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OCULAR Infection & Inflammation

Adenoviral Conjunctivitis

A continuing education newsletter for physicians, pharmacists, and nurses interested in infection & inflammation of the eye

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Activity Title

OCULAR Infection & Inflammation

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Objectives: Adenoviral Conjunctivitis

At the conclusion of this activity, participants should be able to:

- Recognize symptoms and signs of adenoviral conjunctivitis
- Review the differential diagnosis and approach to a patient with acute conjunctivitis
- Perform appropriate diagnostic testing to correctly diagnose adenoviral conjunctivitis
- Review management and current treatments for adenoviral conjunctivitis

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To claim CE credit, individuals must complete Ocular Infection & Inflammation, Vol. 1, Issue 4, Adenoviral Conjunctivitis Post Test, and Program Evaluation Form. Mail or fax these on the CE Request Form to the address below postmarked by November 30, 2011 to:

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INTRODUCTION

Adenovirus frequently causes both systemic and ocular illnesses. It is associated with significant systemic disease such as transient neurologic disease in children, sore throats, diarrhea, and pneumonia. It is responsible for fatalities in transplant patients and other immunocompromised patients, pediatric long-term care facilities, and more recently with the eleven deaths associated with the variant of serotype 14.[1] Because less than 5% of the general population in the United States show natural immunity against adenovirus, every individual is considered susceptible to infection.[2] Often patients infected with adenovirus may exhibit symptoms involving multiple systems.

Acute conjunctivitis defines an inflammation of the conjunctiva, or the mucous membrane lining the inner surface of the eyelids and outer surface of the eyeball extending over the sclera. Adenovirus is the most frequent cause of conjunctivitis worldwide.[2] Other causes of conjunctivitis include infections with bacteria, other viruses, or Chlamydia; inflammation from numerous allergens; or are related to irritation resulting from chemical injury and/or medication. There are 53 different serotypes of human adenovirus including serotypes 2, 3, 4, 7, 8, 11, 14, 19 and 37 that are responsible for most eye infections[3-5], although other serotypes may produce indistinguishable disease. Adenoviral conjunctivitis is associated with significant ocular morbidity and health care costs.[6]

EPIDEMIOLOGY

Acute microbial conjunctivitis is very common. Studies from England show that conjunctivitis comprises about two percent of a general practitioner's practice.[7-8] A National Health Survey reported that conjunctivitis in the U.S. occurs in 13 of every 1000 people between the ages of 1-74.[9] The prevalence is different in pediatric and adult populations. Bacterial conjunctivitis is more common in children than in adults.[10-11] Approximately twenty to seventy percent of infectious conjunctivitis is thought to be of viral etiology[10-16], and between 65-90% is caused by adenovirus.[17-19]

Adenoviral conjunctivitis tends to occur in areas of overcrowding and poor hygiene because of the extreme contagiousness of this disease.[15] The endemic nature of the virus leads to infections that occur both sporadically and epidemically. Adenoviral conjunctivitis tends to be more common in the summer and fall.[20] Approximately 70% of all cases of acute conjunctivitis initially present to a primary care or urgent care provider while 20% of the remaining cases present first to either an optometrist or ophthalmologist.[5]

History, Symptoms & Signs

The clinical presentation associated with acute infectious conjunctivitis caused by both bacteria and viruses is similar. Certain symptoms and signs are presumed to be more likely associated with a bacterial etiology while others are more likely to be seen with viral disease. However, there is considerable overlap in symptoms and signs and the literature supports the fact that there are no classic signs for viral conjunctivitis.[21]

History

The first step in evaluating a patient with a conjunctivitis necessitates obtaining a good history that includes questions about exposure to other individuals, history of a recent upper respiratory infection, history of cold sores or fever blisters (both recent and in the past), history of contact lens use or active rheumatologic disease, and evidence of a recurrent pattern of occurrence. Both infected contact exposure and recent upper respiratory infections are more commonly associated with adenoviral conjunctivitis.

The temporal sequence that certain symptoms and signs develop may help support the clinical diagnosis of acute viral conjunctivitis. Adenoviral conjunctivitis is often explosive in its onset and typically starts in one eye and spreads to the contralateral eye 1-4 days later. Clinical features are less specific when patients are seen early in the course of the disease, before some of the classic signs have time to appear.[22]

Symptoms

Adenoviral conjunctivitis usually presents with moderate injection, watery or mucoserous discharge, and a foreign body sensation that is often described as burning, sandy, or gritty feeling. Patients may report morning crusting and that the eyelids are stuck together in the morning. Eyelid matting was once thought to be seen more often in bacterial conjunctivitis but Rietveld studied a cohort of 184 adults with a red eye and either an eye stuck shut in the morning or purulent or mucopurulent discharge. Among 57 patients with bacterial conjunctivitis, 53 percent had one eye stuck shut and 39 percent had two eyes stuck shut; among 120 patients without bacterial conjunctivitis, 62 percent had one eye stuck shut and 11 percent had two eyes stuck shut.[23] If the cornea is involved, it is not uncommon for the vision to be reduced to the 20/40 range secondary to the accompanying punctuate keratitis.

Signs

It is important to examine the eyes for common signs that may help identify the etiology of the presumed infectious conjunctivitis such as vesicles, papules, ulcerations, crusting,

discharge, and chemosis. Mucoserous discharge tends to occur more often with viral conditions, and purulent discharge tends to occur with bacterial conjunctivitis.[10-15] Pseudomembranes typically occur with adenoviral conjunctivitis, but without a slit lamp bio-microscope, these may easily be mistaken as purulent discharge. Viral disease tends to have more conjunctivitis chemosis.[10]

The palpebral conjunctiva should be examined for the presence of a follicular or papillary reaction. The presence of follicles is more likely found with viral conjunctivitis and a papillary reaction is more common with nonspecific conjunctivitis, allergies, and bacterial disease.[10] However, Moraxella conjunctivitis, a common bacterial cause of conjunctivitis, is known also to cause follicles[24-25]. Often the slit lamp biomicroscopic appearance of the conjunctiva shows follicles, papillae or in some cases a mixed reaction. When there is both follicles and papillae, it may not be easy to determine which pattern is predominating. Furthermore, children may have a benign folliculosis which may confound the clinical picture.

Typically, fifty percent of viral conjunctivitis is associated with tender preauricular lymph nodes and this occurs more often than seen with bacterial conjunctivitis[10]. Other viruses such as the herpes simplex virus (HSV), and bacteria such as Chlamydia trachomatis and Neisseria gonorrhea may also lead to lymphadenopathy.[26-27]The presence of small petechial hemorrhages or larger subconjunctival hemorrhages is highly suggestive of an adenoviral infection.[16] However; such hemorrhages may be infrequently caused by other viruses such as Coxsackie and Enterovirus.[28]

After 7-10 days, some adenoviral infections may develop an inflammatory keratitis. The cornea may develop inflammatory corneal deposits or subepithelial infiltrates[29]. These infiltrates may lead to increasing light sensitivity and reduced visual acuity.

Diagnosis

Misdiagnosis

As described above, it is often challenging to differentiate viral from bacterial conjunctivitis based on clinical signs and symptoms alone.[21,23] Numerous studies demonstrate varying clinical accuracies that range from 40-75% when compared to a laboratory reference test.[11-12,21-23,30-32] For clinicians without access to and/or training on a slit lamp biomicroscope or laboratory-based technology, differentiating viral from bacterial conjunctivitis is even more challenging.[33-34] Because of this difficulty, many patients are presumptively treated with antibiotics.[35-36]

Slit lamp examination.
A slit lamp, with its high magnification, allows the eye care professional to examine the front of the eye. Courtesy of National Eye Institute, National Institutes of Health.

Masquerading Conditions

Adenoviral conjunctivitis can present with marked lid swelling and fever that may mimic periorbital cellulitis.[37] Misdiagnosis may lead to hospitalization and unnecessary intravenous antibiotics. Ruttum prospectively evaluated children who had been referred by a pediatrician or ophthalmologist to the emergency room of Children's Hospital of Wisconsin or already hospitalized by their pediatricians for management of periocular infection.[37] The study revealed that 16% (13/80) of patients with signs of preseptal or orbital infection who were seen in consultation by the Ophthalmology Service during the study period were diagnosed with an adenovirus rather than with a bacteria. Nine children had been treated with oral or topical antibiotics and 11 children who were admitted were hospitalized for a mean of 3.5 days.[37]

Herpes simplex virus is a rare cause of epidemic keratoconjunctivitis (EKC) [27] Herpes simplex virus may cause EKC that is indistinguishable from that of adenovirus.[17,19,27] Clinical studies have shown that HSV may present as conjunctivitis without associated skin lesions in 1-5% of all cases of presumed viral conjunctivitis.[17,19,27] It is especially more common in unilateral cases of conjunctivitis.[27]

Bacterial conjunctivitis may present similarly to adenoviral conjunctivitis. Bacterial conjunctivitis is commonly caused by Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.[38] Like viral conjunctivitis, bacterial conjunctivitis is spread by direct

contact with the patient and his or her secretions or with contaminated objects and surfaces. It can be highly contagious. Several recent outbreaks were thought originally to be viral until cultures confirmed the outbreaks resulted from atypical unencapsulated strains of S. pneumoniae in which attack rates were as high as 14 percent.[39-40]

Laboratory Testing

There are both traditional laboratory and point of care diagnostic methods available for diagnosing adenoviral conjunctivitis. Laboratory diagnosis of adenoviral infections currently is based on cell culture with confirmatory immunofluorescence (CC-IFA), the polymerase chain reaction (PCR), and antigen detection. Cell culture-with confirmatory immunofluorescence is the historical gold standard but is not widely used because of the time delay in receiving results. It may take a few days to 3 weeks for a cell culture to reveal a positive result.[41-42] Polymerase chain reaction is becoming more frequently used as a diagnostic tool for identifying infectious agents since it has demonstrated better sensitivity compared to CC-IFA but typically requires sending a specimen to an outside special laboratory offering this service.[41-42] In general, these laboratory based procedures require technical expertise, present a considerable time delay in receiving results and impose significant costs.

Several types of laboratory antigen tests, including enzyme immunoassays[43], direct immunofluorescence[44], and immunochromatography[45], may be used to identify the presence of adenovirus in conjunctivitis. Most of these are considered too complex for use in a physician office laboratory. Enzyme immunoassays demonstrate sensitivities of 38% that increased to 65% if the test was performed in the first week.[43] Direct immunofluorescence has predominately been used as a confirmation of CC-IFA.[44] Several traditional immunochromatography tests have been developed for detecting adenovirus. These swab based tests show a sensitivity of 54% and specificity of 97% when compared to PCR.[45] Since all of these tests are multi-step procedures, they do not qualify for a Clinical Laboratory Improvement Amendment (CLIA) waiver and remain relegated to laboratory use.

Point Of Care Testing

Recently, the Food and Drug Administration (FDA) cleared and CLIA waived the first point of care test for physician office use. Since it is CLIA waived, it does not require performance in a traditional laboratory setting. It may be performed by a clinician, nurse, or technician. The test is capable of detecting all 53 adenoviral serotypes by identifying a portion of the hexon protein that is conserved among all the different serotypes of adenovirus.[8] This new rapid point of care (POC) immunoassay (RPS Adeno Detector*) provides clinicians with a highly sensitive and specific diagnostic test that may be performed at the office visit.[15]

The immunoassay utilizes direct sampling and micro-filtration technology to achieve high sensitivities.[15] The device consists of two components, a sterile sample collector and a test cassette that house an immunoassay strip. The sterile sample collector both collects and concentrates the adenoviral hexon antigen released during the conjunctival scraping process and then directly transfers this concentrated material without any prior extraction or dilution steps to the test strip.[8] This direct sampling process increases both the ease of use and the sensitivity of the device. Since the test only takes 10 minutes, a patient may be kept in the same room to await the result after administering the test. Antigens present in the tear fluid bind to monoclonal antibodies on the test strip and give either a single-line negative result or a two-line positive result.

When the rapid POC immunoassay was compared to PCR as the gold standard, the sensitivity was found to be 89% and the specificity 94% percent; CC-IFA compared to PCR demonstrated a sensitivity of 91% and specificity of 100% (see Table 1).[15] The rapid POC immunoassay offers a major paradigm shift with such a sensitive and specific device compared to less robust platforms.[43-45]

A rapid POC immunoassay for adenovirus provides numerous clinical benefits. By offering a definitive diagnosis at the office visit, it may lead to better patient management and treatment. Knowing immediate results can reduce the unnecessary topical ophthalmic antimicrobial prescriptions written and this would significantly reduce the number of toxic and allergic reactions, antibiotic resistance, and costs that occur with topical antibiotics.

Classification

Adenoviral conjunctivitis may be associated with a viral prodrome followed by adenopathy, fever, pharyngitis, or an upper respiratory tract infection, and in many cases the ocular involvement may be the only manifestation of the disease. Adenovirus is known to cause four clinical scenarios, and in increasing severity of disease, these include nonspecific follicular conjunctivitis (NFC), pharyngeal conjunctival fever (PCF), acute hemorrhagic conjunctivitis (AHC), and epidemic keratoconjunctivitis (EKC).[2] The most common serotypes to cause ocular disease include 3, 4, 7, 8, 19, and 37.[17-18,46] The duration of disease, infectivity, and clinical course is serotype dependent.

Nonspecific Follicular Conjunctivitis

Nonspecific follicular conjunctivitis is a nondescript form of viral conjunctivitis and is usually caused by serotypes 1-11 and 19.[46] It is very common, tends to occur more often in children, and is often associated with an upper respiratory

infection.[47] Nonspecific follicular conjunctivitis can be unilateral or bilateral and usually resolves within 2 weeks without sequelae. Its vague presentation makes it the most challenging form of adenoviral conjunctivitis to diagnose.

Pharyngeal Conjunctivitis Fever

Pharyngeal conjunctivitis fever tends to occur more often in children and is more likely to be unilateral.[48] Pharyngeal conjunctivitis fever is more common in children and can be accompanied by a mild pharyngitis and low-grade fever. It is highly contagious and is associated with swimming pool and camp epidemics.[49-51] It typical resolves over a 2-week period of time and is thought to have less than a 5% chance for long term morbidity.[48]

Acute Hemorrhagic Conjunctivitis

Acute hemorrhagic conjunctivitis is often felt to be a subset of EKC. It is typically caused by serotypes 11, 19, 37.[52] Epidemics of AHC are most common in developing countries.[53] It is highly contagious. Acute hemorrhagic conjunctivitis is associated with large subconjunctival hemorrhages, preauricular lymphadenopathy, and a keratitis.[54-56] It is usually self limiting but often has a protracted course and is associated with significant long term morbidity.

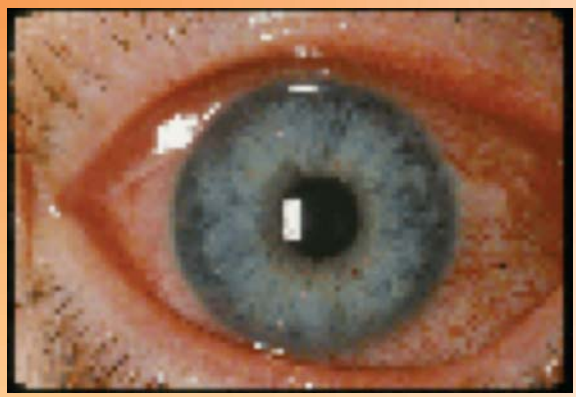
Epidemic Keratoconjunctivitis

Epidemic keratoconjunctivitis is most often a result of the adenoviral serotypes 11, 19 and 37, and is highly contagious.[17,18,46] It is most common in men and women aged 20-40 years.[17-18,46-47] Epidemic keratoconjunctivitis is more clinically obvious and is associated with significant injection, chemosis, and a keratitis. Both membranes and pseudomembranes can occur in EKC. Patients often complain of a significant foreign body sensation and blurred vision. It is usually self limiting but patients may have a protracted course lasting approximately 4 weeks. In addition, it is associated with complications such as subepithelial corneal infiltrates may lead to light sensitivity or impair vision for up to a year or more. [57-59]

Management

The exact duration of infectivity associated with adenoviral conjunctivitis is uncertain. Studies demonstrate that positive cultures could be obtained from 5-10% of the eyes of patients with adenoviral conjunctivitis at 14-16 days.[60-61] Other studies demonstrate that the adenovirus remains in an active or infectious state on hard surfaces for up to 4-5 weeks.[62-64] The transmission rate to close contacts or family members has been shown to be 10-50% depending on the serotype.[49-51,65-69]

Establishing the right diagnose is the first step to providing appropriate patient management. A thorough clinical exam



Viral Conjunctivitis
Courtesy of the David G. Logan Ophthalmic Pathology Collection, National Eye Institute, National Institutes of Health.

is essential, however, it is often insufficient to accurately differentiate viral from bacterial conjunctivitis, especially in early disease. In more advance cases where the clinical exam is more reliable, it is impossible to determine a patient's infectivity based on signs and symptoms alone. 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 empiric therapies. A sensitive and specific rapid point of care immunoassay can provide an immediate diagnosis and trigger the necessary patient management and treatment plans.

Since adenovirus is extremely contagious and associated with significant morbidity, it is recommended that patients with confirmed adenoviral conjunctivitis remain out of work, school, or day care from 5 days to 2 weeks. Institutional policies often mandate a minimum of 2 weeks out of work.[47,70-71] Another reasonable recommendation is to isolate the patient as long as the eyes remain red and tearing for up to 1 week. In contrast, a patient with bacterial conjunctivitis could be allowed to return to work or school 24-48 hours after initiating appropriate treatment. It is imperative to recommend good hand washing, limit touching their face, and to avoid sharing linens and eye cosmetics (e.g., mascara, eyeliner pencils, etc.). Discarding recently used eye cosmetics or contact lenses may help avoid recontamination and reinfection by these products.

Treatment

The treatment of acute conjunctivitis is controversial. Some recent European studies suggest not treating conjunctivitis because the duration of disease is typically only reduced by 1-2 days.[72-74] This recommendation does not account for the reduction in infectivity that presumably occurs with appropriate treatment.[39-40] Thus, topical antibiotics should be considered for suspected bacterial conjunctivitis.

Historically, clinicians have treated adenoviral conjunctivitis with antibiotics because of the potential for a co-infection or super-infection with bacteria. In general, secondary infections are infrequent[10,75] and bacterial infections typically resolve spontaneously without causing complications outside an immunocompromised host.[76] The typical treatment for adenovirus is based on providing supportive care including artificial tears, cool compresses, and occasionally a topical antihistamine if there is significant itching.

There are many potential topical anti-adenoviral treatments currently being evaluated in clinical trials but it is likely to be several years before any is commercially available. However recently, two off-label treatments for adenoviral conjunctivitis, topical povidone iodine and gangciclovir gel, have become more widely used. Although a study examining infected cells exposed to povidone iodine showed potent anti-adenoviral effects[77], this was not demonstrated in a prospective clinical trial.[78] Gangciclovir was developed for the treatment of herpetic keratitis. However, results from a small, randomized, controlled, masked series of 18 patients with confirmed adenoviral conjunctivitis that were treated with gangciclovir had nearly 1 day shorter duration of disease than those patients treated only with preservative free artificial tears.[79-80]

Topical corticosteroids may make patients feel less symptomatic but have an overall negative impact because their use prolongs viral shedding and increases infectivity.[81-85] Clinicians routinely using steroids may contribute to the epidemic problem.

Topical steroids may be required in the presence of specific criteria. Patients that develop a pseudomembrane should have the membrane stripped using a cotton tip applicator or blunt forceps. These patients are at increased risk to develop secondary conjunctival scarring and foreshortening of the conjunctival fornices and topical steroids should be considered to prevent this permanent anatomical scarring with physiologic consequences.

The risk of activating HSV keratitis makes the widespread use of topical combination agents, an antibiotic and a corticosteroid, concerning. It is not uncommon for HSV conjunctivitis to present in an indistinguishable manner from adenoviral disease.[26]

Additionally, subepithelial corneal infiltrates may necessitate treatment with steroids.[29,57-59] These inflammatory infiltrates, or corneal deposits, should be treated with low dose corticosteroids when there is significant light sensitivity or reduced visual acuity. Once corticosteroid treatment is initiated, it may take many months to taper patients off the medication. Cyclosporine may be used as a steroid sparing agent in some cases requiring long term treatment.[86-87]

Follow up for adenoviral conjunctivitis should be recommended for any symptomatic patients at 7-10 days to evaluate for any signs of long term complications.

Morbidity

Adenovirus conjunctivitis is known to cause considerable morbidity. Once the cornea becomes involved, and subepithelial infiltrates develop, it can be months or even years of poor vision, discomfort [29,57-59,88-89], and may necessitate the need for 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[90], and may result in persistent or permanent dry eyes[91], and the need for chronic tear supplementation. Punctal stenosis or canalicular obstruction can also occur and this may manifest as chronic tearing, or epiphora.[92]

Cost Savings

A cost analysis showed more than $430 million annually that could potentially be saved by appropriately diagnosing and treating conjunctivitis.[6] The majority of the cost savings were related to office visits and unnecessary antibiotic use. The study reaffirms that more than a million patients are likely over-treated with antibiotics each year.

Test	Reference Method	Sensitivity	Specificity	Accuracy
RPS Adeno Detector	PCR	89% (42/47)	94% (130/139)	92% (172/186)
CC-IFA	PCR	91% (43/47)	100% (139/139)	98% (182/186)

Table 1. Summary of the RPS Adeno Detector multicenter clinical trial.[8] CC-IFA = Cell culture with confirmatory immunofluorescence. PCR = Polymerase chain reaction. Adapted from Sambursky R, Tauber S, Schirra F, et al. The RPS Adeno Detector for diagnosing adenoviral conjunctivitis. Ophthalmology. 2006;113:1758-64.

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ADENOVIRAL CONJUNCTIVITIS POST TEST

1) In the US, what is the reported prevalence of conjunctivitis in people between the ages of 1-74?
   a) 88 of every 1,000 people
   b) 1 of every 1,000 people
   c) 13 of every 1,000 people
   d) 50 of every 1,000 people

2) The most frequent cause of conjunctivitis worldwide is:
   a) bacterial
   b) herpes virus
   c) fungal
   d) adenovirus

3) Which of the following is not typically part of a good medical history for conjunctivitis:
   a) history of recent upper respiratory infection
   b) history of family cause of death
   c) history of contact lens use
   d) history of active rheumatologic disease

4) Compared to bacterial conjunctivitis, tender preauricular nodes occur with adenoviral conjunctivitis:
   a) more often
   b) less often
   c) with the same frequency
   d) never

5) Which of the following conditions is not usually confused with adenoviral conjunctivitis?
   a) cataract
   b) epidemic keratoconjunctivitis
   c) bacterial conjunctivitis
   d) periorbital cellulitis

6) Which of the following is highly suggestive of adenoviral infection?
   a) watery discharge
   b) mucoserous discharge
   c) stuck eyelids
   d) small petechial hemorrhages

7) Which of the following laboratory tests is not commonly used due to a time delay in receiving results?
   a) polymerase chain reaction
   b) antigen detection
   c) confirmatory immunofluorescence
   d) cell culture

8) There are how many known serotypes of human adenovirus?
   a) 6
   b) 111
   c) 82
   d) 53

9) In which situation is topical steroid use not indicated for treatment of adenoviral conjunctivitis:
   a) to prevent scarring from a pseodomembrane
   b) for subepithelial corneal infiltrates
   c) when poor vision remains over months or years
   d) when a cataract forms

10) How much could be saved annually by appropriate diagnosis and treatment of adenoviral conjunctivitis?
   a) $76 million
   b) $210 million
   c) $430 million
   d) $760 million

OCULAR Infection & Inflammation

Evaluation/Post Test, Ocular Infection & Inflammation
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Objectives:

1) Recognize symptoms and signs of adenoviral conjunctivitis
2) Review the differential diagnosis and approach to a patient with acute conjunctivitis
3) Perform appropriate diagnostic testing to correctly diagnose adenoviral conjunctivitis
4) Review management and current treatments for adenoviral conjunctivitis

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1. A B C D	4. A B C D	7. A B C D	10. A B C D
2. A B C D	5. A B C D	8. A B C D	
3. A B C D	6. A B C D	9. A B C D	

General Evaluation: Please use the scale below to evaluate this educational activity and objectives. Circle your response.

As a result of completing this offering, I am able to meet the following objectives.	4 Strongly Agree	3 Agree	2 Disagree	1 Strongly Disagree
1. Recognize symptoms and signs of adenoviral conjunctivitis	4	3	2	1
2. Review the differential diagnosis and approach to a patient with acute conjunctivitis	4	3	2	1
3. Perform appropriate diagnostic testing to correctly diagnose adenoviral conjunctivitis	4	3	2	1
4. Review management and current treatments for adenoviral conjunctivitis	4	3	2	1
5. Commitment to change	4	3	2	1
6. The content matches the objectives	4	3	2	1
7. Independent study was an effective teaching method	4	3	2	1
8. Is the article free of commercial bias?	4	3	2	1
9. The time required to complete this offering (in minutes) and take the test was	60	75	90	>90