Sensitivity and Specificity of the AdenoPlus Test for Diagnosing Adenoviral Conjunctivitis

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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

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ADENOVIRUSES LEAD TO A broad spectrum of clinical diseases affecting mainly the respiratory, ocular, and gastrointestinal systems. Adenoviral conjunctivitis is the most common viral cause of conjunctivitis and is associated with significant ocular morbidity and health care costs.[1]

Approximately 20% to 70% of infectious conjunctivitis is thought to be of viral etiology[2-9] and between 65% and 90% is caused by adenovirus.[9-11] Furthermore, herpes simplex virus may cause epidemic keratoconjunctivitis that is indistinguishable from that of adenovirus.[9,11,12] Clinical studies have shown that herpes simplex virus may present as conjunctivitis without associated skin lesions in 1% to 5% of all cases of presumed viral conjunctivitis.[9,11,12] It is especially more common in unilateral cases of conjunctivitis.[12]

Adenovirus has 55 known serotypes.[13] Approximately one-third of all serotypes cause conjunctivitis,[14] but it is most commonly caused by serotypes 3, 4, 7, 8, 19, and 37.[15] Adenovirus is also known to cause 1 of 4 clinical ocular syndromes: nonspecific follicular conjunctivitis, pharyngeal conjunctival fever, acute hemorrhagic conjunctivitis, and epidemic keratoconjunctivitis.[16] Nonspecific follicular conjunctivitis is caused by serotypes 1 through 11 and 19; pharyngeal conjunctival fever is caused mainly by adenovirus serotypes 3, 4, and 7; acute hemorrhagic conjunctivitis is caused primarily

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Table 1. Study Population Characteristics

Characteristic	No.							
	SJC	CEE	SSEC	NEI	WEI	MSEC	W/N	OCLI
Youngest age of subject enrolled, y	41	23	19	12	22	5	27	7
Oldest age of subject enrolled, y	45	84	62	78	68	90	65	82
Male	1	4	4	2	10	23	4	4
Female	2	8	3	7	15	27	7	7
White	3	5	7	8	9	41	6	7
Black	0	1	0	0	15	3	1	3
Asian	0	0	0	0	0	0	1	0
Hispanic	0	6	0	1	0	6	1	0
Other	0	0	0	0	1	0	2	1
Mean duration of symptoms, d	3.7	3.1	3.7	3.3	3.5	3.3	2.8	3.2

Abbreviations: CEE, Center for Excellence in Eyecare; MSEC, Manatee Sarasota Eye Clinic; NEI, Northeastern Eye Clinic; OCLI, Ocular Consultants of Long Island; SJC, St Johns Clinic; SSEC, South Shore Eye Center; WEI, Wills Eye Institute; W/N, Weill Cornell Medical College/New York-Presbyterian Hospital.

by adenovirus serotype 11; and the more severe epidemic keratoconjunctivitis form is caused by serotypes 8, 19, and 37.[10,16]

Acute conjunctivitis is primarily a clinical diagnosis. Adenoviral conjunctivitis is often difficult to clinically distinguish from bacterial conjunctivitis,[17] especially early in the course of disease,[18] in unilateral cases[18] or in children with severe periorbital inflammation that mimics orbital cellulitis.[19] Numerous studies have demonstrated a clinical diagnostic accuracy of only 40% to 72% compared with laboratory analysis.[3,4,17,18,20-22] Viral cell culture (CC) with confirmatory immunofluorescence assay (IFA) is rarely performed owing to the delay in obtaining results.[23,24] Polymerase chain reaction (PCR) is becoming more commonly used for detecting adenovirus in tear fluid but requires expensive equipment.[14]

In 2006, the RPS Adeno Detector (RPS AD1; Rapid Pathogen Screening Inc) was both US Food and Drug Administration cleared and Clinical Laboratory Improvement Amendment waived as the first point-of-care test available for detecting adenoviral conjunctivitis.[6] It is an antigen-based immunoassay that uses direct-sampling microfiltration assay technology to enhance sensitivity.

A second generation of the RPS AD1 device, called AdenoPlus (RPS ADP; Rapid Pathogen Screening Inc), was recently Food and Drug Administration cleared. AdenoPlus was developed with modifications to the sampling pad to enhance specimen collection and modifications to the test strip to enhance antigen-antibody interactions. A prospective, sequential, masked, multicenter clinical evaluation was performed to determine the clinical sensitivity and specificity of AdenoPlus at detecting the presence of adenovirus in tear fluid compared with CC-IFA and PCR.

METHODS

LABORATORY CELL CULTURE ANALYSIS

A culture analysis was first performed to demonstrate the ability of the device to detect all common adenoviral serotypes and the lack of cross reactivity to common ocular pathogens known to cause conjunctivitis. As part of an independent laboratory analysis, the Manatee Memorial Hospital Pathology Department tested 45 culture specimens with AdenoPlus. The human cultures tested included 18 adenoviral specimens procured from the American Type Culture Collection including the most common adenoviral serotypes (ie, 1, 3, 4, 5, 7, 8, 11, 14, 15, 31, 19, and 37)[10,16] known to cause conjunctivitis as well as 27 other viral and bacterial pathogens that are associated with conjunctivitis including herpes simplex virus, influenza, chlamydia, staphylococcal species, streptococcal species, moraxella species, and hemophilus species.

Each culture specimen was assigned a number from 1 through 45. Both the technician preparing the culture samples and the pathologist were masked to the nature of the specimens in the numbered samples. Five μL of each of the 45 culture specimens were pipetted onto the AdenoPlus sample collector's Dacron fleece. Per the test's standard instructions for use, the tests were then dipped into an activating buffer for 15 to 20 seconds and allowed to develop during 10 minutes. After the development time was completed, the test results were interpreted.

CLINICAL EVALUATION

First, institutional review board approval was obtained. Then, a prospective, sequential, masked, multicenter clinical trial was performed at a combination of 8 private ophthalmology practices and academic centers. The study enrolled 128 patients with a clinical diagnosis of acute viral conjunctivitis (**Table 1**).

Informed consent was obtained by an investigator. Participation from each subject was a 1-time event limited to their initial presentation and sampling. There were no additional follow-up visits. Patient data were collected and recorded on a case report form. The patients were then clinically evaluated and specimens were collected.

Patients who met the clinical enrollment criteria for a clinical diagnosis of viral conjunctivitis were considered for enrollment. The enrollment criteria included patients of within 7 days of developing a red eye; a history of spread of infection from 1 eye to the other or recent upper respiratory infection; the presence of follicles or a preauricular node; and symptoms of discharge, eyelash matting, itching, or foreign body sensation. Patients with a corneal ulcer, trauma, allergy to Dacron, or recent medication use were excluded.

After enrollment, 3 tear specimens were obtained. Each tear fluid sample was collected in a similar way. A drop of ocular

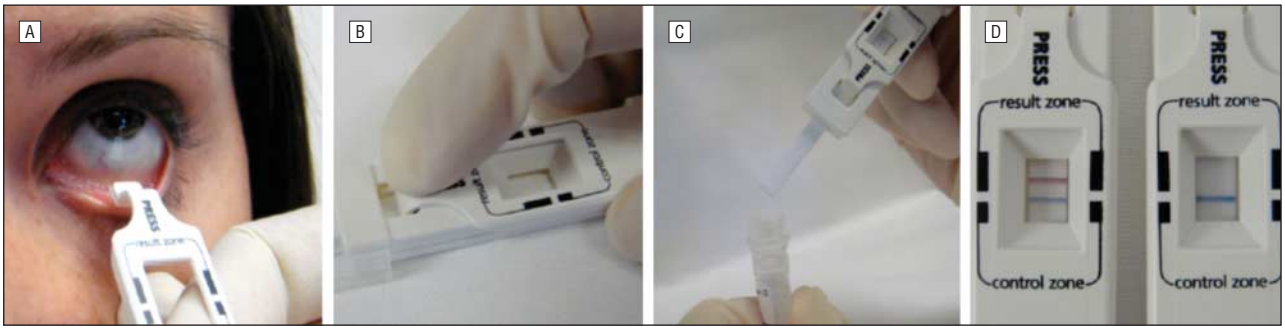

Figure. AdenoPlus steps. Sample collection (A), assembly of the test (B), activation of the test by dipping in buffer solution (C), and positive (1 red line and 1 blue line) and negative (1 blue line) test results.

anesthetic was applied to the affected eye 5 minutes prior to sampling. The inferior eyelid was gently retracted to expose the palpebral fornix conjunctiva. Using a dabbing and dragging motion for the AdenoPlus sample collector and a typical swabbing motion for the Dacron-tipped swabs, 3 tear samples were collected. The first sample was collected with the AdenoPlus sample collector and was followed by the samples for CC-IFA and PCR. Any patient with a positive CC-IFA or PCR result was considered as definitively having adenoviral conjunctivitis. If both the CC-IFA and PCR were negative, the patient's results were considered negative for adenoviral infection.

AdenoPlus SAMPLE

The separately packaged AdenoPlus sterile sample collector, with its Dacron-coated contoured tip, was used to directly obtain the first specimen. A gentle dabbing motion or dab and drag motion was performed 8 to 10 times in multiple locations across the conjunctiva and then the sample collector was allowed to maintain contact between the sampling fleece and the conjunctiva for an additional 3 seconds to saturate the sampling fleece. The sample collector was then assembled to the AdenoPlus test cassette so that the Dacron tip fit appropriately into the AdenoPlus test specimen zone to facilitate direct antigen transfer. The specialized external absorber portion of the test was then placed in 1 mL to 2 mL of a provided buffer solution for 20 seconds, removed, and allowed to sit for 10 minutes.

After 10 minutes, the AdenoPlus test results were analyzed by an independent, masked health care professional. This individual signed and dated a portion of the case report form verifying each AdenoPlus test result. A positive test result required the presence of 1 blue control line and 1 red result line; a negative test result revealed only 1 blue control line. The detectors were interpreted within 1 hour of testing (**Figure**).

SAMPLE FOR THE CELL CULTURE

In a similar fashion to the AdenoPlus sampling just described, the inferior-medial palpebral fornix conjunctiva was exposed by gently retracting the lower eyelid. Using a sterile Dacron swab (Copan Diagnostics), the second sample was collected by performing a gentle swirling motion along the inferior fornix. This sample was placed in 3 mL of multimicrobe medium (M4; Micro Test Inc) and kept refrigerated at below 50°F until it was sent directly to Thomas Jefferson University Hospital Clinical Laboratory (Philadelphia, Pennsylvania) for a combined adenoviral tissue culture with IFA of all negative cultures using standard laboratory techniques.[25] The cell cultures were examined every 2 to 3 days for growth during a 14-day period. If there was no growth during this period, the culture result was considered negative.

SAMPLE FOR PCR

In a similar fashion to the CC-IFA sampling just described, the inferior-medial palpebral fornix conjunctiva was exposed by gently retracting the lower eyelid. Using a sterile Dacron swab, the third sample was collected by performing a gentle swirling motion along the inferior fornix. Polymerase chain reaction specimens were placed into 1 mL of basic saline solution in a conical transport tube (Falcon Blue Max Jr; Becton, Dickinson, and Co) and kept refrigerated below 50°F until it was sent directly to ViraCor Laboratories (Lee's Summit, Missouri) for real-time PCR analysis using its specific specimen-handling methods.[6] All PCR samples were processed within 96 hours of sample collection.

RESULTS

LABORATORY CELL CULTURE ANALYSIS

When compared with 18 adenoviral specimens and 27 other viral and bacterial pathogens in laboratory cell culture analysis, AdenoPlus showed a sensitivity of 100% (18/18) and a specificity of 100% (27/27).

CLINICAL EVALUATION

The sensitivity and specificity percentages of AdenoPlus were identified by comparing them with CC-IFA and PCR results (**Table 2**).

The patients enrolled in the study ranged from 5 to 90 years of age and consisted of 76 females (59%) and 52 males (41%).

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), a specificity of 96% (93/97), a negative predictive value of 97%, a positive predictive value of 88%, and an overall agreement of 95%. When compared only with PCR, AdenoPlus showed a sensitivity of 85% (29/34), a specificity of 98% (89/91), a negative predictive value of 95%, a positive predictive value of 94%, and an overall agreement of 94%. When compared with PCR, CC-IFA showed a sensitivity of 85% (29/34), a specificity of 99% (90/91), a negative predictive value of 95%, a positive predictive value of 97%, and an overall agreement of 95% (Table 2).

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Table 2. Sensitivities and Specificities of the 3 Tests

Test	Reference Method	Subjects, No.	% (No./Total No.)				
			Sensitivity	Specificity	Overall Agreement	Predictive Value	
						Negative	Positive
AdenoPlus	CC-IFA	128	90 (28/31)	96 (93/97)	95 (121/128)	97 (93/96)	88 (28/32)
AdenoPlus	PCR	125	85 (29/34)	98 (89/91)	94 (118/125)	95 (89/94)	94 (29/31)
Cell culture	PCR	125	85 (29/34)	99 (90/91)	95 (119/125)	95 (90/95)	97 (29/30)

Abbreviations: CC-IFA, cell culture with confirmatory immunofluorescence assay; PCR, polymerase chain reaction.

COMMENT

AdenoPlus uses direct-sampling microfiltration technology that allows antigen to be transferred directly to the immunoassay test strip without any pretreatment. This technology enhances sensitivity compared with other lateral flow technologies by concentrating antigen in its native form at the time of collection and eliminates any requirement for pretreatment or subsequent dilution and extraction steps.

AdenoPlus was performed first because this test uses direct sampling, which prohibits splitting a single sample between the reference methods. This inherent testing condition may artificially lead to reduced sensitivity of the gold standard, leading to an apparent false positive because the second and third samples collected, which are serving for the reference analysis, may not have access to the same amount of virus contained in the first swab. It is unlikely but theoretically possible that a 10-μL AdenoPlus sample could contain viral particles below the test's detection limit, leading to a false-negative result on the AdenoPlus test and simultaneously removing all viral elements from the tears; this could result in a negative test result on the reference method causing an artificial inflation of the AdenoPlus sensitivity.

Second, the shell vial technique has been shown to have sensitivities of 92% to 95% within 2 to 3 days when compared with a standard 4-week cell culture. Despite this, shell vial cell cultures in the trial were followed up for a total of 14 days. Because adenovirus is known to cause a positive culture result up to 3 to 4 weeks later,[24,26] it is possible that the extended shell vial culture technique could lead to a possible rare AdenoPlus false-positive result if enough time is not allowed for adequate culture growth. Despite these unique comparison limitations, AdenoPlus demonstrated substantial efficacy at detecting adenoviral conjunctivitis.

AdenoPlus detects the highly conserved viral hexon antigen from all 55 serotypes and from both infectious and noninfectious viruses. Cell culture requires collection, transport, growth, and detection of a single living virus. The process is time consuming and requires technical expertise. Polymerase chain reaction detects viral DNA from both infectious and noninfectious viruses, and it is a complex process requiring expensive equipment and technical expertise.

The original RPS Adeno Detector showed a limit of detection of approximately 60 ng/mL and a clinical sensitivity of 88% and specificity of 91% compared with CC-IFA.[6] The new AdenoPlus test has a limit of detection of approximately 6 ng/mL and demonstrates a clinical sensitivity of 90% and specificity of 96% compared with CC-IFA. Because the intensity of the positive result line is directly proportional to the amount of antigen present, a lower limit of detection leads to more intense lines at greater antigen concentrations. When both AdenoPlus and CC-IFA are compared with PCR, they have identical sensitivity and similar specificity. The enhanced performance of AdenoPlus stems from a combination of an enlarged sample collector fleece that is impregnated with a phenol red indicator to ensure adequate specimen collection and test strip modifications that facilitate stronger antibody-binding reactions with less nonspecific binding that leads to both greater sensitivity and specificity.

A rapid, point-of-care immunoassay for adenovirus provides numerous clinical benefits. The time delay in obtaining results of a traditional diagnostic test, such as CC-IFA or PCR, requires a patient to wait for their results in isolation or encourages the initiation of empirical therapies. Even in clinically more obvious cases that present at an advanced time course where the clinical examination is more diagnostically reliable, it is not possible to clinically determine infectivity. Studies demonstrate positive culture results could be obtained from 5% to 10% of the eyes of patients with adenoviral conjunctivitis at 14 to 16 days.[27,28] AdenoPlus detects the presence of viral particles and correlates with disease infectivity. Thus, a negative test result would suggest that less than 50 viral particles were present in the tear sample. Repeat testing of previously positive results from patients to determine when the virus is undetectable may facilitate a more timely and safe return to school or work, which can have positive economic and epidemiologic ramifications for schools or businesses where the disease tends to circulate among students or staff. Because adenovirus is extremely contagious and associated with close contact transmission rates of 10% to 50%, patients' results confirmed positive for adenoviral conjunctivitis require more time out of school, work, or daycare.[17]

Adenoviral conjunctivitis is also known to cause considerable morbidity. Once the cornea becomes involved and subepithelial infiltrates develop, it can be months or even years of poor vision and discomfort,[29-34] and it may necessitate the need for treatment with corticosteroids with all the attendant complications of chronic corticosteroid use. In other circumstances, pseudomembrane formation may lead to significant conjunctival scarring with loss of goblet cells and symblepharon formation,[35] and it may result

in persistent or permanent dry eyes[36] or tearing.[37] Although obtaining an accurate and rapid diagnosis does not reduce the infected individual's complication rate, reducing the overall spread of disease through patient education and isolation would limit the total number of infected patients, reducing the absolute number of complications.

Obtaining an accurate diagnosis during the patient's initial visit can reduce the number of unnecessary topical ophthalmic antibiotic prescriptions written, significantly reducing the number of toxic and allergic reactions, potential antibiotic resistance, and costs that occur with topical antibiotics. Udeh et al[1] demonstrated more than $400 million could be saved in the United States annually by accurately diagnosing patients with adenoviral conjunctivitis at the office visit.

In addition to the typical management strategy for adenoviral conjunctivitis, 2 novel treatments, topical povidone iodine and ganciclovir gel, have recently become more widely used. One study examining infected cells exposed to povidone iodine showed potent anti-adenoviral effects,[38] although it was not reproducible in a prospective clinical trial.[5] Ganciclovir ophthalmic gel was developed for the treatment of herpetic keratitis. However, results from a small, randomized, controlled, masked series of 18 patients with confirmed adenoviral conjunctivitis who were treated with ganciclovir had nearly 10 days shorter duration of disease than patients treated only with preservative-free artificial tears.[39,40] N-chlorotaurine also demonstrates clinical efficacy for the treatment of adenoviral conjunctivitis.[41] Additionally, Jeng et al[42] showed that the use of cyclosporine A eye drops may be useful in treating patients with subepithelial infiltrates after adenoviral keratoconjunctivitis. Prior to prescribing potentially effective novel therapeutics for the treatment of adenoviral conjunctivitis or its associated morbidities, diagnostic confirmation would be useful.

In conclusion, adenoviral conjunctivitis causes significant morbidity and economic burden. Because patients with conjunctivitis present to a wide variety of medical specialists, a rapid, in-office test that can be performed by a nurse, assistant, or clinician can prevent the misdiagnosis of adenoviral conjunctivitis that leads to the spread of disease, unnecessary antibiotic use, and increased health care costs. AdenoPlus is a very sensitive and specific point-of-care diagnostic test to assist in the confirmation of adenoviral conjunctivitis and lead to the initiation of appropriate management of the disease in a timely manner.

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Ophthalmic Images

Anterior Polar Cataract: A Clinical-Pathologic Correlation

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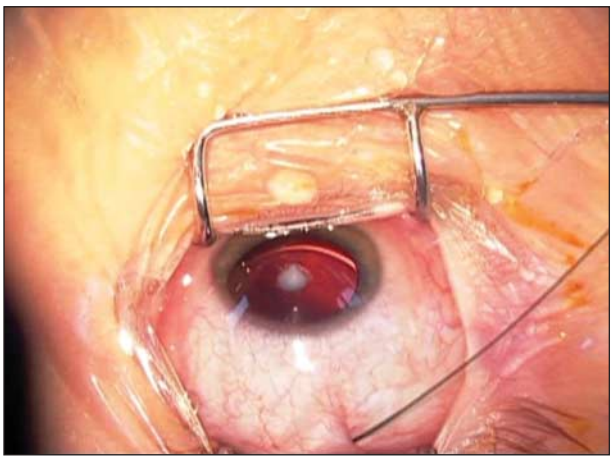

Figure 1. Intraoperative photograph of the right eye of a 6-year-old boy who was undergoing extraction of bilateral, congenital anterior polar cataracts. The photograph shows the anterior capsular plaque with a broad base attaching to the central lens capsule and extending into the anterior chamber without touching the cornea.

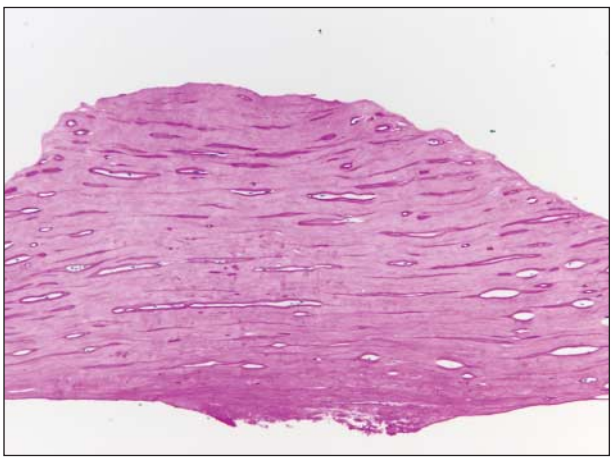

Figure 2. Light microscopy (periodic acid–Schiff, original magnification ×200) microphotograph revealing probable fibrous metaplasia of the lens epithelium.