Systemic Viral Infections and Ocular Complications

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Systemic Infections

- Herpesviridae family:
  - Herpes simplex virus type 1 (HSV1)
  - Herpes simplex virus type 2 (HSV2)
  - Varicella-zoster virus (VZV)
  - Cytomegalovirus (CMV)
  - Human herpes virus type 6 (HHV6)
  - Human herpes virus type 7 (HHV7)
  - Epstein-Barr virus (EBV)
  - Human herpes virus type 8 (HHV8)

- HSV infection is common
  - 25% of people age 4 are seropositive for HSV
  - 100% of people are seropositive for HSV at age 60

Practice Update: A New Vaccine to Prevent HZ

- 50% of pts. Living to 85 will get HZ
- Present vaccine reduces incidence:
  - 70% (50 to 59)
  - 64% (60 to 69)
  - 38% (70 +)
- PHN reduced:
  - 66% (60 to 69)
  - 67% (70 +)

Practice Update: A New Vaccine to Prevent HZ

- Phase 3 trial: (VZV glycoptotein) HZ/su vaccine:
  - Tested in immunocompetent pts:
    - Had a 97.2% efficacy in preventing HZ in all age groups (ages: 50 to 70+).
    - Efficacy did not diminish with age.
    - HZ/su is administered in two doses.
    - Adjuvant: monophosphoryl lipid A, QS21 a saponin compound, formulated with liposomes
    - Side effects were mainly “injection site” rxn.
    - Reduction of PHN: presently being evaluated.
  - Results for this vaccine are “promising”
HSV I vs HSV II

- Humans only natural reservoir of herpes
- DNA virus: important concept for therapy
- Sources of infection: direct contact with lesions, salivary droplets, saliva and fomites of asymptomatic virus shedding carriers.
- Strong suggestion that we will or may already be seeing an increase in incidence of type 2 HSV keratitis*
  - 1 in 4 in US > age 30 infected with HSV 2 *
  - Infection with type I becoming delayed in industrialized countries*
  - Changes is sexual behavior in young adults (oral-genital HSV I infections)*


HSV Systemic Infection Variation

- Subclinical primary infection with herpes viruses is more common than clinically manifest illness
- Spectrum of illness ranges widely from stomatitis and urogenital lesions to facial nerve paralysis (Bell's palsy) and encephalitis (gingivostomatitis / herpes labialis most common cutaneous presentations)
- Variable intervals between exposure to virus and clinical disease (Asymptomatic shedding of either virus is common especially after primary infection or symptomatic recurrences- common time for transmission)

Adenoviruses

- Variant types
  - Adenovirus is a double-stranded DNA virus that measures 70-90 nm and that has an icosahedral capsid
  - Possessing 52 serotypes, adenovirus is recognized as the etiologic agent of various diverse syndromes. It is transmitted via direct inoculation to the conjunctiva, a fecal-oral route, aerosolized droplets, or exposure to infected tissue or blood.
Systemic Manifestations or not?
- Acute respiratory disease (predominantly adenovirus types 1, 2, 5, and 6; occasionally, 3 and 7)
- Adenovirus serotype 14 referred to as the "super cold" in the media, has caused rare outbreaks of ARD since 1955.
- Pharyngoconjunctival fever PCF (predominantly serotypes 3, 4, and 7)
- Epidemic keratoconjunctivitis EKC (predominantly serotypes 8, 19, and 37) Not!!!
- Acute hemorr. cystitis (serotypes 7, 11, 21 & 35)/nephritis
- Gastroenteritis (most commonly associated with serotypes 40 and 41, but others may be involved)
- Adenoviral infections in immunocompromised hosts (multiple serotypes)

Ocular Involvement
Peri-ocular Manifestations
- Adenoviruses
  - Adenopathy (Pre-auricular, submandibular)
  - Fever
  - Pharyngitis
  - URTI
  - Lid swelling

Practice Essentials: Update
- Human enteroviruses are ubiquitous viruses that are transmitted via direct contact or URTI
- A rare polio-like virus has been reported in children in northern California*
- Acute onset, flaccid paralysis of 1 or more limbs, ages ranged from 2 to 16 and the number of cases reached 20 to 25 in one yr.
- Of these cases, 2 patients tested positive for enterovirus-68

Ocular Manifestations of the Viruses
Ocular Involvement
Peri-ocular Manifestations

• HSV
  - Commonly associated conditions: Fever blisters around mouth, nose and eyes often accompany ocular HSV
  - Positive Pre-auricular lymphadenopathy is 80% of patients*
  - Dermatitis/blepharitis: clear vesicles atop an erythematous base (upper or lower lids or lid margins)
  - Conjunctival inflammation precedes corneal vesicles


Follicular Reaction of the conjunctiva is a good indicator!!

Herpes Keratitis in Children: Update

• 30% of HSK in children often mistaken for Staph Disease
• Although unilateral Herpetic disease is more common, bilateral herpetic blepharoconjunctivitis occurs more commonly in children
• HSV recurrence rates are higher in children, upwards of 80%
• HSK-related vision loss in children secondary to corneal scarring or refractive amblyopia (25% of children had 2D of astigmatism or greater)
• ICGA kit (Checkmate Herpes Eye, Wakamoto Pharm Co.) is fast and efficient alternative for detection of HSV epithelial keratitis.
• Oral AV therapy is a desirable tx option in this group.
Anterior Segment Manifestations

- True dendritic lesions show arborization and terminal end bulbs (70+%).
- Associated corneal scarring, corneal hypoesthesia and possible iris atrophy in the affected eye can also be indicators.
- Non-herpetic like entities include keratitis from contact lenses and CL solutions, ocular surface disease, trauma (corneal re-epithelialization), Herpes Zoster corneal infection.

Pseudo-Dendritic lesions

HSV Immune Keratitis

- Herpetic Immune keratitis (6%) may present as (new or after epithelial Dz):
  1. Limbal vasculitis
  2. Wessley immune ring
  3. Necrotic interstitial keratitis
  4. Disciform edema
  5. Endothelitis (usually with elevated IOP)
     - Disciform, diffuse, linear

Stromal / Immune Keratitis

- Hypersensitivity rxn to “fixed” herpes antigen w/in the stromal keratocytes / fibroblasts
- Large “glyco-proteins” on certain HSV strains cause more destructive inflammatory Rxns.
- Stromal Haze in part caused by “toxic” cytokines which alter endothelial function of the cornea.
- Wessley Ring (immune ring of altered keratocytes and stromal ground substance infiltrated with numerous inflammatory cells)
Clinical Presentation of HSV Stromal Keratitis

- **Disciform Keratitis**
  - Blurred vision, photophobia, tearing and mild orbital pain
  - Unlike stromal keratitis, lesions are commonly more uniform

Clinical Presentation of HSV Stromal Keratitis

- **Disciform Keratitis**
  - Intact epithelium with a central or eccentric zone of edema which surrounds a solid disc of edematous stroma
  - Wessley ring possible (Ant./ mid stromal)
  - White (ng) KP’s on endothelial surface

Clinical Presentation of HSV Stromal Keratitis

Disciform Dz:
- Stratified opacities and presence of corneal lamellae
- Corneal necrosis and ground glass appearance of the stroma
- Corneal scarring, facet formation, and possible perforation

Posterior Segment Manifestations

- Retinitis
Adeno-Viral Ocular Infections

Anterior Segment Manifestations of Adenoviruses
- Follicular Conjunctivitis: Pseudomembranes
- Cornea: Superficial keratitis, SEI's
- Eyelids: edematous, blepharospam

Lab/In-office tests for HSV and Adenovirus

Lab Work Up- HSV Epi Keratitis
- Giemsa stain - (multinucleated giant cells)
- PAP Stain: intranuclear inclusion bodies
- RPS adeno detection (In-Office CLIA)
- Viral cultures: HSV antigen detection tests, such as the enzyme-linked virus inducible system (ELVIS) (results 2- 4 hours)
- EIA test (Herp Chek – Boston-in-office) (1 to 2 days)
- Polymerase chain reaction (PCR / Multiplex PCR) using tear samples (3 to 5 days)
Lab Tests

Laboratory Tests for HSV Stromal Keratitis
• Same as for HSV epithelial disease except:
  – Corneal Biopsy sometimes required
• DDx:
  – Acanthamoeba Keratitis (CL wearers)
  – Vaccinia keratitis (Recent Hx of smallpox vaccination)
  – HZO (Hx of dermatologic rash)
  – Neurotrophic Keratopathy

Diagnostic tests & Interpretation
Adenoviruses
• Point of Care immunoassay for adenovirus (RPS)
  – 89% sensitivity, 94% specificity
  – Detects viable and nonviable virus fragments
• Viral Cell Culture
  – 3-21 days to grow
  – “Gold Standard”
  – Only detects “live” virus
• PCR
  – Expensive
  – Not FDA cleared --detects viable and non-viable viral fragments

DDX of Adenoviruses
• Conjunctivitis (bacterial and allergic)
• Episcleritis/scleritis
• Dry eyes
• Keratitis (inflammatory and infectious)
• Uveitis
• ACG
**Topical and Oral Treatments for Viral infections**

**Treatment**

- **Ocular HS**
  - Lid and skin lesions: Acyclovir ophth ung. 3% BID
  - Cornea:
    - Vidarabine (compound labs)
    - Trifluridine 1.0%, 5-9 x per day until healed
    - Ganciclovir gel, 0.15%, 5 x per day until healed
      - Targets only viral DNA
      - **SPK: 12.1% acyclovir ointment vs. 6.8% ganciclovir gel**
  - Systemic Acyclovir only in neonates

*Lindstrom, RL, et. al. Advances in the treatment of acute herpetic keratitis (dendritic ulcers). Primary Care Optometry News October, 2010*  

**HSV Epithelial Disease- Treatment Non-Topical**

- Corneal debridement used in adult if HSK is superficial and no prior use of steroids. (AB for epi. Breakdown- be careful not to break Bowmans layer)
- Oral Acyclovir (400mg 5X/day) - off label but cheap* Oral Valacyclovir (Valtrex) 500mg, Famciclovir 500 mg TID, Acyclovir (Zovirax), suspension 200mg (kids)

*Takemura, T. et al. Acyclovir vs. valacyclovir for the treatment of ophthalmic herpes zoster keratitis (visibel ulcer). Primary Care Optometry News October, 2018*

**Treatment of HS Stromal Disease**

- Topical corticosteroids
- Topical or oral antivirals
- The strategy for topical corticosteroid therapy is frequent initial administration (q1-4h) followed by slow tapering of the dose to the lowest effective amount
- Topical or oral antivirals are recommended to prevent or limit epithelial disease during the course of treatment with corticosteroids. Many recommendations are available on the frequency of administration of antivirals for prophylaxis
Treatment of Stromal Disease

- The Herpetic Eye Disease Study Group recommended using trifluridine 4 times daily for 3 weeks and 2 times daily thereafter.
- Associated elevated intraocular pressure can be treated with timolol and systemic acetazolamide, as necessary.
- Topical cyclosporin A 2% drops in an uncontrolled study showed efficacy in the treatment of stromal disease without the use of corticosteroids. A role may exist for this medication in those patients unable to use corticosteroids.

Treatment of Stromal Disease

- Indolent stromal ulceration is managed with antiviral and corticosteroid therapy along with a soft contact lens (Pro-Kera Contact lens - amniotic membrane) to prevent corneal drying.
- When melting of the cornea occurs, care must be taken not to stop corticosteroid therapy abruptly, as doing so may lead to rebound inflammation and increase the melting process, thereby resulting in perforation.
- The anti-collagenolytic activity of tetracyclines may help retard corneal melting.

Summary of Clinical Recommendations for Herpes Stromal Keratitis (HSK)

- Non-necrotizing or necrotizing HSK**
  - Topical corticosteroids and topical antivirals
- Non-necrotizing or necrotizing HSK, especially cases refractory to steroids or cases with significant adverse effects from steroids**
  - Topical 0.5-2.0% cyclosporine A (CsA) solution and topical antivirals
- Necrotizing HSK, especially cases refractory to antiviral and steroid therapy where corneal perforation is imminent**
  - Amniotic membrane transplantation (AMT) with continued use of antivirals and steroids


Prevention

- Advisable?
- Acyclovir 200 5x/day or 400 BID*

Treatment of Adenoviruses

- **First Line: medications**
  - Refrigerated NPAT’s
  - Topical antihistamines
  - Topical Ganciclovir gel (small randomized controlled masked series showed decrease duration of Dz*)
  - Off label: Topical Betadine (in-office) and Topical Steroid (Qid)


Clinical and antiviral efficacy of an ophthalmic formulation of dexamethasone povidone-iodine in a rabbit model of adenoviral keratoconjunctivitis.***

- **PURPOSE:** To determine the efficacy of a new formulation of topical dexamethasone 0.1%/povidone-iodine 0.4% (FST-100) in reducing clinical symptoms and infectious viral titers in a rabbit model of adenoviral keratoconjunctivitis.
- **FST-100** was the most efficacious in minimizing the clinical symptoms of adenovirus infection in rabbit eyes. FST-100 and 0.5% cidofovir were both equally effective in reducing viral titers and decreasing the duration of viral shedding. By providing symptomatic relief in addition to reducing infectious virus titers, FST-100 should be a valuable addition to treatment of epidemic adenoviral keratoconjunctivitis.


- **Second Line: medications**
  - Topical steroids for SEI’s and Pseudomembranes (Steroids should be avoided in severe disease)
  - Topical NSAID’s (Prolensa)

- **Supportive / General Measures Care:**
  - Freq. hand washing
  - Limit sharing of towels and linens
  - Home disinfection
  - Educate patient on contagion issues

Thank you for your Attention