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Reducing Adenoviral Patient Infected Days (RAPID) Planning Study: Agreement between Clinician and AdenoPlus™ in the Diagnosis of Adenoviral Conjunctivitis (Ad-Cs)

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Introduction

There is no FDA-approved treatment for adenoviral conjunctivitis (Ad-Cs). Ad-Cs is a prevalent and highly contagious eye infection that affects 6 million people each year in the United States.[1] Conjunctivitis can be caused by bacteria, viruses, allergens and toxin exposure, which makes the diagnosis of Ad-Cs especially challenging. Cheung reported that 42% of patients presenting with classic, unilateral conjunctivitis were misdiagnosed as Ad-Cs using viral culture.[2]

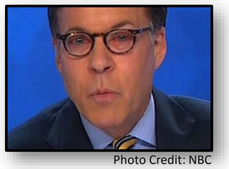


Photo Credit: NBC

The timely and accurate diagnosis of Ad-Cs is crucial to the success of future studies. Clinical treatment trials for Ad-Cs are likely to fail if a large number of patients enrolled are misdiagnosed. For instance, a treatment that is 80% successful will appear to be only 56% successful if 30% of the patients in the trial are misdiagnosed as having Ad-Cs.[3]

AdenoPlus™ (RPS, Sarasota FL), the first CLIA waived point-of-care immunoassay, has been developed to aid clinicians in the differential diagnosis of Ad-Cs and has been reported to have a sensitivity of 90% and specificity of 96%.[4]

The RAPID (Reducing Adenoviral Patient-Infected Days) study is a 2-year NEI/NIH-funded planning study designed to estimate key parameters for a randomized trial that determines whether an in-office application of commercially available 5% Betadine (Povidone-iodine, Alcon Laboratories, Inc., Fort Worth, TX) is effective at reducing viral load and improving symptoms in patients with Ad-Cs. A positive test on the AdenoPlus™ immunoassay is required as entry criteria for all patients enrolled this study.

Purpose

In this study we compare patient-reported symptoms and clinician-graded signs in patients presenting with a red eye that were AdenoPlus-positive to those that had a clinician-reported diagnosis of likely Ad-Cs.

RAPID Planning Study: Methods

- All participating study sites had IRB approval.
- Patients ≥ 18 years of age, who presented with a new onset red eye with symptoms ≤ 4 days, were invited to participate and informed consent was obtained.
- Enrolled patients completed a symptom survey (Table 1) and a clinical evaluation, including visual acuity, lymph node palpation, and slit lamp examination.
- If a patient presented with both eyes affected, the eye with earlier onset was selected. If onset was simultaneous, one eye was selected randomly by a coin toss.
- Based on clinical examination and patient symptoms, clinicians classified probable causes of red eye (bacterial, allergic, dry eye, environmental irritation, contact lens related, or adenoviral) on a scale of "definitely not", "probably not", "probably yes", or "definitely yes". Clinician classifications of "probably yes" and “definitely yes" for Ad-Cs were grouped together and compared to patients with AdenoPlus-positive results.
- In addition to AdenoPlus™ testing, conjunctival samples were collected at each visit. Samples were sent for quantitative PCR (qPCR) analysis to assess changes in adenoviral load over time.

AdenoPlus™ Negative

AdenoPlus™ Positive

- All patients with a positive AdenoPlus™ test were eligible for randomization. Randomized patients received a one-time, in-office lavage of either artificial tears or Betadine 5% sterile ophthalmic prep solution and were followed with clinical exams for up to 21 days.

Results

Table 1. Procedures completed at the baseline and follow-up visits. Procedures in unshaded boxes are performed on screened patients; those in shaded boxes are performed on patients with a positive AdenoPlus™ test who were eligible for treatment randomization. The patient and examiners were both masked to which treatment was received throughout the follow-up period.

Procedure	Screening Exam Pts. ≥ 18 yrs. presenting w red eye	Follow-up Exams Randomized Pts. at 1-2, 4-5, 7, 14, 21 days
Written Informed Consent	X	n/a
Examiner-Administered Symptom Survey	X	X
Medical and Ocular History	X	X
Snellen Visual Acuity (Pinhole if VA worse than 20/20)	X	X
Lymph Node Palpation	X	X
Slit Lamp Examination, Grading of Ocular Signs and Fluorescein Staining	X	X
Clinician Prediction of Pink Eye Etiology	X	n/a
AdenoPlus™ Testing and Photograph of Test Display	X	Continue RPS testing until 2 negative results
Swab for qPCR Analysis Inferior nasal conjunctiva	X	X
Randomization to artificial tears or 5% PVP-I (Betadine 5%)	Randomized treatment by unmasked examiner	n/a
Pt. receives artificial tears	X	X

Patient characteristics

- 48 patients with red eye were screened at 4 clinical sites. (35 at Washington University in St. Louis, 6 at University of Alabama-Birmingham, 4 at Illinois College of Optometry, and 3 at Northeastern State University).
- 71% female.
- Mean age: 40.6 ± 13.4 years.

Agreement between clinician-reported diagnoses and AdenoPlus™ test results

- Clinicians diagnosed Ad-Cs in 75% (36 of 48 eyes) and other causes in 25% (12 of 48 eyes).
- A positive AdenoPlus™ test result was obtained in 33% (16 of 48 eyes).

Table 2. Comparison of Ad-Cs diagnosis by clinicians and AdenoPlus™ result for 48 patients screened in RAPID.

Clinician Prediction of Conjunctivitis Etiology	AdenoPlus™ result		All
	AdenoPlus™ Positive	AdenoPlus™ Negative	
	N	N	N
Probably/Definitely Ad-Cs	14	22	36
Not Ad-Cs	2	10	12
All	16	32	48

- Agreement of Clinician and AdenoPlus™ is 50% (24 of 48) unadjusted for chance agreement.
- Agreement of Clinician and AdenoPlus™ is 0.14 (kappa) adjusted for chance agreement.
- Sensitivity = 88% (14 Ad-Cs diagnoses by clinicians were among 16 AdenoPlus-positive eyes).
- False positive rate = 69% (22 Ad-Cs diagnoses by clinicians were among 32 AdenoPlus-negative eyes).
- Clinicians diagnosed bacterial co-infection in 14 of the 48 eyes (29%).
- 14 (29%) of the 48 patients met eligibility criteria and were randomized. All but 2 of 14 patients completed follow-up to 21 days.

Results

Figure 1. Patient-reported symptoms (median values shown) for 16 patients with AdenoPlus-positive tests and 36 patients diagnosed as Ad-Cs by clinicians. On scale 0 = not at all bothersome and 10 = very bothersome.

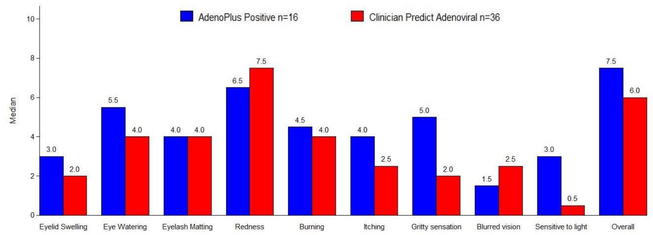
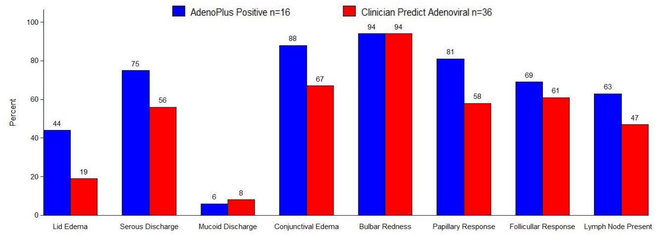


Figure 2. Clinician-graded signs (on slit lamp examination) for 16 patients with AdenoPlus-positive tests and 36 patients diagnosed as Ad-Cs by clinicians. On scale 1 = absent, 5 = severe, data shown reflects those graded 3 or greater.



Conclusions

- Our results indicate that patients with a positive AdenoPlus™ test were likely (88% sensitivity) to have been clinically diagnosed as having an Ad-Cs etiology for their red eye.
- However, a high proportion of patients that were clinically diagnosed with Ad-Cs had a negative AdenoPlus™ test (69% false positive rate). No single clinical sign or symptom was found to significantly distinguish the two patient groups, those with AdenoPlus-positive test results versus those with clinical diagnoses of Ad-Cs.
- Using a positive AdenoPlus™ test criteria as the gold-standard criteria, the false positive rate among clinicians was 69%. If 69% of the patients enrolled in a therapeutic trial were misdiagnosed, a new therapy that was 80% effective would appear to be less than 40% effective. In other words, a valid treatment could potentially be mistakenly found to be non-effective.
- This work further highlights the challenges associated with the identification of the correct etiology for conjunctivitis. Accurate diagnosis of Ad-Cs is essential for clinical trials of potential treatments for this condition.

References

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Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT02472223