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

Mary K Migneco, OD FAAO,1 Mae Gordon, PhD,2 Andrew Hartwick, OD PhD FAAO,3 Julie Huecker, MS4, Spencer Johnson, OD FAAO,5 Jennifer Harthan, OD FAAO,6 Christina Morettin OD FAAO,6 Ellen Shorter, OD FAAO,7 Tammy Than, MS OD FAAO1

1Washington University, St. Louis, 2Ohio State University, 3Northeastern State University, 4Illinois College of Optometry, 5Illinois Eye and Ear Infirmary, 6University of Alabama, Birmingham

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. Conjunctivitis can be caused by bacteria, viruses, allergens and toxic exposure, which makes the diagnosis of Ad-Cs especially challenging. Chung reported that 42% of patients presenting with classic, unilateral conjunctivitis were misdiagnosed as Ad-Cs using viral culture.

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 90% successful will appear to be only 56% successful if 50% of the patients in the trial are misdiagnosed as having Ad-Cs.

AdenoPlus™ (RPS, Sarasota, FL), the first CLA 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 95%.

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 (Povidine-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 in 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 cause 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.

Results

Table 1. Procedures completed at the baseline and follow-up visits. Procedures in unshaded boxes are performed on all patients enrolled in the study. Procedures 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.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Written informed consent</th>
<th>X</th>
<th>AdenoPlus™ test</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examined-Administered Symptom survey</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical and Ocular History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snellen Visual Acuity</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiletta Exam, Grading of Ocular Signs and Fluorescein Staining</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph Node Palpation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular Temperature</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiletta Exam, Grading of Ocular Signs and Fluorescein Staining</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AdenoPlus™ Test and Photograph of Test Drips</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swab for qPCR Analysis Internal Conjunctiva</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization to artificial tears or 5% PVP (Betadine 5%)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt receives artificial tears</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>AdenoPlus™ result</th>
<th>AdenoPlus™ Positive</th>
<th>AdenoPlus™ Negative</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician Prediction of Conjunctivitis Etiology</td>
<td>Probable/Definitely Ad-Cs</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Protoclinician</td>
<td>Not Ad-Cs</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>All</td>
<td>Probable/Definitely Ad-Cs</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Not Ad-Cs</td>
<td>10</td>
<td>13</td>
<td>23</td>
</tr>
</tbody>
</table>

- Agreement of Clinician and AdenoPlus™ is 50% (24 of 48) undecided for chance agreement.
- Agreement of Clinician and AdenoPlus™ is 0.14 (rappap) 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.

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 conjunctivitis.
- 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 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%. 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. 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


Support

The Reducing Adenoviral Patient-Infected Days (RAPID) Study is funded by National Eye Institute (R01EY0263-3/4). This work was also supported by National Eye Institute Center Core Grant (P30EY007003) and an unrestricted grant to the Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness. Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT01713120.