Adenoviral Conjunctivitis: Diagnostic and Therapeutic Update

Spencer Johnson, O.D., F.A.A.O.
Northeastern State University
Oklahoma College of Optometry
johns137@nsuok.edu

• In a recent study, 8 private ophthalmology practices and academic centers enrolled 128 patients presenting with a clinical diagnosis of viral conjunctivitis. Tear samples were collected and analyzed to confirm viral conjunctivitis.

• Approximately 20%-70% of infectious conjunctivitis is thought to be viral.

In 1892, Dmitry Ivanovsky showed that sap from a diseased tobacco plant remained infectious to healthy tobacco plants despite having been filtered.
History of Virology

• In 1898, Dutch microbiologist and botanist Martinus Beijerinck used the term virus to describe this filterable agent.

History of Virology

• The development of the electron microscope in the 1930s finally made it possible to establish the physical nature of viruses.

Virus Structure

I. Nucleic Acid

II. Capsid

III. Envelope +/-
Nucleic Acid

- dsDNA
- ssDNA
- dsRNA
- ssRNA

Capsid

- Composed of repeating protein subunits (capsomers)
  - Helical arrangement
  - Icosahedral arrangement

Capsid

Polyhedral (Bacteriophage)
Spherical (Influenza)
Helical (Tobacco mosaic virus)
Complex (Bacteriophage)
Envelope

• May or may not contain this component

Morphological Classification

• Non-enveloped, helical capsid
• Non-enveloped, icosahedral capsid
• Enveloped, helical capsid
• Enveloped, icosahedral capsid

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>Epithelial Involvement</th>
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<tbody>
<tr>
<td>Adenoviridae</td>
<td>Herpes simplex ocular disease, varicella zoster, cytomegalovirus, and adenovirus 8</td>
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<tr>
<td>Poxviridae</td>
<td>Papilloma (human papilloma virus) of lids and conjunctiva</td>
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<tr>
<td>Paroviridae</td>
<td>Meibomian gland dysfunction of lids and adnexa</td>
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<tr>
<td>Retroviridea</td>
<td>Human immune deficiency virus affects many ocular tissues</td>
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<td>Togaviridea</td>
<td>Rubella retinopathy</td>
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Adenovirus

Structure
- dsDNA
- Non-enveloped/icosahedral capsid

Serotypes
- 7 species
- Over 50 known serotypes
Adenoviral Eye Diseases

- Pharyngoconjunctival fever (PCF)
- Epidemic keratoconjunctivitis (EKC)
- Acute nonspecific follicular conjunctivitis (NCF)
- Chronic keratoconjunctivitis

Diagnosis

- **Symptoms:**
  - Injection
  - Foreign body sensation
  - Watering
  - Burning

- **Signs:**
  - Follicles
  - Preauricular lymphadenopathy
  - Membrane/pseudomembrane

Diagnosis

- Clinical signs and symptoms
- Cell culture
- Polymerase Chain Reaction (PCR)
- RPS AdenoPlus
Cell Culture

Cytopathogenic Effect on Different Cells Lines*

Fibroblasts
Some produce clusters

AS49 cells
Grape-like clusters or "lacy" pattern; 5-8 days

RhMK cells
Some produce clusters

HNK
Grape-like clusters; 5-7 days


Polymerase Chain Reaction

Exponential amplification

http://users.ugent.be/~avierstr/principles/pcrcopies.gif
RPS AdenoPlus

• How good are we at diagnosing adenoviral conjunctivitis?
In 2015, Lee et al. reported a 50% false positive rate of AdenoPlus in a study of 111 pts. Of the 111 pts. who tested positive for adenovirus by AdenoPlus, 50 of 111 tested negative for adenovirus by PCR.
Kam et al. reported a 39.5% false negative rate in the study of 121 pts. presenting with "pink eye". Of the 43 pts who tested positive for adenovirus by PCR, 17 of 43 (39.5%) tested positive by AdenoPlus.

Treatment

- National Guidelines
- Ganciclovir
- Betadine
National Guidelines

• AOA Clinical Practice Guidelines
  • cold compresses, lubricants, and ocular decongestants
  • topical ophthalmic corticosteroids use limited to patients who are significantly symptomatic or who develop visual loss from inflammatory keratitis

• American Academy of Ophthalmology Preferred Practice Patterns
  • artificial tears, topical antihistamines, or cold compresses
  • topical corticosteroids in severe cases with marked chemosis or lid swelling, epithelial sloughing, or membranous conjunctivitis

Zirgan®
ganciclovir ophthalmic gel 0.15%

• Use is off-label

• Clinical trial is currently underway

Betadine™

• Survey at the American Academy of Optometry 2013 Annual Meeting suggests a large minority of optometrists utilize this treatment approach
Betadine™

- Protocol Outlined in Review of Optometry’s Clinical Drug Guide by Ron Melton and Randall Thomas

- No randomized, controlled clinical trial to date to prove or disprove its effectiveness

- Reducing Adenoviral Patient Infected Days (RAPID) Study
  - Randomized, controlled clinical trial to evaluate effectiveness of Betadine™ in treating adenoviral conjunctivitis
  - Received NIH funding for an R-34 planning grant
  - Patient recruitment in ongoing through 2018
Questions

• Is RPS a reliable test for adenoviral conjunctivitis?

• If it’s not adenoviral conjunctivitis, what is it?

• Is Betadine effective in treating adenoviral (or other) conjunctivitis?

0.1% dexamethasone/0.6% povidone-iodine (SHP640)

• Phase 2 multicenter, randomized, double-masked study comparing 0.1% dexamethasone/0.6% povidone-iodine (SHP640) against povidone-iodine (PVP-I) and vehicle in 144 patients with adenoviral conjunctivitis

• Patients’ mean age was 34.5 years, 66.3% were male, and all were Asian
0.1% dexamethasone/0.6% povidone-iodine (SHP640)

- Patients received one drop in both eyes four times a day for 5 days
- Key assessments included clinical resolution and absence of watery conjunctival discharge and bulbar conjunctival redness

At day 6, the percentage of patients with clinical resolution in the primary study eye was 31.3% for the SHP640 group, 10.9% in the vehicle group and 18% in the PVP-I group.

Adenoviral eradication was significantly higher in the SHP640 group (79.2%) compared to vehicle (56.5%) and numerically higher than the PVP-I group (62.0%). Adenoviral eradication was noted in both non-vehicle groups as early as day 3.

Thank You