Anterior HSV Disease

*First things first: What does HSV stand for in this context?*
First things first: What does HSV stand for in this context? Herpes simplex virus
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Herpes simplex virus

How many ‘types’ of the HSV are there, and what are they named?
First things first: What does HSV stand for in this context? Herpes simplex virus

How many ‘types’ of the HSV are there, and what are they named? There are two--HSV-1, and HSV-2
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There are two--HSV-1, and HSV-2

Which bodypart(s) does each have a predilection for?
--HSV-1→?
--HSV-2
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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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--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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- HSV-1 → ‘Above the waist’: The eyes, and perioral area (ie, ‘cold sores’)
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1) Usually a unilateral blepharoconjunctivitis. Presents with lid margin vesicles/ulcers and bulbar conjunctival ulcers.

2) A fundamental way to organize anterior HSV eye dz.

2) ?
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

2) Recurrent ocular disease
Anterior HSV Disease

1) Primary ocular disease
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HSV blepharoconjunctivitis
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In what percent of cases does primary HSV present bilaterally?
Anterior HSV Disease

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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?*
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*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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Where in the body do herpesviruses establish their latency?
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)
Anterior HSV Disease

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

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(think broadly, and anatomically)
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      Not generally—it tends to be self-limited
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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?

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

d) Trabeculitis
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 foreign body sensation. Classic sign: Dendrites
      - **Stromal**:
        - **Interstitial**: Looks like a scar: hazy, with no overlying epithelial defect
        - **Necrotizing**: Looks like an ulcer: Suppurative, with an overlying epithelial defect
      - **Endotheliitis** (aka **disciform keratitis**): Presents as disc-shaped edematous area with KP
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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**
Anterior HSV Disease

1) Primary ocular disease
---Usually a *unilateral* blepharoconjunctivitis
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a) *Blepharoconjunctivitis*: Looks like primary disease
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   --?
   --?
   --?
   *Three specific and distinct keratitis subtypes*
   c) *Iridocyclitis*
d) *Trabeculitis*
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      --Stromal
         --Endotheliitis
   c) Iridocyclitis
   d) Trabeculitis
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Anterior HSV Disease

HSV epithelial keratitis
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How do HSV dendrites stain with fluorescein and rose bengal?
c) Iridocyclitis
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   How do HSV dendrites stain with fluorescein and rose bengal?
   The base stains with fluorescein; the edges stain with rose bengal
c) Iridocyclitis
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The base stains with fluorescein; the edges stain with rose bengal.
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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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Are there other topical treatments available?
Yes--ganciclovir gel (Zirgan)

What is the standard treatment regimen for Zirgan?
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Other than its less-onerous dosing schedule, does Zirgan have any advantages over Viroptic?
Yes--it is probably less toxic to the corneal epithelium
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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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What is the standard treatment regimen for Zirgan?
One drop 5x/d (compared with 9/day for Viroptic)

Other than its less-onerous dosing schedule, does Zirgan have any advantages over Viroptic?
Yes--it is probably less toxic to the corneal epithelium

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Anything coming down the therapeutic pipeline?
Far up the pipeline is a class of meds called helicase primase inhibitors
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c) Iridocyclitis:
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What is the typical treatment for HSV infectious epitheliopathy?
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Why must you stop Viroptic after 2 weeks?
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What alternative antiviral treatment bypasses the risk of epithelial toxicity entirely?
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What is the generic name for Viroptic?
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Are there other topical treatments available?
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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
--Stromal: Interstitial: Looks like a scar: hazy, with no overlying epithelial defect
--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

Is it reasonable to treat infectious HSV epitheliopathy with steroids?
No!

What is likely to develop if infectious HSV epitheliopathy is treated with steroids?
A geographic corneal ulcer
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 foreign body sensation. Classic sign: Dendrites
      --Stromal
         --?
         --?
      --Endotheliitis
   c) Iridocyclitis
   d) Trabeculitis

Two subtypes of stromal keratitis
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**
  --Stromal
    --Interstitial
    --Necrotizing
  --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**
   --Stromal
     --**Interstitial**: Looks like a [ ] : hazy, with no overlying epithelial defect
       --Necrotizing
     --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

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   a) *Blepharoconjunctivitis*: Looks like primary disease
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      --Epithelial: c/o foreign body sensation. Classic sign: Dendrites
      --Stromal
         --*Interstitial*: Looks like a *scar*: hazy, with no overlying epithelial defect
         --Necrotizing
      --Endotheliitis
   c) *Iridocyclitis*
   d) *Trabeculitis*
Study Guide: Anterior HSV dz

HSV interstitial keratitis
Anterior HSV Disease

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  --Presents with lid margin vesicles/ulcers and bulbar conj ulcers

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   --Epithelial: c/o foreign body sensation. Classic sign: Dendrites
   --Stromal
      --*Interstitial*: Looks like a scar: hazy, with no overlying epithelial defect
      --*Necrotizing*: Looks like an ulcer: Suppurative, with an overlying epithelial defect
   --Endotheliitis
c) *Iridocyclitis*
d) *Trabeculitis*
Anterior HSV Disease

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   --Stromal
      --Interstitial: Looks like a scar: hazy, with no overlying epithelial defect
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   --Endotheliitis
c) Iridocyclitis
d) Trabeculitis
Study Guide: Anterior HSV dz

HSV necrotizing keratitis
Anterior HSV Disease

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--Presents with lid margin vesicles/ulcers and bulbar conj ulcers

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a) *Blepharoconjunctivitis*: Looks like primary disease
b) *Keratitis*
   --Epithelial: c/o *foreign body sensation*. Classic sign: *Dendrites*
   --Stromal
     --*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*
Anterior HSV Disease

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  --Presents with lid margin vesicles/ulcers and bulbar conj ulcers

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    --Endotheliitis (aka disciform keratitis): Presents as disc-shaped edematous area with KP

c) Iridocyclitis
d) Trabeculitis
Study Guide: Anterior HSV dz

HSV endotheliitis/disciform keratitis
Anterior HSV Disease

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--Presents with lid margin vesicles/ulcers and bulbar conj ulcers

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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?
d) Trabeculitis
Anterior HSV Disease

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   -- Usually a *unilateral* blepharoconjunctivitis
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c) *Iridocyclitis*

   *What are the three main complications/sequelae of HSV corneal disease?*
   --Toxic epitheliopathy 2° to Viroptic
   --Neurotrophic ulcer
   --Metaherpetic ulcer
d) *Trabeculitis*
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   c) Iridocyclitis
      What are the three main complications?
      -- Toxic epitheliopathy 2o to Viroptic
      -- Neurotrophic ulcer
      -- Metaherpetic ulcer
   d) Trabeculitis

What does this mean?
Keratopathy 2o to decreased sensation
Anterior HSV Disease

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   What are the three main complications:
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Keratopathy 2º to decreased sensation
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      -- Metaherpetic ulcer
   d) Trabeculitis

What does this mean?
Interstitial keratitis with chronic overlying epi defect
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--Toxic epitheliopathy 2° to Viroptic
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What does this mean?
Interstitial keratitis with chronic overlying epi defect
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   c) **Iridocyclitis**
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   What are the three main complications/sequelae of HSV corneal disease?
   -- Toxic epitheliopathy 2° to Viroptic
   -- Neurotrophic ulcer
   -- Metaherpetic ulcer

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

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c) *Iridocyclitis*:
   --Can be granulomatous or non-granulomatous
   --Classic sign: patchy iris transillumination defects
d) *Trabeculitis*:
   --Presents with unilateral elevated IOP

*What are the three main complications/sequelae of HSV corneal disease?*
--Toxic epitheliopathy 2º to Viroptic
--*Neurotrophic ulcer*
--*Metaherpetic ulcer*

*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 epithelium, 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.
Anterior HSV Disease

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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.

What are the three main complications/sequelae of HSV corneal disease?
--Toxic epitheliopathy 2° to Viroptic
--Neurotrophic ulcer
--Metaherpetic ulcer
When performing penetrating keratoplasty for HSV-related corneal disease, is it prudent to use antiviral prophylaxis?
Anterior HSV Disease

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c) *Iridocyclitis*

*When performing penetrating keratoplasty for HSV-related corneal disease, is it prudent to use antiviral prophylaxis?*
Yes!

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c) *Iridocyclitis*

When performing penetrating keratoplasty for HSV-related corneal disease, is it prudent to use antiviral prophylaxis?

Yes!

Topical or PO, and why?
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c) Iridocyclitis

When performing penetrating keratoplasty for HSV-related corneal disease, is it prudent to use antiviral prophylaxis?
Yes!

Topical or PO, and why?
PO (Viroptic will tear up the already-compromised epithelium of the graft)
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   --Endotheliitis (aka disciform keratitis): Presents as disc-shaped edematous area with KP
c) Iridocyclitis
   --Can be Granulomatous? Nongranulomatous? Neither? Both?
   --
d) Trabeculitis
Anterior HSV Disease

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c) *Iridocyclitis*
   --Can be granulomatous or non-granulomatous

d) *Trabeculitis*
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  --Endotheliitis (aka disciform keratitis): Presents as disc-shaped edematous area with KP
c) Iridocyclitis
  --Can be granulomatous or non-granulomatous
  --Classic sign: 

d) Trabeculitis
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--Can be granulomatous or non-granulomatous
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In contrast, what one word describes the appearance of iris transillumination defects after a bout of VZV iridocyclitis?
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In contrast, what one word describes the appearance of iris transillumination defects after a bout of VZV iridocyclitis?
‘Sectoral’
Anterior HSV Disease

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c) Iridocyclitis
   --Can be granulomatous or non-granulomatous
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d) Trabeculitis
   --Presents with key exam finding
Anterior HSV Disease

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d) Trabeculitis
  --Presents with unilateral elevated IOP
Anterior HSV Disease

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

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

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  --Presents with unilateral elevated IOP

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

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

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b) **Keratitis**
   - Epithelial: c/o foreign body sensation. Classic sign: **Dendrites**
   - *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?*
   - Stromal: Interstitial: Looks like a scar: hazy, with no overlying epithelial defect
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c) **Iridocyclitis**
   - Can be granulomatous or non-granulomatous
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d) **Trabeculitis**
   --Presents with **unilateral elevated IOP**
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In the context of ocular HSV dz, what does the acronym HEDS stand for? The Herpetic Eye Disease Study

--Usually a unilateral **blepharoconjunctivitis**
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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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Some authorities opt for PO acyclovir instead of Viroptic in necrotizing stromal keratitis—why? 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.

PO acyclovir

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*In addition to evaluating topical steroids, the HEDS looked also at the role of PO acyclovir in managing HSV stromal keratitis. A portion of the HEDS was a placebo-controlled evaluation of this issue. Was it beneficial?*
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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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   Unclear. The HEDS data were suggestive of a beneficial role, but the N was too small to reach statistical significance.

**The Herpetic Eye Disease Study**

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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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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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- Usually a unilateral **blepharoconjunctivitis**
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2) **Recurrent ocular disease**

a) **Blepharoconjunctivitis**: Looks like primary disease
b) **Keratitis**
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   - Can be granulomatous or non-granulomatous
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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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