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Diagnostic accuracy of clinical signs, symptoms and point-of-care testing for early adenoviral conjunctivitis

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Abstract

Clinical relevance: This study identifies key signs and symptoms of acute conjunctivitis, that when combined with a point-of-care test, can improve clinician accuracy of diagnosing adenoviral conjunctivitis.

Background: Adenoviral conjunctivitis is a common ocular infection with potential for high economic impact due to widespread outbreaks and subsequent furloughs from work and school. In this report, we describe clinical signs and participant-reported symptoms that most accurately identify polymerase chain reaction (PCR)-confirmed adenoviral conjunctivitis.

Methods: Adults with “red eye” symptoms of 4 days or less were enrolled. Participants rated 10 ocular symptoms from 0 (not bothersome) to 10 (very bothersome), and indicated presence or absence of systemic flu-like symptoms. Clinicians determined presence or absence of swollen lymph nodes and rated the severity of 8 ocular signs using a 5-point scale. An immunoassay targeting adenovirus antigen was utilized for the point-of-care test, and conjunctival swab samples were obtained for subsequent adenovirus detection by PCR analyses. Univariate and multivariate logistic regression models were used to identify symptoms and signs associated with PCR-confirmed adenoviral conjunctivitis. Diagnostic accuracy of these clinical findings, and the potential benefit of incorporating point-of-care test results, was assessed by calculating areas under the receiver operating characteristic curves (AUC).

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Results: Clinician-rated bulbar conjunctival redness, participant-rated eyelid swelling and overall ocular discomfort had the best predictive value in the multivariate logistic regression model with an AUC of 0.83. Addition of the point-of-care test results to these three clinical sign/symptom scores improved diagnostic accuracy, increasing the AUC to 0.94.

Conclusions: Conjunctival redness severity and participant-reported eyelid swelling and overall discomfort, along with adenoviral point-of-care test results, were highly predictive in identifying individuals with PCR-confirmed adenoviral conjunctivitis. Improved diagnostic accuracy by clinicians at the initial presenting visit could prevent unnecessary work furloughs and facilitate earlier treatment decisions.

Keywords

Adenoviral conjunctivitis; diagnosis; point-of-care test immunoassay; polymerase chain reaction

Introduction

Adenoviral conjunctivitis is a common ocular infection worldwide. It is associated with significant morbidity and reduced productivity due to work furloughs. Typical symptoms include ocular redness, discomfort, tearing, eyelid swelling, photophobia, and decreased vision. A population-based incidence study of eye related emergency department visits reported 2 million visits per year with 28% of these visits related to a diagnosis of acute or other types of conjunctivitis[1] Up to 26% to 59% of patients develop subepithelial corneal infiltrates following adenoviral conjunctivitis which can cause permanent corneal scarring and visual impairment.[2,3]

The diagnosis of adenoviral conjunctivitis remains challenging despite how common it is. A systematic review of more than 6,800 publications, Rietveld et al. was unable to find evidence of the clinical signs, symptoms or both that were useful for the differential diagnosis of bacterial from viral conjunctivitis.[4] In a study of 1,520 individuals with suspected adenoviral conjunctivitis at Johns Hopkins University, a surprisingly low percentage, only 8.6%, tested positive for adenovirus by polymerase chain reaction (PCR) testing.[5] In 2006, the FDA approved a CLIA-waived, point-of care test for acute conjunctivitis (previously named AdenoPlus® now renamed QuickVue Adenoviral conjunctivitis test, Quidel Corporation, San Diego CA). The point-of-care test provides a binary “yes” or “no’’ result for adenoviral antigen presence in 10 minutes. Sensitivity has been reported to range from 40 to 93% and specificity from 81 to 98%.[3,6-9]

This report describes clinical signs and participant-reported symptoms at presentation that most accurately identify PCR-confirmed adenoviral conjunctivitis and assesses whether the point-of-care test results can further improve diagnostic accuracy.

Methors

Study design

The Reducing Adenoviral Patient Infected Days (RAPID) study is a double-masked, pilot, randomized trial of the safety and efficacy of a single, in-office administration of

5% povidone iodine ophthalmic solution compared to artificial tears[10]. Participants were enrolled at nine clinical sites within the United States. This report is based on data collected from patients presenting with an acute "red eye" at the screening examination for enrollment in the randomized trial. Detailed methods, masking and efficacy results have been reported previously[9-11].

Institutional review board approval was obtained by each study site and the Coordinating Center at Washington University in St. Louis, MO. Study data were collected and managed using REDCap electronic data capture tools hosted at Washington University in St. Louis.[12,13] All study procedures were in compliance with the ethical standards of the Declaration of Helsinki and Good Clinical Practice guidelines, and this clinical trial is registered at https://clinicaltrials.gov/ct2/show/NCT03756753.

Study participants

All participants provided written informed consent and completed a screening examination which included case history, symptom survey, and clinical assessment. Eligible participants were ≥ 18 years of age with duration of "red eye" symptoms ≤ 4 days at presentation. Exclusion criteria included: history of thyroid disease, allergy to iodine or topical anesthetics, ocular surgery within the past 3 months, skin vesicles, corneal dendrites, conjunctival membrane or pseudomembrane, subepithelial corneal infiltrates, corneal ulceration, corneal abrasion, corneal foreign body, anterior chamber inflammation, or pregnancy/nursing. The first affected eye was selected as the study eye. If both eyes were concurrently symptomatic, the study eye was randomly selected.

Study protocol

The screening examination included a 10 item symptom survey. Participants were asked to rate ocular symptoms ("Currently, how bothered are you by each of the following symptoms in your eye?") using a scale of 0 (not bothersome) to 10 (very bothersome). Symptoms included: eye tearing or watering, eyelash matting or discharge, burning or stinging, itching, gritty or sandy sensation in the eye, eyelid swelling, redness, blurred vision, sensitivity to light and overall discomfort. Presence or absence of systemic flu-like symptoms, including coughing, fever, sore throat and runny nose, over the preceding 2 weeks were queried. Exposure to anyone with a "pink eye" in the past month were recorded.

Lymph node examination was performed and the presence or absence of pre-auricular, retro-auricular and submandibular swollen lymph nodes noted. Slit lamp examination was performed by a study clinician trained to use case report forms to grade clinical signs utilizing a scale from 0 to 4+ (0= absent, 1= very slight, 2= slight, 3=moderate, 4= severe) including: lid edema, eyelid matting/crusting, clear serous discharge, mucoid or purulent discharge, bulbar conjunctival edema, bulbar conjunctival redness, and conjunctival papillary and follicular responses. A standardized grading scale was used to grade bulbar redness and conjunctival papillary response.[14]

The QuickVue (Quidel Corporation, San Diego CA) point-of-care test for adenoviral conjunctivitis is an immunoassay that detects adenoviral hexon protein antigen. The test was administered to the palpebral conjunctiva of the eyes after topical anesthesia, using

a technique in accordance with the instructions of the manufacturer. After 5 minutes, conjunctival swab samples were collected and stored in a −80 degree Celsius freezer within four hours of collection. Samples were shipped on dry ice to the Coordinating Center in St. Louis, MO for DNA extraction and subsequent PCR analysis for molecular confirmation of adenovirus presence. Conjunctival samples were molecularly analyzed in batches throughout the study.

Statistical analysis

Participant demographic characteristics and the scores for the clinical signs and symptoms were analyzed using SAS (version 9.4, Cary, NC). Means and standard deviations were calculated for continuous variables, while percentages with and without each categorical variable was determined. Univariate logistic regression was used to assess the predictive value for each variable at screening in identifying PCR-confirmed adenoviral conjunctivitis. Based on probit analysis using SPSS Statistics software (IBM, Armonk NY), the lower limit of detection of adenoviral DNA for the PCR test, with a 95% confidence interval (CI), was determined to be 182 copies/mL.[9]

Two steps were used to select variables for the final multivariable logistic regression model. First, statistically significant variables in univariate logistic regression model were screened for inter-correlations. The participant-reported symptoms were highly inter-correlated and the most clinically relevant variables were selected. Second, a sparse variable selection method with minimax concave penalty (MCP) penalty was used to select variables for a parsimonious multivariate model in R statistical software (http://www.R-project.org/).

Analyses were repeated with the addition of the point-of-care test results (presence or absence of immunoassay-determined adenovirus antigen) to assess whether this factor significantly increased diagnostic accuracy, as measured as the area under the receiver operating characteristic curve. The area under a ROC curve (AUC) provides a measure of the accuracy of a qualitative diagnostic test by representing the relationship between test sensitivity and specificity. A test with no better accuracy than chance has an AUC of 0.5 whereas a test with perfect accuracy has an AUC of 1.0.

Results

Of the 212 screened participants, both point-of-care test and PCR test results were obtained for 186 participants. At the start of the study, conjunctival swabs samples were not collected for PCR analysis in individuals with a negative point-of-care test. The protocol was later amended to collect conjunctival swab samples on all participants. A negative point-of-care test result occurred in 70.0% of (130 of 186) tested eyes, with a positive result in the other 30.1% (56 of 186). Of the 130 participants who tested negative with the point-of-care test, the negative results were confirmed by PCR in 98.5% (128 of 130) of these participants.

Of the 56 participants who tested positive with the point-of-care test, 50% (28 of 56) did not have detectable viral titers as determined by PCR. One participant was missing baseline scores for clinical signs at screening and was excluded from this report. Table 1 reports participants' demographics by PCR status at presentation. Ninety-eight of the 185 (53%)

participants were female, 96 of the 185 (52%) participants were white, and the mean age at screening was 33.9 ± 15.4 years.

Univariate logistic regression odds ratios for participant-reported symptom scores and clinician-graded sign scores are presented in Table 2. All 10 of the self-reported ocular symptoms were significantly ($p < 0.05$) higher in the group with PCR-confirmed adenoviral conjunctivitis, compared to those without. Clinician-graded scores for lid edema, serous discharge, bulbar redness, and conjunctival follicular response were also significantly higher ($p < 0.05$) in the group with PCR-confirmed adenoviral conjunctivitis. A palpable swollen lymph node was present in 56.7% (17/30) participants with PCR-confirmed adenoviral conjunctivitis and in only 37.4% (58/155) of those without PCR-confirmed adenoviral conjunctivitis (Table 2).

Due to high inter-correlations among the 10 self-reported symptoms, clinicians selected 5 symptoms due to high clinical relevance for adenoviral conjunctivitis (tearing, matting, eyelid swelling, redness and overall discomfort). Univariate logistic regression analyses were also performed to evaluate predictive value point-of-care test results, presence of any swollen lymph node and reported recent flu-like systemic symptoms (Table 2 and Table 3) in identifying individuals with adenoviral conjunctivitis.

Twelve candidate variables were selected from univariate logistic regression analyses (5 selected participant-reported symptoms, 4 clinician-graded signs, presence of any swollen lymph node and report of recent systemic symptoms) for inclusion in the MCP sparse selection method to construct the final multivariate models, both with and without the addition of the point-of-care test result (Table 3). The variables selected in the final multivariate model without point-of-care test as having the best predictive accuracy were self-reported eyelid swelling, overall discomfort and clinician-graded bulbar redness. The AUC for the multivariate model with these three variables was 0.83. The addition of the point-of-care test result improved the diagnostic accuracy and increased the AUC to 0.94 (Figure 1).

Because the point-of-care test had very high univariate and multivariate odds ratios, additional analyses were performed to ensure there were no errors or violations in statistical assumptions. There were no outliers, missing values, high standard deviation or correlations identified with the point-of-care test. Additionally, the Hosmer-Lemeshow test, which was used to assess the goodness of fit for the univariate and multivariate logistic regression model with point-of-care test had p-values of 0.66 and 0.91, thereby validating the contribution of point-of-care test to the increased diagnostic accuracy determined by the model.

Discussion

Adenoviral conjunctivitis is highly contagious and its misdiagnosis could lead to widespread outbreaks within clinical settings, homes, schools and places of employment. The condition is often misdiagnosed due to the overlap of patient symptoms and clinical signs with other types of conjunctivitis. Accurate diagnosis of adenoviral conjunctivitis is important to guide

appropriate quarantine recommendations and avoid unnecessary furloughs from school or work.

The economic loss from the misdiagnosis of adenoviral conjunctivitis can have a high cost. Same day PCR testing of employees to confirm adenoviral infection in the previously mentioned study saved a university an estimated 3 million dollars over a seven year period.[5] However, the utilization of PCR testing is limited by cost, time delay in obtaining results and lack of wide spread availability. This report evaluated the accuracy of using clinical signs and symptoms at presentation in predicting the diagnosis of PCR-confirmed adenoviral conjunctivitis and determined whether incorporation of point-of-care test results improved diagnostic accuracy.

Multivariate logistic regression models identified a group of clinician-graded signs and participant-reported symptoms at presentation with an excellent AUC of 0.83 in differentiating between patients who were subsequently determined by PCR to have adenoviral conjunctivitis from those who did not. The best predictors were: (1) participant-reported eyelid swelling, (2) participant-reported overall ocular discomfort, and (3) clinician-graded bulbar conjunctival redness. The AUC improved to 0.94 with the addition of the point-of-care test result to the scores for these clinical signs and symptoms. The point-of-care test results alone had an AUC of 0.87, supporting a conclusion that a diagnostic decision of a clinician regarding adenoviral conjunctivitis can be bolstered by combining the binary results of the point-of-care test with the clinical assessment of a few signs and symptoms.

Although it is generally accepted in ophthalmic clinical literature that adenoviral conjunctivitis is highly associated with conjunctival follicular responses and palpable lymph nodes[15-20], this study found that there may be better clinical symptoms or signs for predicting whether conjunctivitis cases are due to adenoviral infection. Practitioners consistently and significantly overestimate the likelihood of disease (by 2 to 10 times), both before and after clinical testing.[21] Despite reporting a high clinical suspicion for adenoviral conjunctivitis (based on clinician surveys; data not shown) in a large proportion of these individuals presenting with an acute “red eye” in this study, the vast majority (156/186, 83.9%) of eyes were non-adenoviral in etiology based on PCR testing.

The percentage of non-adenoviral cases of conjunctivitis (confirmed by PCR) in patients presenting with an acute “red eye” in US and UK studies has ranged from as high as 91.4% (1390/1520)[5] to a low rate of 44.2% (50/113),[3] with other studies reporting 60.6% (66/109)[7] and 72.8% (91/125) rates.[6] The range of prevalence of adenoviral conjunctivitis across these studies demonstrate the potential value in using a point-of-care test and specific clinical signs/symptoms to appropriately triage patients with acute “red eye.”

There was high agreement between a negative point-of-care test and negative PCR test for adenovirus in this study. Of the 130 participants who tested negative with the point-of-care test, 98.5% were confirmed by PCR to not have an adenoviral infection. Thus, patients with a negative adenoviral point-of-care test result likely do not require the lengthy work furloughs that are often utilized for patients with true adenoviral conjunctivitis. As a

conservative approach, work furloughs can be recommended to patients who test positive on the adenoviral point-of-care test to minimize the risk of transmission of this highly contagious condition.

However, the present data indicates in this study population the adenoviral point-of-care test produced a high rate of positive results (50%). Based on the multivariate modeling described in this study, incorporating findings related to bulbar conjunctival redness, participant-reported lid edema and overall discomfort could supplement the point-of-care test findings and facilitate better clinical determination of whether a conjunctivitis case has an adenoviral etiology.

This report is among the largest prospective samples of patients presenting with acute “red eye” in the US. There was diverse regional representation with nine clinical sites including a military base. Strengths of this study included the incorporation of standardized clinical grading scales and scripted case report forms. Standardization for clinical assessment undoubtedly contributed to the high predictive accuracy (large value for AUC) of certain clinical signs and symptoms in identifying PCR-confirmed adenoviral conjunctivitis. Such standardization is often not attained in clinical practice, and thus the predictive value of the key signs and symptoms identified here may not be as robust in standard clinical practice as found in this study.

Another limitations is the lack of viral serotyping as it is known that certain serotypes cause more severe disease and high frequency of sequelae associated with adenoviral conjunctivitis.[19,22,23] In addition, the participants in this study all presented to an eye care specialist and this group may not be representative of the overall population of patients with acute “red eye”, as the many of these individuals choose to first visit their primary care provider.[23,24] Finally, only patients presenting with presumed conjunctivitis were screened. These patients met strict exclusion criteria to rule out other causes including obvious herpetic disease, corneal abrasion or ulceration. Thus, the clinical features of presenting patients in this study may not be generalizable to acute conjunctivitis patients presenting to a primary care setting.

Conclusion

Using multivariate modeling, clinician-graded ocular redness and participant-reported lid edema and overall discomfort were the three clinical findings that best differentiated PCR-confirmed adenoviral conjunctivitis from other causes of “red eye”. Combining the scores or these three clinical signs/symptoms with the results of an adenoviral point-of-care test further improved the predictive accuracy of correctly identifying adenoviral conjunctivitis. Improving diagnostic accuracy by clinicians for adenoviral conjunctivitis by incorporating both point-of-care test and clinical evaluation of key signs and symptoms could prevent unnecessary work furloughs and facilitate earlier treatment decisions.

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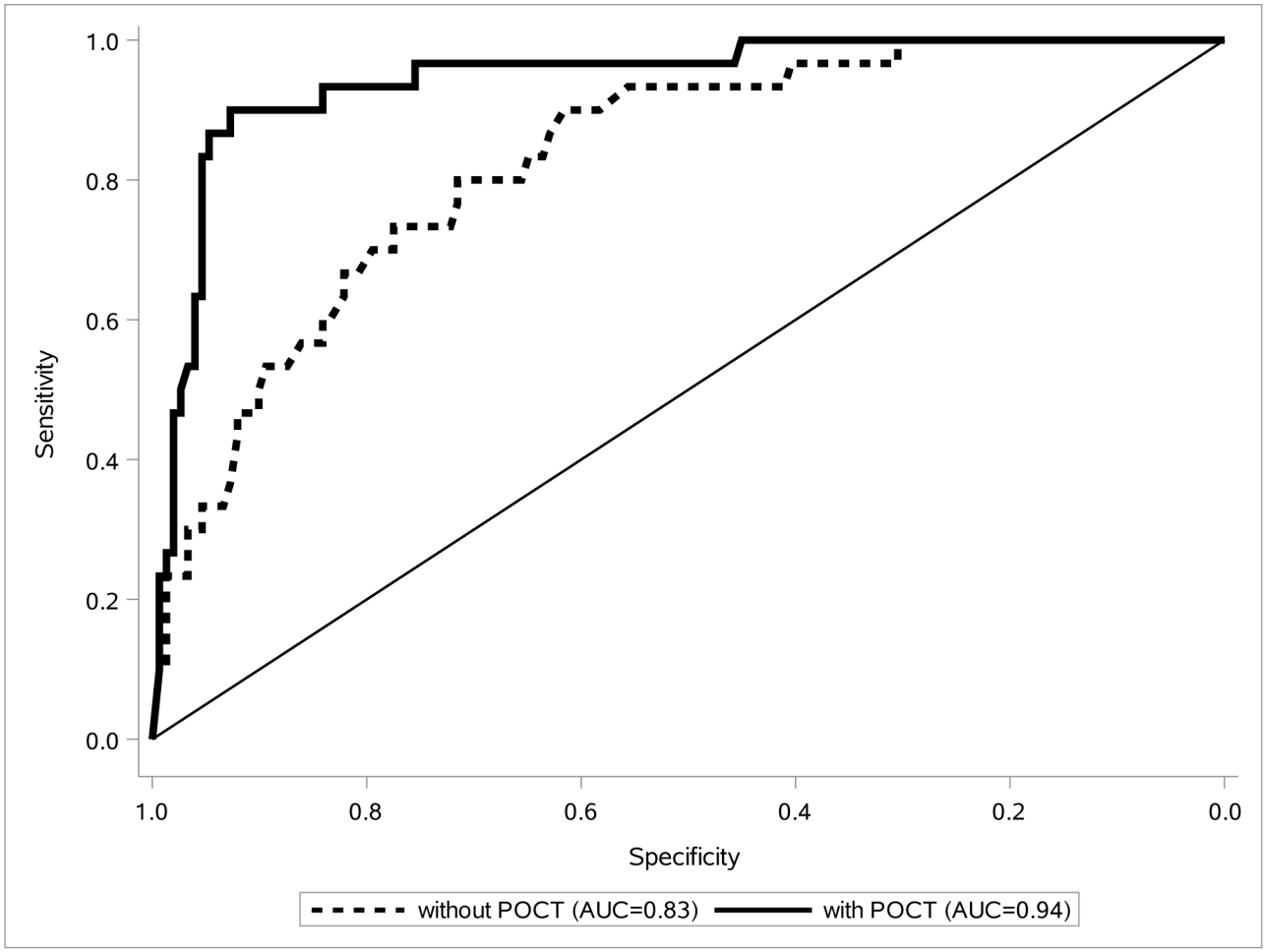

Figure 1.

Receiver operating characteristic (ROC) curves illustrating relationship between sensitivity and specificity for the variables identified by multivariate modeling to be effective predictors of adenoviral conjunctivitis. The area under the curve (AUC) utilizing scores for participant-reported eyelid swelling, overall discomfort and examiner graded bulbar redness is 0.83. The AUC improved to 0.94 with the addition of the point-of-care test results.

Specificity

without point-of-care test (AUC=0.83) With point-of-care test (AUC=0.94)

Table 1.

Demographic information based on PCR status for adenoviral conjunctivitis at the screening visit.

	PCR status			
	Negative N=155		Positive N=30	
	N	%	N	%
Sex				
Male	73	83.9	14	16.1
Female	82	83.7	16	16.3
Racial category				
White	86	89.6	10	10.4
Black or African American	29	72.5	11	27.5
All Others	40	81.6	9	18.4
	Mean	**SD**	**Mean**	**SD**
Age at screening	32.8	15.5	39.1	14.1

Table 2.

Univariate logistic regression results for candidate variables based on PCR status for adenoviral conjunctivitis at the screening visit.

	PCR status				Univariate P-value
	Negative N=155		Positive N=30		
	Mean	SD	Mean	SD	
Self-Reported Symptoms 0=Not at all Bothersome to 10=Very Bothersome					
Eye tearing or watering	4.6	3.1	6.9	2.5	0.0004
Matting or discharge	4.7	3.0	6.6	2.6	0.0021
Burning or stinging	3.7	3.1	5.2	3.1	0.015
Itching	3.9	3.1	5.3	3.1	0.019
Gritty or sandy sensation	3.5	3.3	6.2	3.1	0.0002
Eyelid swelling	3.3	3.1	6.5	3.3	<0.0001
Redness	6.9	2.6	8.9	1.4	0.0002
Blurred vision	3.3	3.1	5.0	3.5	0.011
Sensitivity to light	3.0	3.4	5.1	3.7	0.002
Overall discomfort	5.5	2.6	7.8	2.0	<0.0001
Slit Lamp Examination 0=Absent to 4.2 =Severe					
Lid edema	1.1	1.0	1.8	1.1	0.0006
Eyelid matting/crusting	0.9	0.9	1.2	1.0	0.088
Serous discharge	1.6	1.0	2.4	1.0	0.0001
Mucoid discharge	0.7	0.9	0.8	0.8	0.656
Bulbar edema	1.4	1.0	1.8	1.4	0.071
Bulbar redness	2.4	0.9	3.1	0.7	0.0006
Conjunctival follicular response	1.7	1.0	2.3	1.2	0.0019
Conjunctival papillary response	1.5	1.0	1.8	1.1	0.1498
	n	**%**	**n**	**%**	
Point-of-care-test positive for adenoviral conjunctivitis					
No (reference)	127	98.4	2	1.6	
Yes	28	50.0	28	50.0	<0.0001
Systemic flu-like symptoms					
No (reference)	53	75.7	17	24.3	
Yes	102	88.7	13	11.3	0.028
Exposure to someone with a ‘red eye’					
No (reference)	68	84.0	13	16.0	
Yes	87	83.7	17	16.3	0.993
Any palpable swollen lymph node present					
No (reference)	97	88.2	13	11.8	
Yes	58	77.3	17	22.7	0.046

Table 3.

Multivariate logistic regression results using participant-reported symptoms and clinician-graded signs without and with the addition of the adenoviral point-of-care test.

	Univariate		Multivariate without point-of-care test		Multivariate with point-of-care test	
	Odds Ratio	**P-value**	**Odds Ratio**	**P-value**	**Odds Ratio**	**P-value**
Self-Reported Symptoms 0=Not at all Bothersome to 10=Very Bothersome						
Eye tearing or watering	2.29	0.0004				
Matting or discharge	2.01	0.0021				
Eyelid swelling	2.74	< 0.0001	1.89	0.012	1.28	0.437
Redness	3.36	0.0002				
Overall discomfort	2.93	<0.0001	2.04	0.016	2.90	0.0036
Slit Lamp Examination 0=Absent to 4.2 =Severe						
Lid edema	1.99	0.0006				
Serous discharge	2.36	0.0001				
Bulbar redness	2.44	0.0006	2.23	0.004	1.75	0.130
Conjunctival follicular response	1.92	0.0019				
Other Clinical Findings						
Point-of-care-test	62.00	<..00001			61.13	<.00001
Any palpable swollen lymph node present	2.24	0.046				
Any recent systemic flu-like symptoms	0.41	0.028				