

An Assessment of the AdenoPlus Point-of-Care Test for Diagnosing Adenoviral Conjunctivitis and Its Effect on Antibiotic Stewardship

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Abstract

Objective: To determine the sensitivity and specificity of the AdenoPlus test compared with real-time polymerase chain reaction (PCR) and to determine whether there was a reduction in antibiotic prescriptions with the use of AdenoPlus compared with the previous year.

Patients and Methods: A total of 125 patients with suspected infectious conjunctivitis were accrued from June 4, 2015, through September 27, 2015. Forty-six participants from the prospective cohort completed both AdenoPlus and PCR testing. Two hundred fifty age-matched individuals were in the retrospective cohort.

Results: There was a significant reduction in the percentage of patients who received an antibiotic ophthalmic prescription in the prospective cohort vs the retrospective cohort (32% vs 45%; $\chi^2 P=.01$). AdenoPlus test sensitivity was 50% (5 of 10) and specificity was 92% (33 of 36) compared with real-time PCR testing.

Conclusion: The AdenoPlus test has high specificity for diagnosing adenoviral conjunctivitis but lower sensitivity than has been previously published. These data suggest that negative AdenoPlus results should be confirmed by real-time PCR owing to the low overall sensitivity of AdenoPlus observed.

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Adenovirus is the most common cause of viral conjunctivitis and should be considered in the evaluation of acute eye infections.¹ Up to 70% of cases of acute conjunctivitis are viral, and the number of individuals affected by viral conjunctivitis is estimated to be as high as 15 to 20 million per year in the United States.^{2,3} Patients with conjunctivitis represent a large resource requirement for primary care, urgent care, emergency departments, and walk-in clinics across the United States. According to the American Academy of Ophthalmology's Choosing Wisely (2013) initiative, health care providers are advised against prescribing antibiotic ophthalmic medications for the treatment of adenoviral conjunctivitis.⁴

Unfortunately, adenoviral conjunctivitis is difficult to distinguish clinically from bacterial

conjunctivitis. Adenoviral conjunctivitis may result after systemic illness or may be the sole manifestation, with symptoms lasting 2 weeks or longer.⁵ Currently, the standard of care continues to be antibiotics, regardless of the causative agent.⁶ Establishing an accurate diagnosis of viral conjunctivitis is important to reduce the number of inappropriate ophthalmic antibiotic prescriptions. This may lower overall health care costs and decrease the development of antibiotic resistance and exposure of patients to drug-related topical allergies and toxicity.⁶

Few research studies have examined whether using a point-of-care (POC) test to distinguish between viral and bacterial etiologies could be useful in decreasing the number of antibiotics prescribed. A rapid and accurate test could identify patients with

adenoviral infection, thereby allowing for proper decisions regarding management and restriction from work, school, or day care.

Real-time polymerase chain reaction (PCR) is a sensitive and specific means of detecting adenovirus, but it can be costly and may take up to 24 hours for results to be reported. Although real-time PCR is often considered the criterion standard for the detection of adenovirus, it does not allow for rapid decisions to be made regarding patient management. Recently, the AdenoPlus assay (Rapid Pathogen Screening Inc) was developed as a single-use, POC test for the rapid (10-minute) diagnosis of adenoviral conjunctivitis. AdenoPlus is an antigen-based immunoassay that uses direct sampling microfiltration technology and reportedly detects all known serotypes of adenovirus.² Furthermore, AdenoPlus is a Clinical Laboratory Improvement Amendments—waived test, allowing for health care providers to perform testing at the POC. In a previously published study, the sensitivity and specificity of AdenoPlus were reported to be 85% and 98%, respectively, compared with PCR.² However, another study found the sensitivity to be only 39.5%, with specificity of 95.5%.⁷

In an article by O'Brien et al,⁸ the authors suggest that rapid POC testing for adenoviral conjunctivitis may (1) reduce the number of misdiagnoses, (2) lead to better treatment and management, (3) provide a clinical answer to the patient before he or she leaves the office, (4) give appropriate work/school restrictions, (5) avoid unnecessary antibiotic ophthalmic treatments, (6) quarantine patients before they contaminate health care offices, and (7) reduce health care costs by reducing overtreatment and overpayment for unnecessary antibiotic ophthalmic drops.

In this study, we performed a prospective evaluation of the AdenoPlus test to assess its clinical sensitivity and specificity. A retrospective, age-matched, case-controlled analysis was completed to determine the impact of its implementation on the number of antibiotic ophthalmic prescriptions.

PATIENTS AND METHODS

Institutional review board approval was obtained from Mayo Clinic in Rochester, Minnesota, for enrollment of patients into the

study. It was determined that verbal informed consent for patients aged 18 years and older and assent from minors was adequate for this study because it was considered to be low risk and the AdenoPlus assay was used as intended. Health care providers, specifically nurse practitioners, involved in the study were trained and evaluated for competency by the manufacturer of the AdenoPlus test, and each provider completed research and patient safety training.

In the prospective arm of this study, which was conducted from June 4, 2015, through September 27, 2015, patients presenting with evidence of acute infectious conjunctivitis were read a consent/assent form and signed a Health Insurance Portability and Accountability Act (HIPAA) authorization form. Enrollees (n=134) meeting the inclusion criteria outlined later herein were then tested using the AdenoPlus test according to the manufacturer's instructions. Nine patients were excluded from the analysis because they met 1 or more of the exclusion criteria. Patient data, including age, sex, and symptoms, were recorded. For 46 patients (all ≥ 18 years old), a second swab was collected for routine adenovirus real-time PCR testing, which was performed in a blinded manner as previously published.⁹

In the retrospective portion of this study, a database of patients who had provided previous research consent was reviewed to identify individuals who (1) had visited a Mayo Clinic Express Care site in 2014 (an attempt was made to match the months of patients in the prospective study), (2) were diagnosed as having infectious conjunctivitis, and (3) were age matched (within 3 years) with participants from the prospective study. Whether they were prescribed an antibiotic was determined by an electronic data pull using all possible generic and brand names of ophthalmic antibiotics that are routinely prescribed for conjunctivitis. This process was also verified by individual medical record review.

Procedure and Outline

A procedural manual with the study algorithm was provided to each health care provider to ensure assent/consent, HIPAA, and study protocol adherence. Each patient was assigned a

subject number that allowed for patient anonymity.

Step 1. For those who presented with conjunctivitis symptoms and who did not meet the exclusion criteria, the provider obtained a thorough history and performed an examination.

Step 2. If the provider considered the etiology of conjunctivitis to be infectious, the patient was asked whether he or she was interested in participating in the study via oral assent/consent methods and was given a HIPAA consent form to read. The study was discussed with the patient and, if needed, family members, and the patient or parent/legal guardian signed the consent form if the individual agreed to participate. A consent process checklist was completed, and oral consent/assent scripts for AdenoPlus swab and AdenoPlus and PCR swab for adults were presented by the health care provider to ensure that patient consent was documented.

Step 3. The masked provider performed a POC test on the participant using the AdenoPlus assay. A sterile, separately packaged AdenoPlus collector was first used to obtain the specimen. The lower conjunctiva was exposed by retracting the lower eyelid. The lower conjunctiva was then gently sampled in a “dab-and-drag” motion in 6 to 8 locations as recommended by the manufacturer. The collector was placed into the test cassette, and an external absorber was immersed into the provided buffer vial for at least 20 seconds. The cartridge was then placed horizontally on a flat surface.

After 10 minutes, if the test result was positive (as indicated by the presence of 2 lines, a red test line and a blue control line), a diagnosis of viral conjunctivitis was made and the patient was managed and educated accordingly. If the test result was negative (a single blue control line present), a bacterial, allergic, alternative viral, or chemical irritant etiology was considered and the patient again was managed and educated accordingly. If the blue control line was not present, the test was considered invalid, although this was not observed during the study.

Step 4. A second swab of the conjunctiva was obtained from 46 adult patients (aged ≥ 18 years) for routine real-time PCR analysis. The PCR sampling was obtained in a similar dab-and-drag motion across the lower conjunctiva. The provided PCR label was completed by the health care provider, placed in the provided and appropriately labeled biohazard bag, and placed in the available bin for general service to transport to the clinical virology laboratory.

Step 5. The providers used a visit form data collection worksheet to document patient symptoms, type of swabs obtained (AdenoPlus or AdenoPlus and PCR), AdenoPlus test results, and whether an antibiotic was prescribed. The visit form was initialed by the health care provider.

Step 6. Prospective data were compiled at the end of each month and periodically each week as data were received by the research coordinators and laboratory specialist and were entered into a spreadsheet.

Setting

The study was performed at Mayo Clinic Express Care clinics in Rochester, Minnesota, which serve patients aged 18 months through 75 years.

Participants

One hundred twenty-five prospective patients and 250 retrospective patients were included in the study according to the following inclusion and exclusion criteria.

The inclusion criteria for enrollment in the prospective study were 18 months or older to be tested by the AdenoPlus assay, 18 years and older to be tested by the AdenoPlus assay and real-time PCR, and symptoms consistent with acute infectious conjunctivitis. The exclusion criteria for enrollment in the prospective study were previous failure of topical antibiotic therapy, evidence of periorbital cellulitis, unable to tolerate an ophthalmoscopic examination, severe foreign body sensation that prevented the patient from keeping the eye open, severe headache with nausea, severe photophobia, corneal opacity, ciliary flush, fixed pupil, decreased visual acuity, long-term use of

nonantibiotic prescription drops for chronic eye issues, recent history of eye trauma, any chemical irritation exposure, moderate to severe eye pain, and allergic conjunctivitis.

The inclusion criteria for enrollment in the retrospective study were 18 months and older, previously signed research authorization form allowing for medical record search, treated for acute infectious conjunctivitis in the correlating months as the prospective cohort, and treated for acute infectious conjunctivitis in the subsequent months as the prospective cohort as needed to achieve an age-matched status. The exclusion criteria for enrollment in the retrospective study were treatment for conjunctivitis and no signed research authorization allowing for medical record search and treatment for conjunctivitis that was determined to be caused by a noninfectious etiology.

RESULTS

One hundred thirty-four patients with suspected infectious conjunctivitis were enrolled from June 4, 2015, through September 27, 2015. However, 9 patients were excluded from the analysis because they met 1 or more of the exclusion criteria. Of the 125 patients accrued, 51 (41%) were male and 74 (59%) were female, with a mean age of 29 years (range, 2-65 years). In addition to testing by AdenoPlus, real-time PCR was also performed on specimens from 46 adult patients.

There was a significant reduction in the percentage of patients who received an antibiotic ophthalmic prescription in the prospective cohort vs the retrospective cohort (40 of 125 or 32% vs 113 of 250 or 45%; $\chi^2 P=.01$).

Compared directly with the results of real-time PCR, AdenoPlus showed sensitivity of 50% (95% CI, 18.7%-81.3%) and specificity of 91.7% (95% CI, 77.5%-98.3%). The negative predictive value was 87% (95% CI,

80%-92%), and the positive predictive value was 63% (95% CI, 28%-88%) (Table).

DISCUSSION

With implementation of the AdenoPlus test, we observed a significant ($P=.01$) reduction in the number of antibiotic ophthalmic drops used to treat infectious conjunctivitis compared with the retrospective cohort. It was determined that the AdenoPlus results showed moderate agreement ($\kappa=0.45$; 95% CI, 0.07-0.73) compared with the results of the PCR test. The results of this study indicate that the AdenoPlus assay has high specificity (92%) for the diagnosis of adenoviral conjunctivitis but only moderate sensitivity (50%).

Interestingly, the present reported sensitivity result falls between those previously reported by Sambursky et al² (85%) and Kam et al⁷ (39.5%). A potential cause of the lower sensitivity observed in the present study could be that there were multiple providers ($n=15$) obtaining the swabs rather than a single provider. Therefore, it is possible that variation in the swabbing procedure between providers accounted for some of the differences in test performance. Having a single provider oversee all sampling may have improved the sensitivity of AdenoPlus, but this would not reflect routine clinical practice.

A limitation of this study is that the number of patients who received both the AdenoPlus and the PCR swab was relatively small ($n=46$), primarily because we limited the additional PCR swab to only those older than 18 years. In the study by Sambursky et al,² providers tested patients in a combination of 8 private ophthalmology practices and an academic center and included pediatric patients. Their sample consisted of patients aged 5 to 90 years.² Although it is not mentioned what percentage of the samples were collected from pediatric patients, this may account for

TABLE. Comparison of AdenoPlus Rapid Point-of-Care Assay With Real-time Polymerase Chain Reaction (PCR) for the Diagnosis of Adenoviral Conjunctivitis

	Samples with the indicated result by real-time PCR (No.)		Specificity (% [95% CI])	Sensitivity (% [95% CI])
	Positive	Negative		
Samples with the indicated result by AdenoPlus (No.)				
Positive	5	3	91.7 (77.5-98.3)	—
Negative	5	33	—	50 (18.7-81.3)

the higher sensitivity. Similar to the present study, Kam et al⁷ excluded pediatric patients and included only those older than 16 years (mean age of 40 years) when calculating sensitivity and specificity data.

Currently, in most practice settings, patients presenting with acute conjunctivitis are prescribed an antibiotic, despite the ineffectiveness of antibiotics for viral conjunctivitis. Interestingly, in this study, when the AdenoPlus test result was negative, an antibiotic, in many cases, was still not prescribed. Although this study did not make it abundantly clear what factor or factors may have been responsible for the significant reduction in antibiotic prescriptions, a variety of possibilities exist. One reason may have been that the providers were very aware that they were part of a study and were likely more cognizant of how they were providing care and treating patients. Simply being part of the study may have contributed to a reduction in antibiotic use. This knowledge—coupled with the fact that providers already knew that most conjunctivitis (regardless of viral or bacterial etiology) is self-limiting—may have led to increased discussion between provider and patient regarding the prevalence of viral conjunctivitis. This increased dialogue could have played a role in decreasing antibiotic use.

Using antibiotics for viral conjunctivitis contributes to antimicrobial resistance, which is placing a significant burden on the health care system in the United States and around the world. By implementing a rapid POC test, health care providers may be better informed and able to engage in a discussion with their patients about the appropriateness of antibiotics. With the global health crisis caused by inappropriate antibiotic use, this is one step that can be made to reduce the development of resistant organisms. The use of rapid POC tests may also reduce potential morbidities associated with conjunctivitis and decrease potential adverse effects (eg, pain, swelling, allergic reactions) associated with taking unnecessary antimicrobial agents.¹⁰

The average cost for topical conjunctivitis treatment is \$12 to \$60 for generic drops and ointments, but newer brand-name drugs can cost more than \$130.¹⁰ Another important financial impact for patients with conjunctivitis is that work, school, and day care may require

individuals to stay home for at least 24 hours and often require antibiotics to be taken before returning. Despite the use of antibiotics, patients with viral conjunctivitis may continue to be contagious. Therefore, antibiotic agents may give a false sense of security that patients are no longer contagious and are ready to return to work or school. Implementation of rapid POC tests, such as AdenoPlus, may improve patient education, which is crucial in reducing the spread of viral conjunctivitis. By reducing the number of antibiotic ophthalmic prescriptions, this may decrease health care costs and the development of antibiotic resistance.

The results of this study are comparable with previously published data from O'Brien et al⁸ in that use of the AdenoPlus test (1) led to a decrease in the number of antibiotic ophthalmic drop prescriptions, (2) provided a clinical answer to patients who had positive test results, (3) provided appropriate work/school restrictions, and (4) reduced health care costs by decreasing unnecessary ophthalmic antibiotic use.

CONCLUSION

The AdenoPlus POC test provided a rapid (10-minute) result with high specificity. However, the present data suggest that negative AdenoPlus results should be confirmed by real-time PCR owing to the low overall sensitivity (50%) observed for AdenoPlus. Future studies are needed to further examine the performance of this assay using a larger number of patients and including pediatric patients, and for a longer duration, if possible. These results emphasize the importance of performing independent assessments on POC tests before considering their routine implementation in clinical practice.

Abbreviations and Acronyms: HIPAA = Health Insurance Portability and Accountability Act; POC = point-of-care; PCR = polymerase chain reaction

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