Efficacy of a Single Administration of 5% Povidone-Iodine in the Treatment of Adenoviral Conjunctivitis

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• PURPOSE: To evaluate the safety and efficacy of a single, in-office administration of 5% povidone-iodine (PVP-I) compared to artificial tears (AT) for adenoviral conjunctivitis (Ad-Cs).

• DESIGN: Double-masked pilot randomized trial.

• METHODS: Patients presenting with presumed adenoviral conjunctivitis were screened at 9 U.S. clinics. Inclusion criteria: ≥18 years of age, symptoms ≤4 days, and a positive AdenoPlus test. Exclusion criteria: thyroid disease, iodine allergy, recent ocular surgery, and ocular findings inconsistent with early-stage Ad-Cs. Randomization was to a single administration of 5% PVP-I or AT in 1 eye and examinations on days 1-2, 4, 7, 14, and 21 with conjunctival swabs taken at each visit for quantitative polymerase chain reaction. Primary outcome was percent reduction from peak viral load. Secondary outcomes were improvement in clinical signs and symptoms.

• RESULTS: Of 56 patients randomized, 28 had detectable viral titers at baseline. Day 4 posttreatment, viral titers in the 5% PVP-I and AT groups were 2.5% ± 2.7% and 14.4% ± 10.5% of peak, respectively ($P = .020$). Severity of participant-reported tearing, lid swelling, and redness as well as clinician-graded mucoid discharge, bulbar redness, and bulbar edema were lower in the 5% PVP-I group than AT group on day 4 ($P < .05$). After day 4, viral titers and severity of signs and symptoms decreased markedly in both groups and no differences between groups were detected.

• CONCLUSIONS: Pilot data suggest a single, in-office administration of 5% PVP-I could reduce viral load and hasten improvement of clinical signs and symptoms in patients with Ad-Cs. (Am J Ophthalmol 2021;231: 28–38. © 2021 Elsevier Inc. All rights reserved.)

HUMAN ADENOVIRUSES ARE ESTIMATED TO ACCOUNT for approximately 65%-90% of the viral conjunctivitis cases.[1] Adenoviral conjunctivitis (Ad-Cs) is typically associated with significant discomfort, tearing, discharge, lid swelling, and photophobia. More rarely, there can be permanent corneal scarring owing to inflammation. Ad-Cs is highly contagious, as the virus is resistant to standard disinfectants, including 70% isopropyl alcohol and 3% hydrogen peroxide, and can persist on fomites at room temperature for 5-7 weeks.[2] Secondary transmission of Ad-Cs to members of the same household is estimated to occur at a rate of 20%.[3,4] Outbreaks frequently occur in schools, military units, nursing homes, workplaces,[5,6] community,[7,8] and health care facilities.[3,9-14] Because of its epidemic potential, the reporting of Ad-Cs is mandatory in Germany and Japan, though voluntary in the United States.[15,16] An estimated $670 million is spent annually on the management of Ad-Cs.[17] A typical furlough from work for Ad-Cs is 1-2 weeks, which can cause a loss of 25%-50% in monthly earnings.[18] An intervention capable of reducing Ad-Cs transmission or duration of infection could have substantial clinical and economic impact.[3,19]

There is no U.S. Food and Drug Administration–approved treatment for Ad-Cs. In vitro testing has demonstrated virucidal activity of povidone-iodine (PVP-I) against adenovirus.[20,21] More than 2 decades ago, an article in *Ophthalmology Management* recommended that 5% PVP-I was a "good treatment for such external ocular infections as Ad-Cs."[22] This "off-label" use of 5% PVP-I as a treatment option for Ad-Cs has continued to gain credence, with its promotion in influential editorials and reviews that have wide distribution within the optometric and ophthalmologic communities.[23-25] The annual publication "Clinical Guide to Ophthalmic Drugs" states that "…a one-time

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application of povidone-iodine should be sufficient for alleviating the condition."[24] A 2013 survey of more than 600 eye care providers found that one-third used off-label 5% PVP-I as part of their management of Ad-Cs.[26]

Only a few clinical trials have investigated the efficacy of PVP-I alone for Ad-Cs; a greater number of trials have assessed PVP-I in combination with dexamethasone. A single-arm trial of 61 patients prescribed 2% PVP-I 4 times daily reported that all clinical signs showed statistically significant improvement by 1 week and 77% of the patients reported ocular comfort had returned to "normal."[19] In a double-masked 3-arm trial of 0.6% PVP-I alone, 0.6% PVP-I / 0.1% dexamethasone, and placebo, nearly 4 times as many participants treated with 0.6% PVP-I alone achieved viral eradication by day 3 than in the placebo group (32.0% vs 8.7%).[27] In a single-arm study of 0.4% PVP-I / 0.1% dexamethasone used 4 times daily for 5 days, 6 of 6 eyes with Ad-Cs confirmed by polymerase chain reaction (PCR) had marked reduction in viral titers by days 3, 4, or 5.[28] These studies suggest that PVP-I alone can be effective in reducing viral titers, symptom severity, and/or duration of symptoms.

Larger, double-masked, placebo-controlled randomized trials of fixed-combination PVP-I and dexamethasone have shown efficacy in reducing the severity and duration of Ad-Cs. Combination 0.4% PVP-I / 0.1% dexamethasone 4 times daily for 7 days reduced symptom duration from 12.2 days to 9.8 days ($P = .018$) compared to placebo among 72 patients with PCR-confirmed Ad-Cs.[29] Combination 1% PVP-I / 0.1% dexamethasone 4 times a day for 7 days reduced severity of clinical signs and symptoms as well as viral load in patients with quantitative PCR (qPCR)–confirmed Ad-Cs.[30] In a multicenter trial conducted in India, treatment with 0.6% PVP-I / 0.1% dexamethasone eradicated virus in 35.4% vs 8.7% in the placebo group by day 3, achieved a higher rate of clinical resolution (31.3% vs 10.9%), and reduced conjunctival discharge (54.2% vs 26.1%) and redness (33.3% vs 13.0%), respectively.[31] Taken together, these results suggest that PVP-I can be effective in reducing viral titers and symptom severity/duration. While promising, these trials also identified some recurring issues. Discomfort upon instillation of PVP-I/dexamethasone, which could reduce treatment adherence, was reported by 22% of the participants in 1 study[29] and 31.8% in another study.[27] The 4-times-a-day dosing for 5-7 days could also reduce treatment adherence. Thus, a 1-time, in-office administration of 5% PVP-I for Ad-Cs administered after topical anesthesia merits evaluation.

METHODS

• **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% PVP-I compared to artificial tears (AT) funded by a National Eye Institute R-34 planning grant. Institutional review board approval was obtained by each study site and the Coordinating Center at Washington University in St. Louis, Missouri, USA. Data were collected in compliance with HIPAA guidelines. All study procedures were in compliance with the ethical standards of the Declaration of Helsinki and Good Clinical practices and the study is registered at https://clinicaltrials.gov/ct2/show/NCT03756753.

Participants were enrolled at 9 U.S. clinics. Written informed consent was obtained from all screened participants. One eye of each participant was randomized to 5% ophthalmic PVP-I or preservative-free AT. Posttreatment examinations were on days 1-2, 4 (days 3-5), 7 (days 6-10), 14 (days 11-17), and 21 (days 18-21). The primary outcome was percent reduction from peak viral load. Secondary outcomes included improvement in clinician-graded clinical signs and participant-reported symptoms.

• **STUDY PARTICIPANTS:** Inclusion criteria included age ≥18 years, symptom onset of ≤4 days, and a positive AdenoPlus point-of-care immunoassay in the study eye.[32] If both eyes were affected, the first affected eye was selected. If both eyes became symptomatic at the same time, 1 eye was selected randomly as the study eye. Exclusion criteria included a history of thyroid disease, allergy to iodine or study medications, 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.

At baseline and follow-up, severity of symptoms was assessed by participant rating of the "bothersomeness" of 10 symptoms: tearing, eyelash matting, burning, itching, gritty/sandy, eyelid swelling, redness, blurred vision, sensitivity to light, and overall discomfort on a scale of 0 (not at all bothersome) to 10 (very bothersome). Clinical examination included Snellen visual acuity (corrected, uncorrected, or pinhole if less than 20/20), slit-lamp examination grading findings on a scale from 0 (absent) to 4 (severe), lymph node palpation, and grading of corneal fluorescein staining as 0 (none), 1 (micropunctate), 2 (macropunctate), 3 (coalescent macropunctate), or 4 (patch) in 5 corneal sectors using the Brien Holden Vision Institute visual grading system.[33] Grades for the 5 sectors were summed for analysis.

• **CONFIRMATION OF ADENOVIRAL CONJUNCTIVITIS:** AdenoPlus point-of-care immunoassay (now named QuickVue Adenoviral Conjunctivitis Test; Quidel Corporation, San Diego, California, USA) was used to test for adenovirus at baseline and at follow-up until 2 consecutive tests were negative.

Conjunctival swab samples of screened participants were collected from the inferior palpebral conjunctiva at least 5

minutes after instillation of topical anesthetic and AdenoPlus testing. The samples were stored in a -80 C freezer within 4 hours of collection. Samples were shipped on dry ice to Washington University (St. Louis, Missouri, USA) for DNA extraction and qPCR analysis for adenovirus. After completion of all study visits, qPCR analysis was performed with all samples for a given participant in a single batch. Viral genomic DNA was extracted using NucliSENS easyMAG (BioMereius, Lyon, France). qPCR was performed on the LIAISON MDX instrument (DiaSorin Molecular LLC, Cypress, California, USA), using the Universal Disc (96 wells) and adenovirus analyte-specific reagents that included a fluorescein (FAM)-labeled integrated probe and 3′ and 5′ adenovirus hexon primers (DiaSorin Molecular LLC). Standard curves were constructed using the Adenovirus Molecular Control (DiaSorin Molecular LLC). Each standard was extracted in a singlicate with each extract amplified in quadruplicate in a single run, and standard curves were used for all subsequent viral load determinations. Based on probit analysis using SPSS Statistics software (IBM, Armonk NY), the lower limit of detection, with a 95% confidence interval (CI), was determined to be 182 copies/mL. Specificity of the assay was assessed using samples from clinical patients known to be positive for common viruses, including cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, human herpesvirus 8, parvovirus B19, varicella-zoster virus, human immunodeficiency virus 1, hepatitis C virus, herpes simplex virus 1, herpes simplex virus 2, and human polyomavirus 2. No cross-reactivity was observed for any of the viruses tested.

• **RANDOMIZATION AND TREATMENT:** The Coordinating Center distributed randomization assignments in sealed, numbered envelopes contained within sealed, coded boxes with either ophthalmic 5% PVP-I (Alcon, Fort Worth, Texas, USA) or preservative-free AT. At baseline, the unmasked clinician instilled 1 drop of proparacaine followed by 4-5 drops of either 5% PVP-I or AT. Participants were instructed to close their eyes for 2 minutes and rotate their eyes in all positions of gaze. A 2" × 2" gauze pad moistened with the randomized study treatment, either 5% PVP-I or artificial tears, was wiped along the eyelid margins of the study eye of participants. Nonpreserved buffered sterile saline solution was used to lavage the eye and a gauze pad moistened with sterile saline was used to wipe the eyelid margins of all participants. Participants received written instructions on preventing infection transmission. Participants were also instructed to administer single-use, preservative-free lubricant eye drops to be used 4 times daily for the study duration. Masked clinicians performed all follow-up examinations.

• **TOLERABILITY AND SAFETY OF 5% POVIDONE-IODINE:** Safety was assessed by comparing visual acuity at pretreatment baseline and day 1 visit and corneal fluorescein staining at pretreatment baseline, immediate posttreatment, and day 1. Tolerability was assessed by participant-rated overall ocular discomfort at pretreatment baseline, immediately posttreatment, and on day 1.

• **ASSESSMENT OF ADEQUACY OF MASKING:** Masking of participants was assessed immediately after treatment instillation and 4 days posttreatment, by asking participants, "Which treatment do you think you received?" Masking of clinicians was assessed at each follow-up visit, by asking clinicians to guess which treatment the participant had received. Response options for participants and clinicians were: "betadine" (the trade name for PVP-I), "artificial tears," or "unsure."

• **INFECTION CONTROL:** Infection control measures included (1) participant handwashing upon entering examination room, (2) signing 2 original consent forms to avoid photocopying the original for the participant and storing the clinic's signed consent form in a red folder marked "biohazard," (3) giving the pen used to sign the consent form to the participant, (4) reading of symptom surveys by clinicians/technicians with participants responding verbally by selecting responses printed in large font on a single-use 8 1/2" × 11" sheet of paper, (5) clinicians donning fresh gloves prior to performing procedures with participant contact, (6) disposing of all materials potentially contaminated by participant contact in a biohazard container, and (7) disinfecting the examination room and waiting area with germicidal disposable wipes that meet U.S. Centers for Disease Control and Occupational Safety and Health Administration guidelines.

• **STATISTICAL ANALYSIS:** As this was a pilot study with no data available for estimating treatment effect sizes or variances, no formal statistical power analyses were performed and a target sample size of 40 (20 per group) was selected. To decrease the probability of failing to reject a null hypothesis, corrections for multiple comparisons were not performed.

The primary efficacy outcome was percent reduction of DNA copies per mL from the participant's peak viral load. The Data and Safety Monitoring Committee approved a modified intention-to-treat analysis (mITT) to test the primary hypothesis in participants with detectable viral load by qPCR at baseline. The mITT analysis does not introduce bias because samples for qPCR were taken from all screened patients prior to randomization and qPCR results were never disclosed to participants or study personnel. Safety was assessed per intention-to-treat using all randomized participants receiving 5% PVP-I or AT.

Percent reduction from peak viral load, clinical signs, and symptoms were compared at each visit by randomization group using nonparametric Wilcoxon rank order tests. The exact *P* value was calculated by a computational network algorithm, since asymptotic results assuming a normal dis-

tribution could not be assumed given the small sample size. Nominal variables were analyzed using Fisher exact test.

RESULTS

The Data Safety and Monitoring Board monitored study outcomes from September 2015 through September 2018 and data analyses were completed in July 2020. Between March 2015 and July 2018, 212 patients who presented with presumed conjunctivitis were screened; 56 (21.2%) were eligible and randomized to a single, in-office administration of 5% PVP-I (n = 30) or AT (n = 26). Reasons for exclusion included a negative AdenoPlus test (n = 148), history of thyroid disease (n = 2), conjunctival pseudomembrane/membrane (n = 1), corneal infiltrates (n = 3), and corneal ulcer (n = 2).

Of the 212 screened participants, 186 participants had both AdenoPlus and qPCR results. Of these 186 participants, 70.0% (130 of 186) participants tested AdenoPlus negative and were excluded and 30.1% (56 of 186) tested AdenoPlus positive and were clinically eligible. Of the 130 participants who tested AdenoPlus negative, results were confirmed by negative qPCR tests in 98.5% (128 of 130) of these participants. Of the 56 participants who tested AdenoPlus positive, 50% (28 of 56), results were not confirmed by negative qPCR tests at baseline and at all follow-up visits as well as by negative AdenoPlus tests at days 2 and 7.

Baseline demographic and clinical characteristics are reported for all randomized participants by whether they tested negative (n = 28) or positive (n = 28) for adenovirus by qPCR (Table 1). Only participants who tested qPCR positive for adenovirus at baseline were included in the mITT subgroup analysis. Mean duration of symptoms at presentation by self-report in the qPCR-positive subgroup was 2.4 days (range 1-4 days). Baseline characteristics for this subgroup are reported by randomization group (Table 2). A consort diagram (Figure 1) illustrates randomization and visit completion rates by participant qPCR status.

• **POVIDONE-IODINE INSTILLATION PAIN, CORNEAL STAINING, AND VISUAL ACUITY:** Thirty of the 56 participants were randomized to receive 1 in-office administration of 5% PVP-I. On the 10-point scale, the mean pretreatment and immediate posttreatment discomfort did not differ, 6.0 ± 3.0 standard deviation (SD) and 6.2 ± 2.8 SD (P = .78), respectively. On a point scale of 0-5, corneal staining increased from a pretreatment mean of 1.3 ± 2.0 SD to a posttreatment mean of 3.3 ± 3.3 SD (P = .004), but day 1 corneal staining mean (1.6 ± 2.2 SD, P = .63) did not differ from pretreatment. Pretreatment logMAR visual acuity was 0.08 ± 0.12 and 0.07 ± 0.15 at the day 1 visit.[34]

• **ADEQUACY OF MASKING:** Masking is optimal when 50% of the respondents guess "incorrectly" or are "unsure" of their randomization assignment. Immediately after treatment instillation, 34% (10 of 29) of the participants who received 5% PVP-I and 69% (18 of 26) of the participants who received AT guessed incorrectly or were unsure of their treatment. One participant treated with 5% PVP-I was not queried regarding treatment guess. On day 4, 38% (8 of 21) of the 5% PVP-I participants and 52% (11 of 21) of the AT participants guessed incorrectly or were unsure of their treatment. On follow-up days 1-2, 4, 7, 14, and 21, masked clinicians guessed assignment of 5% PVP-I participants incorrectly or were unsure in 53%, 50%, 40%, 39%, 42%, respectively, and 44%, 35%, 38%, 35%, and 39% of the AT participants, respectively.[35]

• **VIRAL LOAD, SYMPTOMS, AND CLINICAL SIGNS:** In accordance with the modified intention-to-treat analysis approved by the Data and Safety Monitoring Committee, viral load, symptoms, and clinical signs are reported for the subset of 28 participants with detectable adenovirus by qPCR at baseline (12 randomized to AT, 16 randomized to 5% PVP-I). Viral load, participant-reported symptoms, and examiner-graded clinical signs were lower in the 5% PVP-I group compared to the AT group on day 4 but did not differ at any other follow-up visit. On day 1-2, mean percent of peak viral load was 67.1% ± 37.4% SD in the 5% PVP-I group and 54.8% ± 43.6% SD in the AT group (P = .63); on day 4, mean percent of peak viral load was 2.5% ± 2.7% (95% CI 0.63 to 4.37) in the 5% PVP-I group and 14.4% ± 10.5% (95% CI 7.12 to 21.7) in the AT group (P = .020) (Figure 2 and Supplemental Table 1; Supplemental Material available at AJO.com). These differences may not be clinically significant. After day 4, viral titers continued to decrease sharply in both groups. No differences between groups were detected on days 7, 14, or 21. By day 7 viral titers were undetectable by qPCR in 54% of participants in the 5% PVP-I group and 44% of the participants in the AT group. By day 21, no participant in either group had detectable viral titers. No difference was found between randomization groups in length of time before viral titers became undetectable (P = .942).

Mean participant-reported severity of symptoms was lower on day 4 in the 5% PVP-I group compared to the AT group on a 0 (not at all bothersome) to 10 (very bothersome) scale for tearing (3.8 ± 2.3 [95% CI 2.21 to 5.39] vs 6.6 ± 2.4 [95% CI 4.94 to 8.26], P = .035), lid swelling (2.0 ± 2.3 [95% CI 0.41 to 3.59] vs 6.3 ± 3.2 [95% CI 4.08 to 8.52], P = .012), and redness (4.8 ± 3.1 [95% CI 2.65 to 6.95] vs 8.0 ± 2.1 [95% CI 6.25 to 9.75], P = .039) (Figure 3). After day 4, severity of symptoms in both groups continued to decline and no differences were detected between groups. No statistically significant differences between groups were found for eyelash matting, burning, itching, gritty/sandy, blurred vision, sensitivity to light, or overall discomfort at any visit. Mean symptom

TABLE 1. Baseline Demographics, Viral Titers, Participant-Reported Symptoms, and Clinician-Graded Signs for 56 Randomized Participants by qPCR Status (Negative or Positive) for Adenovirus

Characteristic	Baseline qPCR Status			
	qPCR Negative		qPCR Positive	
	N	%	N	%
Sex ($P = .42$)				
Male	16	55.2	13	44.8
Female	12	44.4	15	55.6
Racial category ($P = .01$)				
Other	3	25.0	9	75.0
African American	6	35.3	11	64.7
White	19	70.4	8	29.6
	N	Median	N	Median
qPCR viral titer	28	0	28	2.65×10^6
	N	Mean (SD)	N	Mean (SD)
Age at screening ($P = .007$)	28	29.0 (12.5)	28	39.3 (14.5)
Symptoms (0 = not at all bothersome; 10 = very bothersome)				
Tearing ($P = .002$)	28	4.6 (2.6)	28	6.9 (2.6)
Matting ($P = .007$)	28	4.9 (2.7)	28	6.7 (2.7)
Burning ($P = .006$)	28	3.1 (2.5)	28	5.4 (3.2)
Itching ($P = .004$)	28	2.8 (2.7)	28	5.3 (3.1)
Gritty ($P = .0001$)	28	2.8 (2.9)	28	6.4 (3.1)
Swelling ($P = .002$)	28	3.6 (3.3)	28	6.5 (3.4)
Redness ($P = .0006$)	28	6.5 (2.8)	28	8.9 (1.4)
Blurred vision ($P = .039$)	28	3.2 (3.1)	28	5.1 (3.5)
Sensitive to light ($P = .0075$)	28	2.4 (3.2)	28	5.3 (3.7)
Overall discomfort ($P < .0001$)	28	4.8 (2.7)	28	7.9 (2.0)
Slit-lamp signs (0 = absent; 4 = severe)				
Lid edema ($P = .66$)	28	1.7 (1.2)	28	1.8 (1.1)
Lid matting ($P = .23$)	28	1.0 (1.0)	28	1.3 (1.0)
Mucoid discharge ($P = .81$)	28	1.0 (1.2)	28	0.8 (0.8)
Serous Discharge ($P = .07$)	28	1.9 (1.1)	28	2.4 (1.0)
Bulbar edema ($P = .91$)	28	1.7 (1.1)	28	1.8 (1.4)
Bulbar redness ($P = .09$)	28	2.7 (0.9)	28	3.1(0.7)
Follicular response ($P = .59$)	28	2.2 (1.1)	28	2.3 (1.2)
Papillary response ($P = .58$)	28	2.1 (1.1)	28	1.9 (1.1)

severity and *P* values are reported by randomization group for each visit in Supplemental Table 2 (Supplemental Material available at AJO.com).

The severity of clinical signs graded by masked clinicians was lower on day 4 in the 5% PVP-I group compared to the AT group. On a scale from 0 (absent) to 4 (severe), mean severity in the 5% PVP-I group compared to AT was lower (Figure 4) for mucoid discharge (0.0 ± 0.0 [95% CI 0.0 to 0.0] vs 1.3 ± 1.2 [95% CI 0.47 to 2.13], $P = .03$), bulbar redness (1.7 ± 0.8 [95% CI 1.15 to 2.25] vs 3.3 ± 0.7 [95% CI 2.81 to 3.78], $P = .003$), and bulbar edema (1.0 ± 1.2 [95% CI 0.17 to 1.83] vs 2.5 ± 0.9 [95% CI 1.88 to 3.12], $P = .009$). After day 4, clinical signs in both groups continued to resolve and no differences between groups were detected thereafter. Severity of clinical signs is reported by randomization group at each visit in Supplemental Table 3 (Supplemental Material available at AJO.com).

Fourteen of 25 participants (56.0%, 95% CI 34.9%-75.6%) who were qPCR positive for adenovirus developed either a subepithelial infiltrate (5% PVP-I, n = 7; AT, n = 4) or a pseudomembrane (5% PVP-I, n = 3; AT, n = 1). One participant had both complications. There was no difference between randomization groups in the incidence of subepithelial infiltrates ($P = .69$) or pseudomembrane ($P = .60$).

Participants who tested negative for adenovirus by qPCR at baseline had less severe clinical signs and symptoms at baseline and follow-up compared to participants who tested positive for adenovirus. Furthermore, among participants who tested negative for adenovirus, no differences between randomization groups were detected for any participant-reported symptoms (Supplemental Table 4; Supplemental Material available at AJO.com) or any clinical signs (Sup-

TABLE 2. Baseline Demographic, Viral Titers, Participant-Reported Symptoms, and Clinician-Graded Signs for 28 Participants who Are qPCR Positive for Adenovirus by Randomization Group

Characteristic	Randomization Group			
	5% PVP-I		Artificial Tears	
	N	%	N	%
Sex ($P = .72$)				
Male	8	61.5	5	38.5
Female	8	53.3	7	46.7
Racial category ($P = .45$)				
White	3	37.5	5	62.5
African American	7	63.6	4	36.4
Other	6	66.7	3	33.3
	N	Median	N	Median
qPCR viral titers ($P = .91$)	16	2.8×10^6	12	2.6×10^6
	N	Mean (STD)	N	Mean (STD)
Age at screening ($P = .67$)	16	38.5 (15.3)	12	40.3 (14.0)
symptoms (0 = not at all bothersome; 10 = very bothersome)				
Tearing ($P = .67$)	16	6.9 (2.3)	12	7.0 (3.0)
Matting ($P = .43$)	16	6.4 (2.6)	12	7.0 (2.9)
Burning ($P = .57$)	16	5.7 (3.0)	12	4.9 (3.4)
Itching ($P = .72$)	16	5.4 (3.3)	12	5.0 (2.9)
Gritty ($P = .51$)	16	5.9 (3.6)	12	7.0 (2.3)
Swelling ($P = .95$)	16	6.5 (3.5)	12	6.6 (3.5)
Redness ($P = .89$)	16	8.9 (1.5)	12	8.9 (1.4)
Blurred vision ($P = .29$)	16	4.6 (3.7)	12	5.9 (3.4)
Sensitive to light (P=0.12)	16	4.3 (3.8)	12	6.6 (3.1)
Overall discomfort ($P = .38$)	16	7.4 (2.4)	12	8.4 (1.3)
Slit-lamp signs (0 = absent; 4 = severe)				
Lid edema ($P = .69$)	16	1.9 (1.1)	12	1.8 (1.3)
Lid matting ($P = .68$)	16	1.3 (0.9)	12	1.2 (1.1)
Mucoid discharge ($P = .87$)	16	0.8 (0.7)	12	0.9 (1.0)
Serous discharge ($P = .72$)	16	2.4(1.1)	12	2.4 (0.8)
Bulbar edema ($P = .29$)	16	1.5 (1.3)	12	2.1 (1.5)
Bulbar redness ($P = .72$)	16	3.0 (0.6)	12	3.2 (0.9)
Follicular response ($P = .84$)	16	2.4 (1.0)	12	2.2 (1.5)
Papillary response ($P = .70$)	16	1.7 (1.0)	12	2.0 (1.3)

plemental Table 5; Supplemental Material available at AJO.com) at any visit.

DISCUSSION

Adenoviral conjunctivitis continues to be a major public health problem in developed and developing countries. The ideal treatment for Ad-Cs would be safe, effective, well tolerated, inexpensive, and readily available. The safety profile of PVP-I has been demonstrated with decades of use as a topical antiseptic in neonates, children, and adults. Surveys have suggested that a growing number of eye care practitioners use 5% PVP-I administered as an off label, 1-time, in-office administration for the treatment Ad-Cs.[26] The RAPID pilot study was designed specifically to explore the feasibility of a definitive trial to test the safety and efficacy of this practice. The RAPID study demonstrated that an in-office administration of 5% PVP-I following proparacaine instillation was well tolerated by participants.[34] There was no evidence of increased ocular discomfort immediately after instillation of 5% PVP-I compared to pretreatment discomfort. Within 24 hours postinstillation, corneal staining returned to pretreatment levels and visual acuity was virtually unchanged from the pretreatment baseline.

This pilot study provided evidence that 5% PVP-I decreased viral load and severity of signs and participant-reported symptoms compared to AT in participants who were Ad-Cs positive at baseline by qPCR. However, the difference was statistically significant only on day 4 of a 21-day follow-up period. On day 4, percent of peak viral load was 2.5% in the PVP-I group and 14.4% in the AT group ($P = .020$). These differences may not be clinically signif-

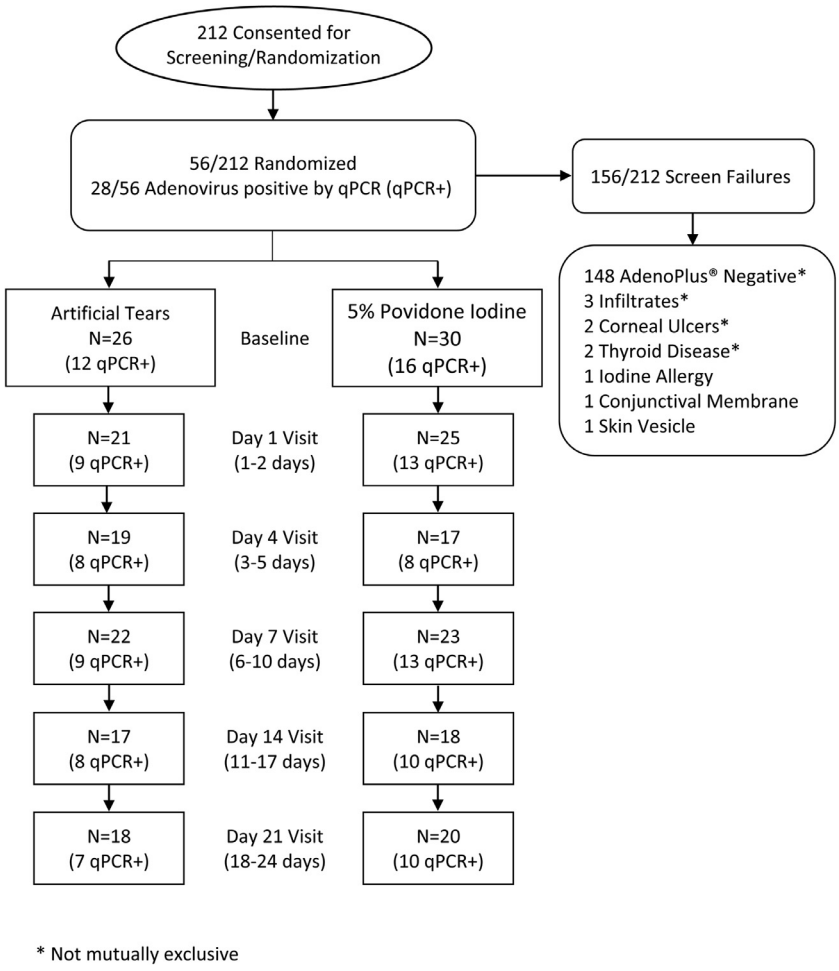

FIGURE 1. Consort diagram of participant flow.

icant. By day 7, both groups showed marked reduction in viral load and improvements in signs and symptoms, which is consistent with the natural history of Ad-Cs.[30,36] By day 21, no participant had detectable adenovirus by qPCR. The clinical significance of these findings is not entirely clear, but these results suggest that patients with Ad-Cs could experience relief 3-4 days earlier with 5% PVP-I treatment than without treatment. Among randomized participants who tested negative at baseline for Ad-Cs by qPCR, there was no evidence that 5% PVP-I reduced signs or symptoms at any follow-up visit.

It was hypothesized that 5% PVP-I would reduce the incidence of ocular sequelae of Ad-Cs. However, the incidence of corneal infiltrates and pseudomembranes was higher in the 5% PVP-I group compared to AT, although not statistically significant. These findings were not expected and the small sample size makes interpretation challenging.

The incidence of pseudomembranes in our study was 16% which is comparable to the 24% reported by Butt and associates.[37] The incidence of infiltrates was 56% in this study and is consistent with Lee and associates' prospective study of 500 patients in 4 countries, which reported an incidence of 59% over 18 days of follow-up.[36] A retrospective study of 110 patients in the United States reported an incidence of infiltrates of 49%.[37] A higher incidence of infiltrates has been reported for adenovirus type D.[36,38] Serotyping, which may have provided additional understanding as to which patients develop these ocular sequelae, was not done in this study.

The efficacy of topical PVP-I/dexamethasone combinations in the management of Ad-Cs has been demonstrated in open-label, single-arm as well as double-masked randomized trials.[28-31] However, poor adherence might explain why treatment benefit has not consistently been demonstrated for several measures of efficacy. Poor adherence could be related to the 4-times-daily regimen of PVP-I/dexamethasone for 5-7 days. A study of medication adherence found that adherence to 3-times-a-day dosing was only 38%.[39] In addition, stinging upon instillation, reported by as many as 22% to 32% of patients receiving PVP-I/dexamethasone combinations, could further reduce treatment adherence.[27,29] Issues of treatment adherence are

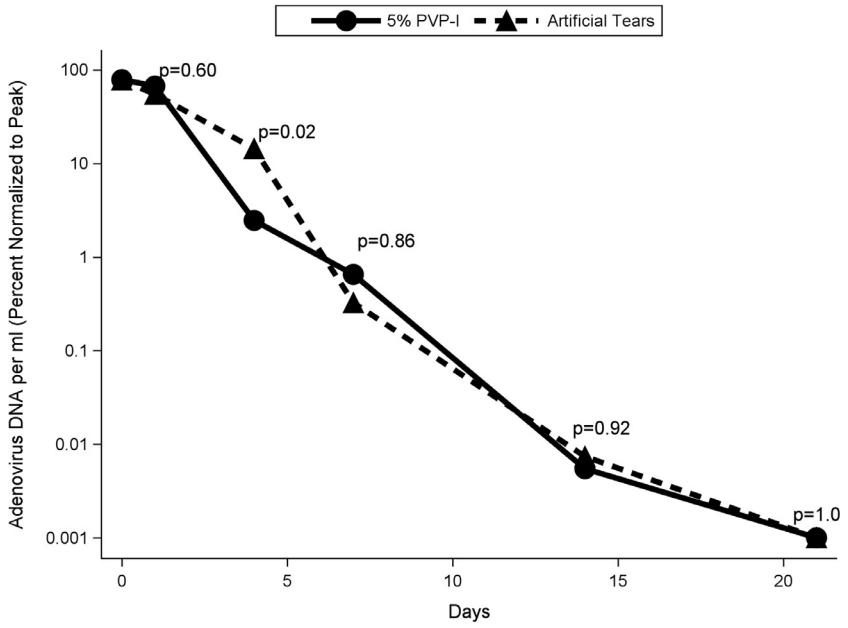

FIGURE 2. Percent of peak viral load for 5% povidone-iodine (PVP-I) and artificial tears groups at days* 1-2, 4, 7, 14, and 21 among participants qPCR+ for adenovirus. *Wilcoxon rank sum test, exact *P* value to compare 5% PVP-I vs artificial tears groups was calculated at each visit.

avoided by a single, well-tolerated in-office administration of 5% PVP-I following topical anesthesia.

An important goal of this pilot study was to explore whether double-masking could be achieved given the distinctive color and odor of 5% PVP-I. A threshold for optimal masking is 50% incorrect/unsure guesses. Participants were incorrect or unsure of their treatment 34%-69% of the time. Masked clinicians were incorrect or unsure of the participants' treatment 35%-53% of the time throughout follow-up. Though unmasking cannot be ruled out entirely, our results increase confidence that participant-reported symptoms and clinician-graded signs were not substantially biased by knowledge of randomization assignment.

The lack of an accurate, real-time Ad-Cs diagnosis poses a serious challenge both to the clinical management of patients presenting with acute conjunctivitis and to treatment trials of these patients.[40] Diagnosis of Ad-Cs based on clinical signs and symptoms is known to be highly variable, ranging from 40% to 72% compared to laboratory confirmation.[41,42] Enrollment of patients in an Ad-Cs therapeutic trial who are negative for Ad-Cs can dramatically reduce observed efficacy and statistical power (Mae O. Gordon, Julia A Beiser, Leonard Haertter. Diagnostic misclassification: Possible explanation for unsuccessful therapeutic trials of "pink eye". Presented at: Society for Clinical Trials. May 16, 2015. Arlington, VA)..[43] One trial reported that "not enough patients with confirmed adenoviral conjunctivitis (n=32/132) were enrolled to assess the primary endpoint…"[27] Lee and associates reported that 50% of the participants who tested positive for Ad-Cs using a point-of-care immunoassay did not have detectable adenovirus by qPCR (Cecilia S. Lee, Aaron Y. Lee, Lakshmi Akileswaran, et al. The evaluation of worldwide distribution of adenoviral genotypes in acute/epidemic keratoconjunctivitis and adenoviral-negative keratoconjunctivitis with next generation sequencing. Poster presented at the Association for Research in Vision and Ophthalmology; May 1-5, 2016; Seattle, WA)..[44] Similarly, 50% of the participants in RAPID who tested positive by a point-of-care immunoassay tested negative by qPCR.[45] Because the false-positive rate of the available point-of-care immunoassay can be high, it is important that future trials consider an *a priori* modified intention-to-treat analyses of case-positive patients. The true-negative rate of the available point-of-care immunoassay was high in RAPID (98.5%) as well as in other studies using PCR as the comparator.[41] Thus, a negative test result on the available point-of-care immunoassay is likely to be correct and therefore helpful for ruling out Ad-Cs.

An objective in the RAPID pilot study was to quantitate the natural history of viral load in the artificial tears group. After 7 days of follow-up, a marked reduction in viral titers and a concomitant reduction in the severity of signs/symptoms was observed in the AT group, a finding that has also been reported in the placebo control groups of other studies.[30,31] By day 7, most patients are nearly fully recovered without treatment, though inflammatory sequelae can persist after clearance of viral titers. Since most studies require that patients present within 4 days of symptom onset, the day 7 follow-up visit equates to 11 days, at most, after symptom onset.[30,31,36] The rapid reduction in

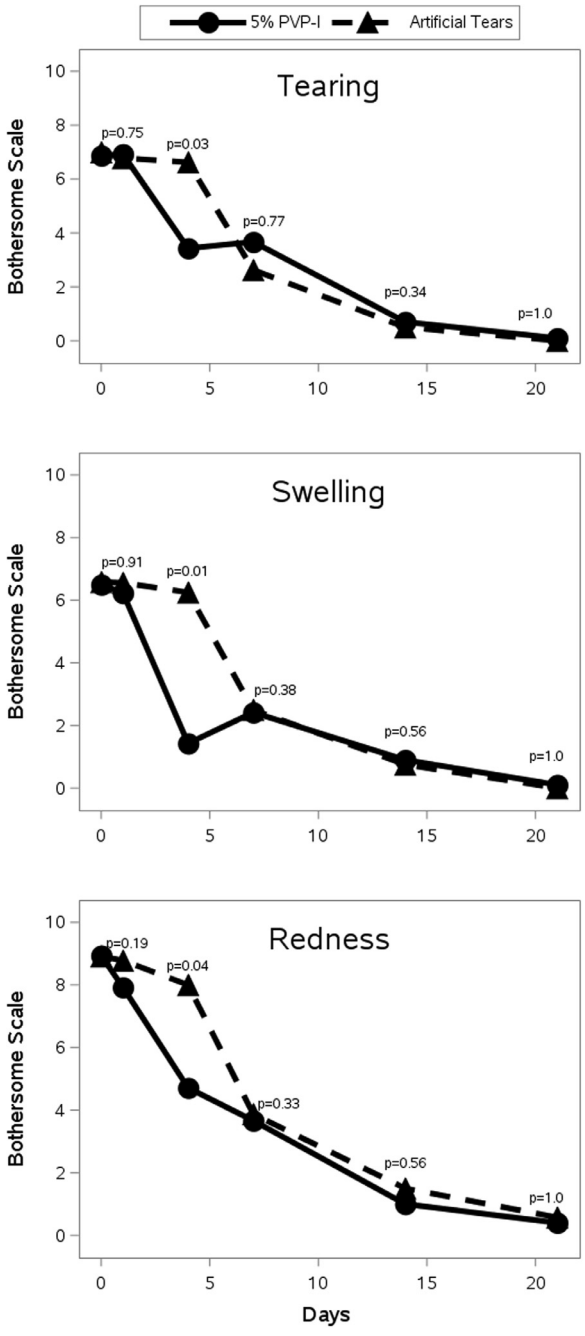

FIGURE 3. Severity of participant-reported symptoms in the 5% povidone-iodine (PVP-I) and artificial tears groups at days 1-2, 4, 7, 14, and 21 among participants qPCR+ for adenovirus. Scale from 0 = "not at all bothersome" to 10 = "very bothersome."

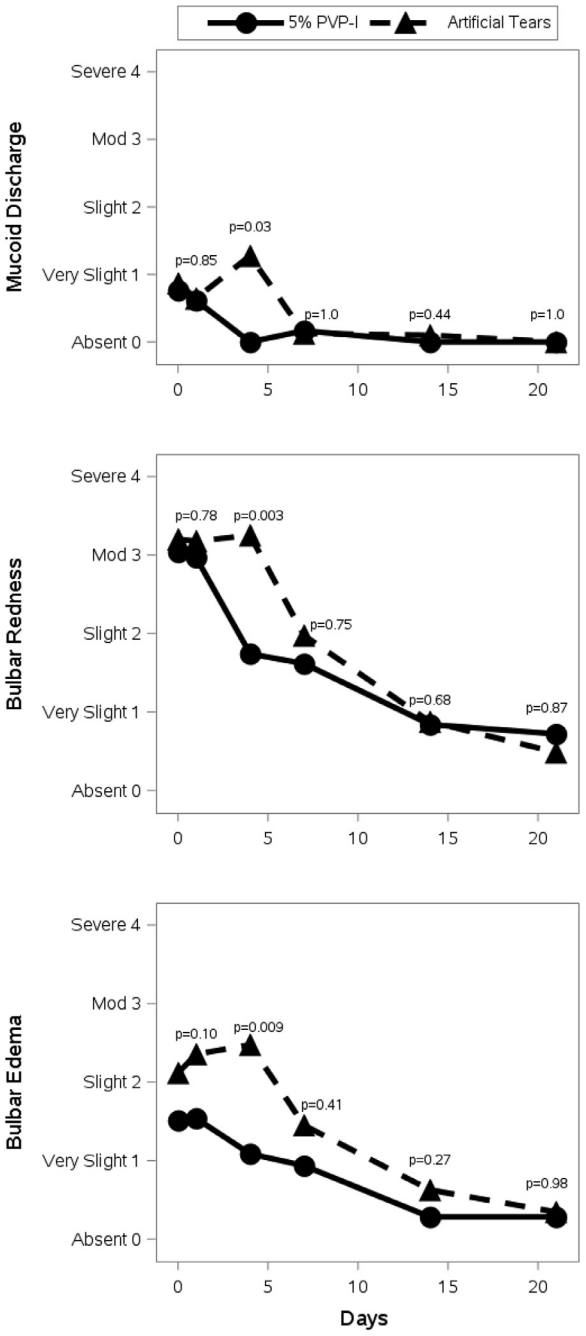

FIGURE 4. Severity of masked clinician–graded signs in the 5% povidone-iodine (PVP-I) and artificial tears groups at 1-2, 4, 7, 14, and 21 days among participants qPCR+ for adenovirus. Scale from 0 = "absent" to 4 = "severe."

viral load and signs and symptoms by study day 7 implies that the therapeutic window to shorten the course of Ad-Cs in clinical trials may be relatively brief. Unfortunately, many patients wait more than 3-4 days after symptom onset to seek care, and this may reduce the effectiveness of any treatment for Ad-Cs. The reduction of viral load and signs and symptoms by day 7 of follow-up suggests that therapeutic "successes" observed in single-arm studies[19,28] and case series,[46] which lack a concomitant, parallel control group, may be due partly to the self-limiting nature of Ad-Cs.

Strengths of this pilot study include centralized masked randomization, diverse participant sample, masking of clinicians and participants, and monitoring of viral load

through 21 days by qPCR. The concentration of 5% PVP-I was selected to evaluate the off-label use of 5% PVP-I that has been adopted by some eye care practitioners to treat Ad-Cs. This particular formulation was used because ophthalmic PVP-I is currently commercially available only in a 5% concentration. Our results should be considered in light of limitations of this study. The study was designed as a pilot study and was not powered for a definitive test of the efficacy of 5% PVP-I. Additional limitations include a sample of adults only, loss to follow-up, lack of serotyping, and a high false-positive rate of point-of-care immunoassay, which necessitated a modified intention-to-treat analysis among participants positive for Ad-Cs by qPCR. These limitations directly affect the application of results to clinical practice. First, this protocol applies only to patients who present within 4 days of symptom onset. Second, the high false-positive rate of point-of-care immunoassay implies many patients who test positive for Ad-Cs using this immunoassay may not benefit from treatment because they do not actually have Ad-Cs.

Larger studies are needed to replicate our results. However, this pilot study suggests that a single, in-office administration of 5% PVP-I may accelerate reduction in viral load and hasten improvement of clinical signs and symptoms in individuals with Ad-Cs who present within 4 days of symptom onset.

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REFERENCES

1. Kuo IC. Adenoviral keratoconjunctivitis: Diagnosis, management, and prevention. *Curr Ophthalmol Rep*. 2019(7):118–127.
2. Gordon YJ, Gordon RY, Romanowski E, TP Araullo-Cruz. Prolonged recovery of desiccated adenoviral serotypes 5, 8, and 19 from plastic and metal surfaces in vitro. *Ophthalmology*. 1993;100(12):1835–1839 discussion 1839-1840.
3. Colon LE. Keratoconjunctivitis due to adenovirus type 8: Report on a large outbreak. *Ann Ophthalmol*. 1991;23(2):63–65.
4. Vastine DW, West CE, Yamashiroya H, et al. Simultaneous nosocomial and community outbreak of epidemic keratoconjunctivitis with types 8 and 19 adenovirus. *Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol*. 1976;81(5):826–840.
5. Sanders MG. FD. Epidemic keratoconjunctivitis. Clinical and experimental study of an outbreak in New York City: Further observations on the specific relationship between a virus and the disease. *JAMA*. 1943(121):250–255.
6. Doyle L, Gallagher K, Heath BS, Patterson WB. An outbreak of infectious conjunctivitis spread by microscopes. *J Occup Med*. 1989;31(9):758–762.
7. Reilly S, Dhillon BJ, Nkanza KM, et al. Adenovirus type 8 keratoconjunctivitis–An outbreak and its treatment with topical human fibroblast interferon. *J Hyg (Lond)*. 1986;96(3):557–575.
8. Cooper RJ, Hallett R, Tullo AB, Klapper PE. The epidemiology of adenovirus infections in Greater Manchester, UK 1982-96. *Epidemiol Infect*. 2000;125(2):333–345.
9. Jackson WB, Davis PL, Groh V, Champlin R. Adenovirus type 19 keratoconjunctivitis in Canada. *Can J Ophthalmol*. 1975;10(3):326–333.
10. Laibson PR, Ortolan G, Dupre-Strachan S. Community and hospital outbreak of epidemic keratoconjunctivitis. *Arch Ophthalmol*. 1968;80(4):467–473.
11. Stasiuk RM, Robertson IF. Adeno-viral kerato conjunctivitis. *Aust J Ophthalmol*. 1981;9(1):55–58.
12. Faden H, Wynn RJ, Campagna L, Ryan RM. Outbreak of adenovirus type 30 in a neonatal intensive care unit. *J Pediatr*. 2005;146(4):523–527.
13. Viney KA, Kehoe PJ, Doyle B, et al. An outbreak of epidemic keratoconjunctivitis in a regional ophthalmology clinic in New South Wales. *Epidemiol Infect*. 2008;136(9):1197–1206.
14. Warren D, Nelson KE, Farrar JA, et al. A large outbreak of epidemic keratoconjunctivitis: Problems in controlling nosocomial spread. *J Infect Dis*. 1989;160(6):938–943.
15. Meyer-Rusenberg B, Loderstadt U, Richard G, Kaulfers PM, Gesser C. Epidemic keratoconjunctivitis: The current situation and recommendations for prevention and treatment. *Dtsch Arztebl Int*. 2011;108(27):475–480.
16. Aoki K, Tagawa Y. A twenty-one year surveillance of adenoviral conjunctivitis in Sapporo, Japan. *Int Ophthalmol Clin*. 2002;42(1):49–54.
17. Udeh BL, Schneider JE, Ohsfeldt RL. Cost effectiveness of a point-of-care test for adenoviral conjunctivitis. *Am J Med Sci*. 2008;336(3):254–264.
18. Kuo IC, Espinosa C, Forman M, Valsamakis A. A polymerase chain reaction-based algorithm to detect and prevent transmission of adenoviral conjunctivitis in hospital employees. *Am J Ophthalmol*. 2016;163:38–44.

19. Trinavarat A, Atchaneeyasakul LO. Treatment of epidemic keratoconjunctivitis with 2% povidone-iodine: A pilot study. *J Ocul Pharmacol Ther*. 2012;28(1):53–58.
20. Yates KA, Shanks RMQ, Kowalski RP, Romanowski EG. The in vitro evaluation of povidone-iodine against multiple ocular adenoviral types. *J Ocul Pharmacol Ther*. 2019;35(2):132–136.
21. Kawana R, Kitamura T, Nakagomi O, et al. Inactivation of human viruses by povidone-iodine in comparison with other antiseptics. *Dermatology*. 1997;195(Suppl 2):29–35.
22. Abel AD. Adenoviral conjunctivitis. How to use povidone-iodine for treatment.. *Ophthalmology Management*. February 2000. https://www.ophthalmologymanagement.com/issues/2000/february-2000/adenoviral-conjunctivitis.
23. Abelson M, Shapiro A. A guide to understanding adenovirus, the diseases it causes and the best ways to treat these conditions. Review of Ophthalmology Web site. Published 2010. Available at https://www.reviewofophthalmology.com/article/a-guide-to-understanding-adenovirus-the-diseases-it-causes-and-the-best-ways-to-treat-these-conditions. Accessed June 28, 2021
24. Shovlin JP. What's the Buzz About Betadine? Review of Ophthalmology Web site. Published 2011. Available at https://www.reviewofoptometry.com/article/whats-the-buzz-about-betadine. Accessed June 28, 2021.
25. Pernicky J. [Personal experience with the use of Betadine gtt. in the treatment of epidemic viral keratoconjunctivitis]. *Cesk Oftalmol*. 1994;50(5):323–324.
26. Than T, Hartwick A, Shorter E, et al. How to manage adenoviral conjunctivitis. Optometry Times Web site. Available at http://optometrytimes.modernmedicine.com/optometrytimes/news/how-manage-adenoviral-conjunctivitis. Published 2014. Accessed June 28, 2021.
27. Pepose JS, Narvekar A, Liu W, Haque R. A randomized controlled trial of povidone-iodine/dexamethasone ophthalmic suspension for acute viral conjunctivitis. *Clin Ophthalmol*. 2019;13:535–544.
28. Pelletier JS, Stewart K, Trattler W, et al. A combination povidone-iodine 0.4%/dexamethasone 0.1% ophthalmic suspension in the treatment of adenoviral conjunctivitis. *Adv Ther*. 2009;26(8):776–783.
29. Pinto RD, Lira RP, Abe RY, et al. Dexamethasone/povidone eye drops versus artificial tears for treatment of presumed viral conjunctivitis: A randomized clinical trial. *Curr Eye Res*. 2015;40(9):870–877.
30. Kovalyuk N, Kaiserman I, Mimouni M, et al. Treatment of adenoviral keratoconjunctivitis with a combination of povidone-iodine 1.0% and dexamethasone 0.1% drops: A clinical prospective controlled randomized study. *Acta Ophthalmol*. 2017;Dec;95(8):e686–e692.
31. Pepose JS, Ahuja A, Liu W, Narvekar A, Haque R. Randomized, controlled, phase 2 trial of povidone-iodine/dexamethasone ophthalmic suspension for treatment of adenoviral conjunctivitis. *Am J Ophthalmol*. 2018;194:7–15.
32. QuickVue Adenoviral Conjunctivitis Test: Manufacturer's Instructions. Quidel Corporation Web site. Available at http://www.quidel.com/sites/default/files/product/documents/EF1361400EN00.pdf. Accessed June 28, 2021.
33. Terry RL, Schnider CM, Holden BA, et al. CCLRU standards for success of daily and extended wear contact lenses. *Optom Vis Sci*. 1993;70(3):234–243.
34. Shorter E, Whiteside M, Harthan J, et al. Safety and tolerability of a one-time, in-office administration of 5% povidone-iodine in the treatment of adenoviral conjunctivitis: The Reducing Adenoviral Patient Infected Days (RAPID) study. *Ocul Surf*. 2019;17(4):828–832.
35. Whiteside M, Shorter E, Migneco M, et al. Reducing Adenoviral Patient Infected Days (RAPID) study: Success in masking subjects and clinicians from identifying treatment with ophthalmic povidone-iodine 5% (PVP-I). *Invest Ophthalmol Vis Sci*. 2018;59(9).
36. Lee CS, Lee AY, Akileswaran L, et al. Determinants of outcomes of adenoviral keratoconjunctivitis. *Ophthalmology*. 2018;125(9):1344–1353.
37. Butt AL, Chodosh J. Adenoviral keratoconjunctivitis in a tertiary care eye clinic. *Cornea*. 2006;25(2):199–202.
38. Yanoff M, Sassani JW. *Ocular Pathology*. 8th edition. Elsevier, Inc; 2020.
39. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes Care*. 1997;20(10):1512–1517.
40. Ung L, Bispo PJM, Doan T, et al. Clinical metagenomics for infectious corneal ulcers: Rags to riches? *Ocul Surf*. 2020;18(1):1–12.
41. Sambursky R, Trattler W, Tauber S, et al. Sensitivity and specificity of the AdenoPlus test for diagnosing adenoviral conjunctivitis. *JAMA Ophthalmol*. 2013;131(1):17–22.
42. O'Brien TP, Jeng BH, McDonald M, Raizman MB. Acute conjunctivitis: Truth and misconceptions. *Curr Med Res Opin*. 2009;25(8):1953–1961.
43. Gordon M. Diagnostic misclassification: Possible explanation for unsuccessful therapeutic trials of "pink eye. *Presented at: Society for Clinical Trials*. May 16, 2015 Arlington, VA.
44. Lee CS. *The evaluation of worldwide distribution of adenoviral genotypes in acute/epidemic keratoconjunctivitis and adenoviral-negative keratoconjunctivitis with next generation sequencing*. Association for Research in Vision and Ophthalmology; May 1-5, 2016 Poster presented atSeattle, WA.
45. Hartwick A, Than T, Rodic-Polic B, et al. *Reducing Adenoviral Patient-Infected Days (RAPID) Study: A randomized trial assessing efficacy of one time, in-office application of 5% povidone-iodine in treatment of adenoviral conjunctivitis*; 2019 *Investigative Ophthalmology & Visual Science*;60:6257.
46. Abel R, Abel AD. Use of povidone-iodine in the treatment of presumptive adenoviral conjunctivitis. *Ann Ophthalmol & Glaucoma*. 1998;30(6):341–343.