8.4.2. Infectious Diseases of the External Eye (II): DNA Viruses (I): Herpes Simplex

- DNA virus
- nearly 100% >60 years harbor HSV in their trigeminal ganglia
  - 40%–80% of adults have serum antibodies to HSV-1
- types
  - type 1 (HSV-1) — orofacial and ocular infection
  - type 2 (HSV-2) — genital infection
- Primary HSV-1 infection
  - skin and mucosal surfaces innervated by CN V
  - nonspecific upper respiratory tract infection
  - latent infection in sensory nerve ganglia
- Recurrent HSV-1 infection
  - reactivation of the latent virus in a sensory ganglion
    - reinfection of ocular surface epithelia
  - environmental triggers
    - psychological stress
    - systemic infection
    - sunlight exposure
    - menstrual cycle
    - contact lens wear
    - HIV infection — equal in severity to that occurring in immunocompetent patients
    - not confirmed by RECIEB
  - typically unilateral — bilateral (2%) — r/o immune dysfunction (e.g. atopic dermatitis)
- pathogenesis

Primary ocular infection

- clinical presentation
  - blepharoconjunctivitis
    - follicular
    - palpable preauricular lymph node
    - Vesicles on the skin

Figure 4-2 (© 2020 American Academy of Ophthalmology)

    - Vesicles on the eyelid margin

Figure 4-3 (© 2020 American Academy of Ophthalmology)

  - epithelial keratitis

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  - stromal keratitis and uveitis are uncommon
  - differential diagnosis with adenovirus
    - cutaneous/eyelid margin vesicles (HSV)
    - ulcers on the bulbar conjunctiva (HSV)
    - dendritic epithelial keratitis (HSV)
    - conjunctival membranes/pseudomembranes (adenovirus)
    - both conditions can be either unilateral or bilateral
      - HSV — more commonly unilateral
      - adenovirus — more commonly bilateral
- laboratory evaluation
  - indications
    - diagnosis is uncertain
    - suspected neonatal herpes
  - Serologic tests
    - rising antibody titer during primary infection
    - no diagnostic assistance during recurrent episodes
    - generally helpful only when negative
  - culture — vesicular fluid
  - cytology — Scrapings from the vesicle base
  - antigen detection
  - PCR
- management
  - self-limited
  - Oral antiviral therapy — speeds resolution — See Table 4-5

Recurrent infection: Blepharoconjunctivitis

- clinically indistinguishable from primary infection
- self-limited
- antiviral agents to shorten the course of illness

Recurrent infection: Epithelial keratitis

- symptoms
  - foreign-body sensation
  - tight sensitivity
  - redness
  - blurred vision
- clinical findings
  - punctate epithelial keratitis
  - dendritic epithelial ulcers with terminal bulbs
    - edge stains with rose bengal and lissamine green

Figure 4-5 (© 2020 American Academy of Ophthalmology)

    - bed stains with fluorescein

Figure 4-6 (© 2020 American Academy of Ophthalmology)

  - geographic epithelial ulcer

Figure 4-7 (© 2020 American Academy of Ophthalmology)

  - ciliary flush and mild conjunctival injection
  - mild stromal edema and subepithelial white blood cell infiltration
    - scarring
    - ghost dendrite

Figure 4-8 (© 2020 American Academy of Ophthalmology)

  - reduction in corneal sensation — not a reliable sign of herpetic disease
- most common cause of neurotrophic keratitis
- conditions that may produce dendritform epithelial lesions
  - VZV
  - epithelial regeneration line
  - Acanthamoeba epithelial keratitis
  - neurotrophic keratopathy (postherpetic, diabetes mellitus)
  - soft contact lens wear (thimerosal)
  - topical medications (antivirals, β-blockers) — cause neurotrophic keratitis
  - epithelial deposits (iron lines, Fabry disease, tyrosinemia type II, systemic drugs)
  - EBV (rare)
  - adenovirus (uncommon)
- laboratory evaluation
  - corneal scrapings
    - multinucleated giant cells (nonspecific)
    - intranuclear inclusions (more specific)
  - tissue culture
  - antigen detection techniques (ELISA)
  - PCR
- management
  - Most cases of HSV epithelial keratitis resolve spontaneously
  - antiviral therapy
    - shortens the clinical course
    - may reduce
      - associated herpetic neuropathy
      - subepithelial scarring
      - risk of immune-mediated diseases
  - epithelial debridement — speeds resolution
  - blocks DNA polymerase
    - x10–14 days
    - topical trifluridine 1% solution — 9x/day
    - acyclovir 3% ophthalmic ointment — 5x/day
    - topical ganciclovir 0.15% gel — 5x/day — less toxic than trifluridine
    - pyrimidine analogue
    - prodrug of acyclovir
    - valacyclovir
      - oral
      - thrombotic thrombocytopenic purpura/hemolytic uremia syndrome in severely immunocompromised patients — use with caution if immune status unknown
    - oral acyclovir — as effective as topical antivirals — no ocular toxicity
    - topical corticosteroids — contraindicated in the presence of active herpetic epithelial keratitis
    - patients on systemic corticosteroids should be treated aggressively with systemic antiviral therapy

Recurrent infection: Stromal keratitis

- most common cause of infectious corneal blindness in the United States
- each episode of stromal keratitis increases the risk of future episodes
- pathogenesis
  - HSV-specific CD4 and CD8 T lymphocytes
  - anti-HSV antibodies
  - bystander effects of proinflammatory cytokines
- nonnecrotizing
  - Herpetic interstitial keratitis
    - unifocal/multifocal interstitial haze/whitening of the stroma

Figure 4-9 (© 2020 American Academy of Ophthalmology)

Figure 4-10 (© 2020 American Academy of Ophthalmology)

    - no epithelial ulceration
    - mild stromal edema
    - corneal vascularization
      - long-standing/multiply recurrent HSV interstitial keratitis

Figure 4-11 (© 2020 American Academy of Ophthalmology)

    - differential diagnosis
      - VZV keratitis
      - Acanthamoeba keratitis
      - syphilis
      - EBV keratitis
      - mumps keratitis
      - Lyme disease
      - sarcoidosis
      - Cogan syndrome
    - visually significant herpetic interstitial keratitis — treatment
      - prophylactic antiviral drug
        - taper every 1–2 weeks — 1% prednisolone drops every 2 hours
        - topical trifluridine 4 times daily
        - acyclovir 400 mg twice daily
        - valacyclovir 500 mg once a day
        - until using less than 1 drop of 1% prednisolone per day
  - Herpetic disciform keratitis
    - clinical findings
      - primary endothelitis
      - corneal stromal and epithelial edema
      - round or oval
      - keratic precipitates
      - Indocyclitis
        - stromal edema and keratic precipitates out of proportion to the anterior chamber reaction
    - treatment
      - penetrates intact cornea — oral acyclovir
      - not absorbed through intact epithelium — topical antiviral medications
      - identical to disciform keratitis due to VZV
- necrotizing
  - indistinguishable from fulminant bacterial or fungal keratitis
  - suppurative corneal inflammation
    - edges of the epithelial ulcer do not stain with rose bengal
    - epithelial ulceration is common
      - may occur somewhat eccentric to the infiltrate
  - differential diagnosis
    - microbial keratitis due to bacteria, fungi, or acanthamoebae
    - retained foreign body
    - anesthetic abuse
    - diagnosis of exclusion
  - treatment
    - topical corticosteroids — twice-a-day
    - antiviral
      - oral antiviral preferred
      - topical antivirals are toxic and can confuse the clinical picture
- management
  - topical corticosteroids
    - prophylactic antiviral
    - reduce persistence/progression of stromal inflammation
      - shorten the duration of HSV stromal keratitis
  - long-term prophylactic oral acyclovir
    - reduces the rate of recurrent HSV keratitis — 50%
    - for patients with multiple recurrences of HSV stromal keratitis
    - no additional benefit
  - oral acyclovir
    - used for active HSV stromal keratitis in patients receiving topical corticosteroids + trifluridine
    - given briefly with trifluridine in an episode of epithelial keratitis
    - did not prevent subsequent HSV stromal keratitis or iritis

Recurrent infection: Indocyclitis

- setting
  - necrotizing stromal keratitis
  - independent of corneal disease
- clinical findings
  - granulomatous or nongranulomatous
    - elevated intraocular pressure — trabeculitis
    - patchy iris transillumination
  - HSV has been cultured from the anterior chamber
- treatment
  - topical steroid
  - statistical trend toward benefit — + oral acyclovir (400 mg, 5 times daily)

Complications

- Epithelopathy
  - prolonged topical antiviral treatment
  - diffuse punctate epithelial erosions
  - conjunctival injection
- Neurotrophic keratopathy
  - Punctate epithelial erosions
    - chronic epithelial regeneration lines
  - neurotrophic ulcers
    - clinical findings
      - gray elevated appearance
        - round or oval
        - central or inferior cornea
        - rolled epithelial edge
      - relative absence of rose bengal staining
    - similar to epithelial ulceration of necrotizing herpetic stromal keratitis
    - similar to metaherpetic ulcer
    - treatment
      - nonpreserved lubricating drops, gels, and ointments
      - punctal occlusion
      - if no response to conservative therapy — tarsorrhaphy
- metaherpetic ulcer
  - chronic epithelial defect over active/resolving interstitial stromal keratitis that does not stain with rose bengal
- persistent bullous keratopathy
  - secondary to severe or long-standing disciform keratitis
- permanent corneal scarring
  - gas-permeable contact lens — irregular astigmatism
- secondary lipid keratopathy
  - may improve with time
  - topical corticosteroids

Surgical treatment

- Penetrating keratoplasty (PK)
  - visually significant stromal scarring and astigmatism not correctable by spectacle or contact lens
  - may improve graft survival
  - allows more liberal use of topical corticosteroids
  - Oral antiviral therapy
    - preferable to topical antivirals
  - 80% success in eyes without signs of active inflammation > 6 months
  - in inflamed herpetic eyes delay PK until inflammation is controlled
  - in suspending surface/corneal perforation
  - neurotrophic/ischemic corneal perforation
  - graft failure
  - complications
  - in inflamed herpetic eyes delay PK until inflammation is controlled
- conjunctival flaps
- amniotic membrane transplantation
- keratoprostheses
- anterior lamellar keratoplasty

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