disease

In the context of ocular HSV dz, what does the acronym HEDS stand for?

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In the context of ocular HSV dz, what does the acronym HEDS stand for? The Herpetic Eye Disease Study

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The HEDS examined whether PO acyclovir (added to a Viroptic drops regimen) reduced the risk of later developing HSV stromal keratitis and/or iritis after an episode of HSV epithelial keratitis. Did it?

No. A short course of PO acyclovir did nothing to reduce the risk of future stromal keratitis or iritis.
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   --Prior to the HEDS, the use of **topical steroids in the management of HSV stromal keratitis** was controversial. A portion of the HEDS was a placebo-controlled evaluation of this issue. Were steroids beneficial?
c) **Iridocyclitis**
   --Can be granulomatous
   --Classic sign: patchy iris transillumination defects
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c) Iridocyclitis
   --Can be granulomatous or non-granulomatous
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In the context of ocular HSV dz, what does the acronym HEDS stand for? The Herpetic Eye Disease Study
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Recall that necrotizing stromal keratitis includes an epithelial defect. The Viroptic will interfere with healing epithelium, and will incur damage in uninfected cells to boot.

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‘Possible’? What’s up with that? Was PO acyclovir beneficial in HSV-related stromal necrotizing keratitis, or not?
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This is controversial. A subset analysis was not done, but many researchers felt the antivirals were useful in a treatment sense, not just prophylactically
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Unclear. A positive trend in the data was noted, but the number of cases was too small to reach statistical significance.
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Who was enrolled?
Pts with a history of HSV eye disease, but without active disease at the time of enrollment. N was ~700.

How much acyclovir did they receive, and for how long?
400 mg PO bid (or placebo) for one year

Was it beneficial?
Yes--the rate of recurrent HSV disease was cut by ~50%

Was there a rebound effect, ie, an increased rate of recurrent HSV dz after cessation of acyclovir therapy?
No

How long should prophylactic PO acyclovir be continued?
No one knows for sure
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HEDS tl;dr

The main contribution of the HEDS to clinical ophthalmology is the clarity it provided regarding the best way to manage stromal keratitis. The key takeaways from the HEDS are as follows:

--Topical steroids (in conjunction with a prophylactic antiviral) are an effective tx;
--prophylaxis w/ oral acyclovir reduces the recurrence rate and preserves vision; and
--in pts with a hx of multiple recurrences, lifelong prophylaxis should be pursued.

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