You Were Expecting Viral Conjunctivitis

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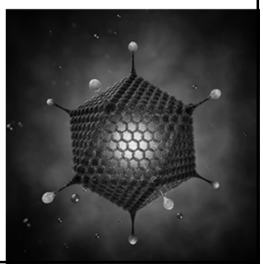


Disclosures

- The lecturer had no financial interest in any of the products or services mentioned in the presentation

- 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.

Sambursky R, Trattler W, Tauber S, Starr C, Friedberg M, Boland T, et al. Sensitivity and specificity of the AdenoPlus test for diagnosing adenoviral conjunctivitis. JAMA ophthalmology. 2013;131(1):17-22.

Diagnosis

Diagnosis

- Clinical signs and symptoms
- Cell culture
- Polymerase Chain Reaction (PCR)
- RPS AdenoPlus
- Next Generation Sequencing

Clinical Signs and Symptoms

- Signs:
  - Follicles
  - Preauricular lymphadenopathy
  - Membrane/pseudomembrane
- Symptoms:
  - Injection
  - Foreign body sensation
  - Watering
  - Burning

Clinical Signs and Symptoms

- Kam, K.Y.R., et. al., (2015) "No single sign or symptom of adenoviral conjunctivitis was found to be an accurate predictor of being test positive by PCR in patients with adenovirus."
- Shorter, E., et. al., (2017), American Academy of Optometry Poster Session "No single sign or symptom clearly distinguished qPCR positive patients from other patients who presented with red eye."

Cell Culture

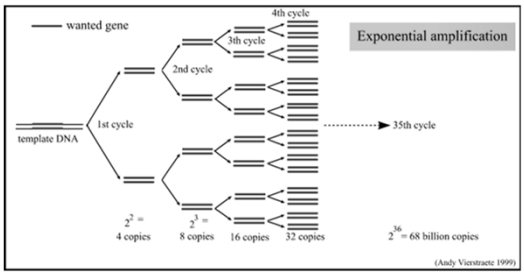
STT1820125
20x125 mm Threaded Test Tube

Cytopathogenic Effect on Different Cells Lines*

Fibroblasts	A549 cells	RhMK cells	HNK
Some produce clusters	Grape-like clusters or "lacy" pattern; 5-8 days	Some produce clusters	grape-like clusters; 5-7 days

*Clin Microbiol Rev. 2007 Jan; 20(1): 49–78.

Polymerase Chain Reaction



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

RPS AdenoPlus

History of Virology

History of Virology

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

http://en.wikipedia.org/wiki/Dmitri_Ivanovsky

History of Virology

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

http://en.wikipedia.org/wiki/Martin...

History of Virology

"First Ruska Electron Microscope - Deutsches Museum - Munich.edit" by J Bew

- 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 +/-

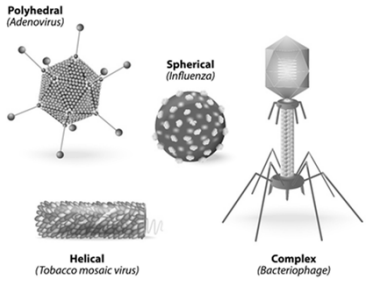
Nucleic Acid

- dsDNA
- ssDNA
- dsRNA
- ssRNA

Capsid

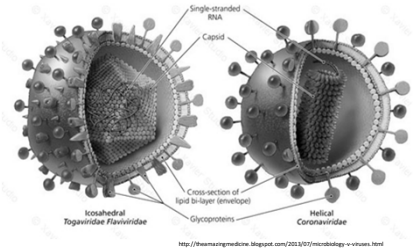
- Composed of repeating protein subunits (capsomers)
  - Helical arrangement
  - Icosahedral arrangement

Capsid



Envelope

- May or may not contain this component

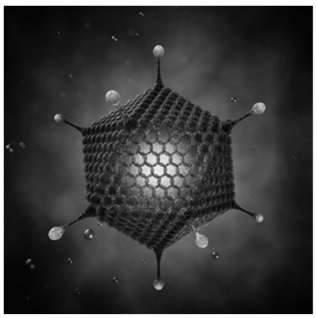


http://theamazingmedicine.blogspot.com/2013/07/microbiology-v-viruses.html

Morphological Classification

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

Adenovirus



Structure

- dsDNA
- Non-enveloped/icosahedral capsid

Serotypes

- 7 species
- Over 50 know serotypes

RPS AdenoPlus

- How good is the RPS AdenoPlus?

CLINICAL TRIALS

Sensitivity and Specificity of the AdenoPlus Test for Diagnosing Adenoviral Conjunctivitis

Robert Sambursky, MD; William Trattler, MD; Shachar Tauber, MD; Christopher Starr, MD; Murray Friedberg, MD; Thomas Boland, MD; Marguerite McDonald, MD; Michael DellaVecchia, MD, PhD; Jodi Luchs, MD

Objective: To compare the clinical sensitivity and specificity of the AdenoPlus test with those of both viral cell culture (CC) with confirmatory immunofluorescence assay (IFA) and polymerase chain reaction (PCR) at detecting the presence of adenovirus in tear fluid.

Methods: A prospective, sequential, masked, multicenter clinical trial enrolled 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis from a combination of 8 private ophthalmology practices and academic centers. Patients were tested with AdenoPlus, CC-IFA, and PCR to detect the presence of adenovirus.

Main Outcome Measures: The sensitivity and specificity of AdenoPlus were assessed for identifying cases of adenoviral conjunctivitis.

Results: Of the 128 patients enrolled, 36 patients' results were found to be positive by either CC-IFA or PCR and 29 patients' results were found to be positive by both CC-IFA and PCR. When compared only with CC-IFA, AdenoPlus showed a sensitivity of 90% (28/31) and specificity of 96% (93/97). When compared only with PCR, AdenoPlus showed a sensitivity of 85% (29/34) and specificity of 98% (89/91). When compared with both CC-IFA and PCR, AdenoPlus showed a sensitivity of 93% (27/29) and specificity of 98% (88/90). When compared with PCR, CC-IFA showed a sensitivity of 85% (29/34) and specificity of 99% (90/91).

Conclusion: AdenoPlus is sensitive and specific at detecting adenoviral conjunctivitis.

Application to Clinical Practice: An accurate and rapid in-office test can prevent the misdiagnosis of adenoviral conjunctivitis that leads to the spread of disease, unnecessary antibiotic use, and increased health care costs. Additionally, AdenoPlus may help a clinician make a more informed treatment decision regarding the use of novel therapeutics.

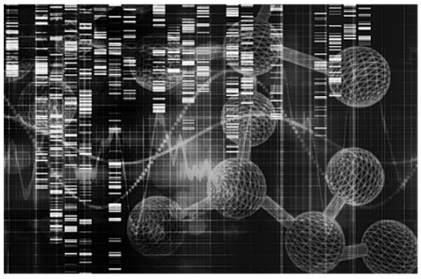
Trial Registration: clinicaltrials.gov Identifier: NCT00921895

JAMA Ophthalmol. 2013;131(1):17-22

RPS Studies to Date

Year	Author	n	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
2013	Sambursky, et al	125	85%	98%	94%	95%
2015	Kam, et al	109	40%	96%	85%	71%
2017	Holtz, et al	46	50%	92%	63%	83%
2018	Lee, et al	500	XX	XX	78%	XX
ongoing	RAPID Study	168	93%	81%	50%	98%
	Aggregate	394	67%	90%	76%	89%

Next Generation Sequencing



captodayonline.com

Treatment

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
- Limited published clinical trials

Ganciclovir

- Ozen, et al, (2017) 200 patients using Zirgan
- Huang, et al, (2014) In vitro study
- Yabiku, et al, (2011) 34 patients, Zirgan
- Tabbara, et al, (2001) at ARVO reported that ganciclovir significantly reduced time of virus recovery and ocular complications compared to artificial tears; however, these promising results have never been published

Ozen, S. & Ozer, M.A. Int Ophthalmol (2017) 37: 245

- Patients who were within the first 3 days of adenoviral eye infection (AEI)
- Divided into two groups:
  - Group 1 with 100 patients who used artificial tears
  - Group 2 with 100 patients who used ganciclovir ophthalmic gel (GOG) plus artificial tears (GAT)
- All patients underwent an eye examination by the same ophthalmologist on the 1st, 5th, 10th, and 15th day after treatment

Results

- Group 2 showed better and faster response to treatment.
- There was less transmission to the contralateral eye and environment, and less formation of corneal subepithelial infiltrate and conjunctival pseudomembrane in Group 2
- A comparison of each group pre-treatment and during treatment revealed improved signs and symptoms in Group 2 ($p < 0.005$)
- The study showed a trend toward more rapid improvement, less corneal and conjunctival involvement, and less transmission to the contralateral eye and environment in the GAT group

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

Povidone-Iodine Treatment

- Betadine 5% Sterile Ophthalmic Prep Solution (30ml opaque bottle), Alcon
- A broad-spectrum microbicide.
- Indicated for "pre-operative prep and irrigation of the ocular and periocular surfaces."
- Off label use: Tx adenoviral keratoconjunctivitis
  - Anesthetize with proparacaine
  - Instill one or two drops of NSAID
  - Instill several drops Betadine 5% in eye(s); close eye(s)
  - Swab or rub excess over eyelid margin
  - After one minute, irrigate with sterile saline
  - Instill one or two drops of NSAID
  - Rx steroid QID for four days
- Avoid use if patient is allergic to iodine.
- CPT code 99070—materials and supplies

Betadine™

- 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 mid-2018

Questions

- Is RPS a reliable test for adenoviral conjunctivits?
- 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

Dexamethasone/povidone-iodine effective against adenoviral conjunctivitis. (2017, October 17). Retrieved October 27, 2017, from https://www.healio.com/optometry/cornea-external-disease/news/online/%7B6477e505-389d-476b-977b-5ffecb6f95375/70/dexamethasonepovidone-iodine-effective-against-adenoviral-conjunctivitis?

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

Dexamethasone/povidone-iodine effective against adenoviral conjunctivitis. (2017, October 17). Retrieved October 27, 2017, from https://www.healio.com/optometry/cornea-external-disease/news/online/%7B6477e505-389d-476b-977b-5ffecb6f95375/70/dexamethasonepovidone-iodine-effective-against-adenoviral-conjunctivitis?

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

- 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

Dexamethasone/povidone-iodine effective against adenoviral conjunctivitis. (2017, October 17). Retrieved October 27, 2017, from https://www.healio.com/optometry/cornea-external-disease/news/online/%7B6477e505-389d-476b-977b-5ffecb6f95375/70/dexamethasonepovidone-iodine-effective-against-adenoviral-conjunctivitis?