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## Review

# Adenoviral keratoconjunctivitis: An update<sup>☆</sup>

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## ABSTRACT

The objective of this review is to describe the clinical and epidemiological characteristics of adenoviral conjunctivitis, as well as to present a practical update on its diagnosis, treatment and prophylaxis.

There are two well-defined adenoviral keratoconjunctivitis clinical syndromes: epidemic keratoconjunctivitis and pharyngoconjunctival fever, which are caused by different adenovirus serotypes. The exact incidence of adenoviral conjunctivitis is unknown. However, cases are more frequent during warmer months. Contagion is possible through direct contact or fomites and the virus is extremely resistant to different physical and chemical agents. The symptomatology of conjunctival infection is similar to any other conjunctivitis, with a higher incidence of pseudomembranes. In the cornea, adenoviral infection may lead to keratitis nummularis. Diagnosis is mainly clinical, but its etiology can be confirmed using cell cultures, polymerase chain reaction or immunochromatography. Multiple treatments have been tried for this disease, but none of them seems to be completely effective. Prevention is the most reliable way to control this contagious infection.

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## Queratoconjunctivitis adenovíricas: actualización

### RESUMEN

El objetivo de esta revisión es resumir las características clínicas y epidemiológicas de las queratoconjunctivitis adenovíricas (QCA), así como presentar una actualización práctica sobre el diagnóstico, tratamiento y prevención de estas infecciones oculares.

Dentro de las QCA, existen dos síndromes clínicos claramente diferenciados, la queratoconjunctivitis epidémica y la fiebre faringoconjuntival, que están causados por diferentes serotipos de adenovirus. Su incidencia exacta es desconocida, y los casos son más frecuentes durante los meses cálidos. El contagio se produce mediante contacto directo y por fómites, y los virus son extremadamente resistentes a diferentes agentes físicos y químicos. La sintomatología conjuntival es semejante a la de otras conjuntivitis, con una mayor predilección por la formación de pseudomembranas. En la córnea, la infección adenovírica puede producir infiltrados subepiteliales. El diagnóstico es fundamentalmente clínico, aunque el

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diagnóstico etiológico puede confirmarse mediante cultivos celulares, reacción en cadena de la polimerasa o inmunocromatografía. Se han probado múltiples tratamientos para esta enfermedad, aunque ninguno parece ser completamente eficaz. El método más eficaz para controlar esta infección es la prevención del contagio.

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## Introduction

Infectious keratoconjunctivitis due to adenovirus is an extremely frequent ophthalmological disease produced by various serological subtypes of human adenovirus (HAV) which can present with various symptoms and signs. As there is no exact correlation between the HAV serotypes and the clinical expressions they produce, adenoviral keratoconjunctivitis (AKC) is the term used to define ocular surface infections produced by any of the known HAV serotypes.

AKC comprises 2 clearly differentiated clinical syndromes, i.e., epidemic keratoconjunctivitis (EKC) and pharyngoconjunctival fever (PCF).

The objective of this review is to summarize the clinical and epidemiological characteristics of AKC and to present a practical update on the diagnosis, treatment and prevention of said ocular infections.

## Microbiology

Adenovirus were first described in 1953 by Rowe et al.<sup>1</sup> who observed that the human lymphoid tissue suffered a characteristic spontaneous degeneration when maintained in culture several weeks after surgical extraction. In 1955, Jawetz et al.<sup>2</sup> were the first to attribute the etiology of EKC to the infection of ocular surface tissue caused by HAV.

Since their discovery, 51 different types of adenovirus have been described.<sup>3</sup> Among them, 7 have high affinity with the conjunctival epithelium and can produce AKC (serotypes 3,<sup>4</sup> 4,<sup>5</sup> 7, 8,<sup>2,6</sup> 11, 19,<sup>6</sup> 37<sup>7,8</sup>).

Adenovirus are virus with double-stranded DNA having 90–100 nm diameter, without cover and with icosahedral capsid having 20 sides and 12 vertices, made up of 252 subunits called capsomeres. DNA has a molecular weight of  $23 \times 10^6$  Da, and represents 10–15% of the virus mass.<sup>9</sup>

HAV are able to interact with human cells in 3 ways:

- *Lytic infection*, involving epithelial cells. The virus completes its multiplication cycle, producing cellular death and releasing between  $10^4$  and  $10^6$  new viruses, of which between 1% and 5% are infectious.
- *Latent infection*, involving lymphoid cells such as those in which the virus was first isolated.<sup>1</sup> Only small amounts of virus are released and the cellular death rate is offset by normal multiplication.
- *Oncogenic transformation*. The viral DNA is included in the cellular genetic material and replicates inside it without producing a new infectious virus.

HAV are very stable against chemical and physical agents as well as in adverse pH conditions. This allows them to survive for long periods of time outside the body and water. Studies have demonstrated that they are able to remain feasible maintaining infectious concentrations even after 28 days on a metal or plastic surface.<sup>10,11</sup>

## Epidemiology

AKC is one of the most frequent ocular diseases, exhibiting ubiquitous distribution. Due to its high frequency and that many of the cases do not obtain medical help it is impossible to develop precise statistics about its incidence. In addition, there are no reliable data about the social and health costs caused by this disease.

HAV can give rise to epidemic outbreaks both in the general population and in hospital environments. In fact, AKC is the most frequent hospital ophthalmological disease.<sup>7,12</sup> The incidence of AKC, particularly the one related to serotypes 3, 4 and 37, increases in summer when temperature rises.<sup>13</sup> EKC outbreaks have been mainly associated to serotypes 8, 19 and 37, while PCF cases have been related more with serotypes 3, 7 and 11.<sup>14</sup>

The most frequent transmission of HAV is direct from person to person through the respiratory or fecal-oral pathways, although transmission can also occur through fomites. The virus can be easily isolated from ocular secretions of patients for at least 9 days since the onset of symptoms.<sup>15</sup> In the ophthalmology practice there is a risk of transmission through contact tonometry, use of eyedrops and through the hands of health professionals.<sup>7,10,16</sup> In the general population the risk of contagion from the patients to domestic contacts is of approximately 10%, with the risk increasing in cases of prolonged disease.<sup>6</sup>

## Clinical syndromes

HAV infections can produce 2 different clinical syndromes with ocular involvement: EKC and PCF.

### Epidemic keratoconjunctivitis

EKC is a form of conjunctivitis that produces epidemic outbreaks in hospitals,<sup>7</sup> swimming pools,<sup>4,5</sup> barracks, schools and other communities. The incubation period varies between 4 and 24 days and, even though it is likely that the disease is no longer contagious during this period, Kimura et al.<sup>17</sup> did not find virus through the polymerase chain reaction (PCR) in conjunctival exudates obtained previously at the onset of symptoms. EKC is a slow onset and predominantly

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