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Review

Prevalence of adenoviruses as ocular disease causatives in Saudi Arabia

Saleha Kheder Alatawi^a, Hanan E Alyahyawi^b, Naseem Akhter^b, Raed A. Alharbi^b,
Waled AM Ahmed^c, Shaia Saleh R. Almalki^{b,*}^a Department of Optometry, Faculty of Applied Medical Sciences, Albaha University, Saudi Arabia^b Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Saudi Arabia^c Department of Nursing, Faculty of Applied Medical Sciences, Albaha University, Saudi Arabia

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ABSTRACT

Although Human Adenoviruses outbreaks are rare, there still could be a potential chance for those viruses to mutate and spread quickly in human populations with severe public health and socioeconomic consequences. Outbreaks often spread fairly quickly with considerable morbidity/mortality. Saudi Arabia's geopolitical and religious significance bring with it, millions of pilgrims, and tourists yearly. This presents a significant potential for HAdVs epidemics. This review shows that even with the mushrooming serotypes and genotypes, the scholarly knowledge on the nature, structure, transmission, and management of HAdVs is already well-established. Significant research is ongoing on pharmacological interventions, which, presently remain speculative and lacking in effectiveness. This review similarly uncovers a shortage of literature, both recent and dated, on epidemic keratoconjunctivitis in either Saudi Arabia or the Middle East.

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* Corresponding author at: Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Albaha Saudi Arabia.

E-mail addresses: almalkishaia@hotmail.com, shalmalki@bu.edu.sa (S. Saleh R. Almalki).

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1. Introduction

Human adenoviruses (HAdVs) are among the most prevalent pathogens. HAdVs diseases are ordinarily mild, but some serotypes can cause acute infections that present severe and even fatality risks in immunosuppressed patients, the elderly, and children. (Crenshaw et al., 2019; Dodge et al., 2021) At present, there are up to 67 known HAdVs serotypes (and upwards of 85 genotypes), that have been identified and comprise 7 species (HAdVs A–G). (Lion, 2014; Horton and Miller, 2015) The different species present in different tissue tropism, causing equally varied clinical manifestations. (Ismail et al., 2016) Some of species are linked to severe infections leading to conjunctivitis, gastroenteritis and diarrheal illnesses, febrile respiratory illness, pharyngoconjunctival fever, acute haemorrhagic cystitis, and meningitis. (Crenshaw et al., 2019) The current review begins with an overview of viruses with known severe ocular manifestations before delving into HAdVs. The review identifies and critically discusses the extant literature on the HAdVs' structure, transmission, replicative cycle, current pharmacological and therapeutic management approaches, as well as the relevance of the same in Saudi Arabia.

1.1. Search strateg

This study adopted two search strategies: HAdV/viruses that cause ocular diseases and HAdV/EKC in Saudi Arabia. The following databases were searched: PubMed, ProQuest, Google Scholar, Medline, ProQuest, EBSCO, and Scopus. The search strings were derived from the preliminary reviews. The search strings included “epidemic keratoconjunctivitis/EKC”, “adenoviruses structure”, “adenovirus management”, “epidemic keratoconjunctivitis/EKC in Saudi Arabia”, “EKC epidemiology in Saudi Arabia”, “prevalence of EKC in Saudi Arabi”, “EKC in Saudi Arabia”, “treatment of EKC in Saudi Arabia”. Searches using strings modified with serotypes HAdV-3, HAdV-4, HAdV-8 (Lei, et al., 2016), HAdV-19, HAdV-22, and HAdV-37. HAdV-8, HAdV-37, HAdV-53, HAdV-54, HAdV-57, and HAdV-64 were similarly conducted. In respect to the first phase of the review, all peer-reviewed works (including textbooks and journals) were selected based on the subjective relevance in answering the research question. In respect to the second phase of the study, only peer-reviewed, primary research sources that covered HAdV outbreaks, incidences, detection, infection control knowledge, and management of epidemic keratoconjunctivitis or any other HAdV serotypes (with ocular involvement) between 1970 and 2021 as very few sources were found. A total of 5 sources met the inclusion criteria for Saudi Arabia. There were no papers that met this criteria.

1.2. Viruses causing eye infections

A large number of viral infectious diseases have ocular manifestations that include keratitis, retinitis, uveitis, conjunctivitis, intraocular/orbital worm, Parinaud's oculoglandular syndrome, proptosis, and lesions of the adnex. (Guerrant et al., 2011; Ritterband and Friedberg, 1998) These infections, particularly onchocerciasis, leprosy, trachoma, and measles cause significant visual loss. (Ritterband and Friedberg, 1998) Eye infections often follow direct external exposure to viruses, either through infected secretions inside the birth canal (e.g., human papillomavirus and herpes simplex), or airborne particles (rhinovirus), or on fomites (adenovirus). (Alves et al., 2013; Ocular and Overview, 2008) The viruses may also be acquired via viremia (e.g., measles and human cytomegalovirus, measles virus), ([10]) extensions from contiguous adnexal disease, upper respiratory tract spread, and transplacental passage. (Guerrant et al., 2011; Cunningham and Zierhut, 2020)

The ocular manifestation of enteroviral infections, including coxsackievirus, echovirus, poliovirus, and enterovirus, such as acute haemorrhagic conjunctivitis, and dysfunction in acute enteroviral neuropathy is common. (Guerrant et al., 2011) While acute haemorrhagic conjunctivitis (AHC) is often caused by adenoviruses, it is mainly caused by two enteroviruses, coxsackie A24 variant and enterovirus 70. (Guerrant et al., 2011; Romero and Modlin, 2015) AHC epidemics due to coxsackie A24 have been reported in Pakistan, Spain, China, India, Korea, and Singapore since 2000. (Romero and Modlin, 2015) Non-enteroviral infectious agents, including *Neisseria* species, pneumococci, haemophilus species, herpes virus, (Romero and Modlin, 2015) Newcastle disease virus, and Chlamydia may similarly cause haemorrhagic conjunctivitis. (Guerrant et al., 2011) Hyperacute conjunctivitis is caused by *Neisseria gonorrhoeae*, (Isada and Meisler, 2008) and *Neisseria meningitidis*, (Dryden, 2016).

Poliomyelitis rarely has ocular manifestations. (Guerrant et al., 2011) Some patients, however, experience an involvement of the 9 and 10 cranial nerves, with more than 10% of them presenting with cranial nerve effects on the eyes and orbital musculature. (Guerrant et al., 2011) Conjunctivitis can present as part of influenza infection, particularly of Avian influenza A (H5N1 and H7N7). (Guerrant et al., 2011) According to Fouchier, et al., for example, up to 90% of patients with H7N7 during the 2003 epidemic in the Netherlands presented with conjunctivitis. (Fouchier et al., 2004) Lymphocytic choriomeningitis virus can induce illnesses similar to influenza. (Bonthius, 2012) Like influenza, other RNA viruses infect nearly all ocular tissue. (Chodosh et al., 2008) When the rubella virus is acquired in utero, it can have severe effects on the eye. (Chodosh et al., 2008)

According to Winchester, et al., Khazaeni, and Guerrant, epithelial keratitis occurs in patients with rubella virus, adenovirus, herpes simplex virus, herpes zoster virus, mumps virus, measles virus, enterovirus, and Rift Valley fever virus. Keratitis occurs in up to 10% of patients with rubella virus. (Guerrant et al., 2011) Its ocular manifestations can occur in more than 50% of neonates and are characterised by patchy black retinal pigmentation even though visual acuity may not be affected. Cataracts present in more than 15% of patients with congenital rubella, while other patients may present with glaucoma, microphthalmia, buphthalmias, nystagmus, and retinal neovascularization. (Khazaeni, 2017; Arnold et al., 1994)

Haemorrhagic conjunctivitis due to viral infection could be caused by haemorrhagic fever virus (such as Ebola). (Guerrant et al., 2011) Mumps, on the other hand, produces dacryoadenitis, which may present as erythema and edema of the conjunctiva and the supertemporal lid. Other viruses include: Rift Valley fever virus, hepatitis viruses, cytomegalovirus, herpes simplex viruses, herpes zoster virus, rubella virus, Epstein–Barr virus enterovirus, influenza viruses, hantavirus is also linked to posterior uveitis and anterior uveitis. (Guerrant et al., 2011)

Ocular morbidity was associated with the viral infections by Herpesviruses, varicella-zoster virus (VZV). (Gargouri et al., 2016) Cytomegalovirus (CMV), (Ritterband and Friedberg, 1998) and herpes simplex (HSV). (Carmichael, 2012)

While the ocular disease is typically caused by type 1 (HSV-1) herpes simplex, type 2 (HSV-2) variety is also known to cause asymptomatic as well as active disease in a large variety of ocular structures. (Guerrant et al., 2011; Carmichael, 2012) Up to 6% of herpes infections are not ocular. Ocular and skin/vesiculation involvement present in up to 20% of infected patients/neonates, ordinarily as non-follicular conjunctivitis but may also involve cataracts, optic neuritis, iritis, chorioretinitis scarring, keratitis, acute necrotizing, optic neuritis, iritis, and optic atrophy. Non-neonatal ocular HSV manifestation can be due to both primary infection and reactivation, of which, epithelial keratitis, is the most common

manifestation. (Guerrant et al., 2011; Ritterband and Friedberg, 1998)

Human immunodeficiency viruses also have ocular manifestations, including opportunistic ocular infections. (Grulich and Vajdic, 2015) Epstein–Barr Virus, on the other hand, manifests as mild conjunctivitis as well as stromal and superficial keratitis. (Cunningham and Zierhut, 2020; Longo et al., 2018) More recent literature, including Seah and Agrawal show that SARS-CoV-2 may cause ocular infection in animals through diverse mechanisms, manifesting in the form of anterior segment pathologies like conjunctivitis as well as anterior uveitis to severe conditions like optic neuritis and retinitis. (Seah and Agrawal, 2020)

Other microorganisms that cause haemorrhagic conjunctivitis include the following bacteria: Pneumococci, (Marimon et al., 2013; Norcross et al., 2010) haemophilus species, (Inada et al., 2019) Neisseria species, trichinella species, (Luis Muñoz-Carrillo et al., 2019) as well as some of rickettsia species. (Brissos et al., 2015)

1.3. Adenovirus

Initially isolated from adenoid tissue in 1953, HAdVs are non-enveloped, double-stranded DNA viruses (diameter of 70 to 100 nm) with more than 60 types3, (Yao et al., 2019) The initial 51 serotypes were classified by way of serum neutralisation based on the epsilon determinant, but these approaches have since been superseded by whole genome sequencing and molecular genotyping. Up to 103 HAdV genotypes and more than 60 serotypes belonging to the genus Mastadenovirus (of the adenoviridae family) have been identified and comprise 7 species (HAdVs A–G). (Lion, 2014; Jonas et al., 2020) New types are created in settings of co-infection by way of homologous recombination during viral replication. (Ismail et al., 2016)

The different species present in different tissue tropism, causing equally varied clinical manifestations. (Ismail et al., 2016; Yao et al., 2019; Pscheidt et al., 2021) Species B, C, and E (serotypes 3, 5, and 7) mainly cause respiratory infections (Scott et al., 2016); F and G (serotypes 40 and 41) affect the gastrointestinal tract; and B, D, and E (serotypes 3, 7, 8, 11, 19, and 37), are associated with conjunctival infections (Jonas et al., 2020); (Pscheidt et al., 2021; Walter and Wunderink, 2017); According to Hashimoto et al., as cited in Jonas, et al., the recent isolation of HAdV-85 from subepithelial infiltrations-associated adenoviral conjunctivitis suggests that not all possible etiologies of EKC-causing etiologies have been elucidated, effectively meaning that the understanding of the same remains limited. Important lessons may be drawn from the inaccurate ascription of HAdVD19 as the primary cause of EKC, which persists in some literature. (Jonas et al., 2020)

The primary sites of infection for HAdVs include the intestinal tract (diarrheal and gastroenteritis illness), the respiratory tract, and the corneal epithelia. (Lynch et al., 2019) They (mainly serotypes 1–7) are estimated to account for 1%–10% of respiratory infections, more than 80% of which occur in children below the age of 5. (Lynch et al., 2019; Khanal et al., 2018; Huang et al., 2014; Pond, 2005). Urinary tract involvement is equally possible, particularly among transplant recipients, presenting as allograft dysfunction or haemorrhagic cystitis. (Khanal et al., 2018; Pond, 2005)

1.4. Structure

The virus is such that the core proteins and viral DNA are encased inside an icosahedral capsid, with 20 triangular faces (and 12 fivefold (240) capsid vertices) that primarily contain hexon/capsid protein, fibre proteins, and penton. (Jonas et al., 2020) Towards the proximal end, the elongated fibres are bound

to pentameric structures (penton bases), while at the distal ends, the fibres form into globular domains. The fibre knobs act as primary attachment sites for cellular receptors. The penton bases, on the other hand, are generally involved in secondary interactions necessary for the virus to gain entry into the host cells. (Dodge et al., 2021; Jonas et al., 2020; Aoki et al., 2011; Cheng et al., 2016) Since they are non-enveloped, HAdVs have been shown to survive environmental desiccation for up to two months. (Ganime et al., 2014) While HAdVs can resist many disinfectants, (Dodge et al., 2021; Cheng et al., 2016; Kaneko et al., 2008), Mattner, et al. show that they can be inactivated by 95% ethanol solution, heat, bleach, and formaldehyde.

1.5. Transmission

HAdVs are ordinarily spread from person to person. (Dodge et al., 2021) HAdVs can infect and replicate within epithelial cells in the respiratory tract, urinary bladder, eyes, and gastrointestinal tract. (Crenshaw et al., 2019) They cause latent infections in lymphoid cells. Infections occur from exposures to infected persons through respiratory routes (inhalation of aerosolised droplets), faecal contamination or faecal-oral spread e.g., through contaminated food/water and ineffectively chlorinated public swimming pools, (Aoki et al., 2011) conjunctival inoculation, and/or direct bodily contact with contaminated fomites. (Dodge et al., 2021; Khanal et al., 2018) Latent infections can become reactivated. Lastly, viral mutations can cause new zoonotic infections. (Dodge et al., 2021) Consequently, close exposure to infected persons, lack of proper hand hygiene, and food/water contamination are the main risk factors. (Crenshaw et al., 2019)

The three-phase viral entry into cells and the replicative cycle are both dynamic and complex. It begins with the elongated fibre proteins attaching to the coxsackie and HAdV receptors that are found on several membrane cofactor proteins (for HAdV-C). Other HAdVs use CD46, CD80, CD86, heparan sulfate, GD1a, sialic acid, desmoglein-2, or polysialic acid for attachment. (Khanal et al., 2018) Except for variant D, the receptors are not used simultaneously. Once the virus binds itself to the receptor, a clathrin-dependent internalization process occurs, ordinarily mediated by an RGD peptide in the base penton, which acts as a recognition site for multiple cellular integrins belonging to the heterodimeric adhesion receptors ($\alpha\beta$). When the integrins, specifically vitronectin receptors $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 1$, $\alpha 5\beta 1$, and $\alpha 3\beta 1$ engage with the penton case, the PI3 kinase, P130, Rho GTPases, and other signals are emitted to initiate viral internalisation. (Khanal et al., 2018; Lyle and McCormick, 2010; Zhang and Bergelson, 2005) Once internalised, integrin-mediated endocytosis occurs, causing viral particles to be uncoated. (Zhang and Bergelson, 2005) The virion undergoes dynein-dependent translocation inside the cytoplasm, where virion structural proteins direct the partially disassembled viral particles towards the nuclear pore complex by way of microtubules. (Khanal et al., 2018) The virion detaches and binds onto the nuclear pore complex once it arrives at the perinuclear microtubule organizing centre, causing the capsid to disassemble before the associated PVII core proteins organize the HAdV genome into structures similar to nucleosomes. (Dodge et al., 2021; Zhang and Bergelson, 2005)

Several components of acquired and innate immunity are capable of blocking receptor interactions, viral entry, endosomal penetration, and ultimately, translocation. (Khanal et al., 2018; Smith and Nemerow, 2008) According to Khanal, et al., for example, human alpha-defensins that bind directly to, and prevent viral capsid, have shown considerable potential, but more empirical backing of the same is still needed.

Once a person becomes infected, the incubation period for EKC is about a week and the virion remains highly infectious between

2 days and 14 days. (Dodge et al., 2021; Aljohani et al., 2021; Gonzalez et al., 2019; Tabbara et al., 2003) According to Aoki, et al., patients are contagious when they become symptomatic and remain so for up to two weeks afterward. Outbreaks occur in crowded populations, including military bases, schools, and nosocomial facilities. (Aljohani et al., 2021)

1.6. Epidemiology

While the incidence and prevalence of adenoviral infections are largely unknown since the majority of cases are mild (self-limited or managed by optometrists and general practitioners), (Pond, 2005; Lynch and Kajon, 2016) they are abundant and widespread. (Lynch and Kajon, 2016; Wu et al., 2008) In the recent few years, particularly in Asia (China, Malaysia, and South Korea), HAdVs outbreaks have been reported. (Yao et al., 2019; Wu et al., 2008) Latent HAdVs, which may reside in the renal parenchyma, lymphoid tissue, as well as other tissues following inoculation, can be reactivated among immunosuppressed patients (Lynch & Kajon, 2016). Immunosuppressed patients may present with more severe/disseminated infections and reactivations. (Yao et al., 2019) Ismail, et al. and Jonas, et al., the isolation of HAdV species D (serotypes 43–51) were isolated from HIV/AIDS patients, in part because immunosuppression creates conditions that favour viral persistence as well as co-infection, which in turn generate homologous recombination among viruses. According to Khanal, et al., HAdV diseases in immunosuppressed patients may be associated with de novo infection or reactivations of latent viral pools. (Khanal et al., 2018)

HAdVs species A-F circulate globally, with types varying from one time period, country, and geographical region, to another. (Yao et al., 2019; Khanal et al., 2018) People can carry HAdVs asymptomatically for up months, with such infections spreading in closed populations. (Cheng et al., 2016) According to Ryan and Lynch & Kajon, adenovirus is the leading cause of viral ocular infection. Khanal, et al. and Dodge, et al. estimate that HAdV, specifically variants B, D, and E (serotypes 8,19, and 37) account for up to 90% of all viral conjunctivitis infections. The majority of patients complain of flu-like symptoms including malaise, fever, diarrhoea, myalgia, and respiratory symptoms. (Khanal et al., 2018)

Acute infections produce a stereotypic change in ocular tissues, inducing the formation of ulcers and vesicles. (Chodosh et al., 2008) Viral conjunctival infections cause vasodilation, severe discharge, hyperplasia of conjunctival lymphoid follicles, inflammation of corresponding draining lymph nodes, and serous discharge. Severe infections may scar the globe permanently and turn the eyelashes in against the eye. (Gonzalez et al., 2019)

1.7. Keratoconjunctivitis

Initially described in the 19th century as superficial punctate keratitis and nummular keratitis, EKC is primarily associated with serotypes HAdV-3, HAdV-4, HAdV-8 (Lei, et al., 2016), HAdV-19, HAdV-22, and HAdV-37. (Aoki et al., 2011; Lynch and Kajon, 2016) HAdV-8, HAdV-37, HAdV-53, HAdV-54, HAdV-57, and HAdV-64 lead to severe tissue inflammation. (Jonas et al., 2020) It is a key cause of ocular morbidity and may lead to complete visual loss. (Aoki et al., 2011) Its clinical ocular manifestations are threefold: pharyngoconjunctival fever (serotypes 3, 7, and 14), epidemic keratoconjunctivitis (EKC), and non-specific/follicular conjunctivitis (serotypes 3, 4, and 7). (Jonas et al., 2020; Aoki et al., 2011; Lynch and Kajon, 2016; Lynch et al., 2011) EKC is a severe infectious eye infection that is often related to HAdV-8, which has been isolated in both sporadic and epidemic cases. (Lei et al., 2017)

The literature emphasises the need for continued research to identify diagnose and investigate causal/transmission routes as a way of stopping the spread of EKC. (Dodge et al., 2021; Aoki et al., 2011; Lei et al., 2017) Lei, et al.'s investigation of the 2016 EKC outbreak in China, for example, associated the outbreak with HAdV-8, which had been circulating in Tibet for more than eight months before the actual outbreak. However, the lack of epidemiological surveillance meant that both the route and origin of HAdV-8 transmission remained unknown. (Lei et al., 2017)

In addition to the common HAdVs associated with EKC, HAdV-53, HAdV-54, and HAdV-56 have been identified in EKC outbreaks in China and Japan. (Huang et al., 2014; Walsh et al., 2009) Surveillance data in Japan for ocular infections over three decades revealed an increase in the EKC frequency involving HAdV-53, HAdV-54, and HAdV-56 over ten years since 2008. According to the report, the outbreaks resulting from recombinant strains across Europe, America, and Asia caused heightened awareness of the need for surveillance/control as well as the establishment of comprehensive criteria for diagnosing EKC and developing antiviral treatments. (Institute and of Infectious Disease and Tuberculosis and Infectious Diseases Control Division. Adenovirus infections, 2008) Owing to the contagiousness and epidemic potential of EKC, an increasing amount of literature focuses on EKC's clinical features and diagnostic challenges. (Aoki et al., 2011) Aoki, et al., for example, analysed and compared clinical features of adenoviral conjunctivitis against non-adenoviral follicular conjunctivitis at first contact with a health facility. (Aoki et al., 2011)

1.8. Clinical features

There is no perfect etiological or clinical diagnostic approach for EKC, with current methods being dependent on antigen detection by way of immunochromatography or immunofluorescence, molecular methods like a polymerase chain reaction, as well as culture isolation. (Gonzalez et al., 2019) This is even more so because infections by agents such as herpes simplex, Coxsackievirus group serotype A24, enterovirus 70, and Chlamydia exhibit similar symptoms. (Dodge et al., 2021; Jonas et al., 2020) While immunochromatography kits are fairly cheap and efficient, their accuracy is heavily limited by both the stage of infection and sensitivity of up to 91% depending on the number of viral copies in the eye. (Gonzalez et al., 2019)

It is characterised by conjunctival follicular hyperplasia and exudation, punctate or geographical epithelial keratitis, as well as conjunctival epiphora and chemosis. (Khanal et al., 2018) Its defining feature is the corneal subepithelial infiltrates that cause sensations of foreign objects, glare, reduced/blurred vision, and photophobia, which may persist for years after treatment. Others include pain, conjunctival haemorrhage, and preauricular lymphadenopathy. (Kaneko et al., 2008; Aoki et al., 2011; Gonzalez et al., 2019; Abdelkader, 2014) In some cases, patients present with flu-like symptoms such as fever and myalgia. Whenever infections affect the cornea, corneal erosion, ulceration, and filamentous keratitis may occur, coupled with the formation of several subepithelial corneal infiltrates that are induced by the inflammatory response. Spotted opacities under the epithelium may persist for up to several months/years and ultimately cause sight degradation, irregular astigmatism, and glare sensation. (Horton and Miller, 2015; Aydin Kurna et al., 2015) MRI imaging of typical EKC cases shows inflammatory processes extending deep into the orbit. (Horton and Miller, 2015) In a study of 102 potential cases of EKC, Horton and Miller suggested that acute bilateral follicular conjunctivitis, multiple subepithelial corneal infiltrates, and intrafamilial infection are strong symptoms of EKC in the earliest stages of infection. Even so, Gonzalez, et al., 50% of cases hardly

present with multiple subepithelial corneal infiltrates. (Gonzalez et al., 2019)

Mochizuki, et al., Gonzalez, et al., and Dodge, et al. find that adenoviral EKC is distinguishable by punctate haemorrhage within the palpebral conjunctiva that could be distinguished from the spots of minor haemorrhage on the bulbar conjunctiva that presents in patients with severe haemorrhagic conjunctivitis, particularly among paediatric patients with EKC (even though the possibly immature conjunctival epithelial cell layer in infants may mean that similar symptoms may present for chlamydia). (Dodge et al., 2021)

1.9. EKC epidemiology in Saudi Arabia

According to Tabbara, et al., Saudi Arabia's position in Islam and as a destination for Hajj and Umrah pilgrimages, is such that it received between 2.5 and 7.5 million pilgrims annually in 2012 to 2019. (Demography, 5/2018.; Puri-Mirza, 2020) This brings with it a broad range of infections, including adenoviruses. (Tabbara et al., 2003; Tabbara et al., 2010) Ocular infections with adenovirus 21, for example, were originally isolated in Saudi Arabia in 1960 from a visiting Italian family. It was subsequently isolated in the Netherlands, the UK, and India. (Darougar et al., 1978) Kamalpour, et al. found that 22.7% of 338 Iranian Hajj pilgrims tested positive for HAdVs, of which HAdV-6 was the most frequently detected, followed by HAdV-1, 2, 5, and 57. Akhtar, et al. provided the first detailed epidemiological study of gastrointestinal adenoviral infections in Saudi Arabia. There is, however, little literature on the epidemiology and management of ocular HAdVs in Saudi Arabia.

Tabbara, et al. sought to determine adenoviral infections among patients presenting with viral keratoconjunctivitis at an eye clinic in Riyadh and their correlations with the severity of complications with the variants. (Tabbara et al., 2003) Of the 37 patients with viral keratoconjunctivitis, 68% tested positive for HAdV-8, while 56%, 19%, and 10% tested positive for HAdV-37, 22, and 19, respectively. Up to 83% and 57% of the patients of serotypes 8 and 57 presented with preauricular lymph node, respectively, while 42% and 50% of patients with HAdV-8 and 27 presented with pseudomembranous conjunctivitis. Both persistent nummular corneal opacities and superficial punctate keratitis were presented among patients with HAdV-8 and 19. HAdV-4, 22, and 37 were associated with mild follicular conjunctivitis or other corneal complications. (Tabbara et al., 2003)

Until Tabbara, et al., there had been no studies into the clinical manifestations of adenoviral keratoconjunctivitis as well as their correlations with HAdVs serotypes in Saudi Arabia (Tabbara et al., 2010). This study undertook a non-interventional observational study using a sample of 65 patients (aged 2–63 years) at an eye clinic in Riyadh with symptoms of acute adenoviral keratoconjunctivitis. A substantial proportion of keratoconjunctivitis are HAdVs negative at presentation and subsequently developed subepithelial infiltrates (SEIs). HAdVs serotypes 3, 5, 8, and 37 were identified in 11%, 6.8%, 67.1%, and 8.2% of the patients, respectively. HAdVs serotypes 14, 19, and 22 were identified in 1.4%, 2.7%, and 2.7% of the patients, respectively. (Tabbara et al., 2010) Further, Tabbara, et al. determined that the prevalence of membranous conjunctivitis occurred in 83% of eyes with HAdV serotype 37, while subepithelial corneal opacities was identified in 47% of eyes with HAdV serotype 37. The immunochromatography test returned a positive result in 65% of the eyes. (Tabbara et al., 2003; Tabbara et al., 2010)

Abdelkader documents the 2013 outbreak of EKC in southern Saudi Arabia using a sample of 250 patients with patterns of EKC at a corneal specialty facility in Abha, including a description of a range of HAdV. The most common symptoms of EKC included follicular conjunctivitis (100%), subepithelial infiltrates (76%),

enlarged pre-auricular lymph nodes (68%), bilateral preauricular lymphadenopathy, and conjunctival chemosis (76.8%). Pseudo membranes (clots of exudates adhered to the lower or upper tarsal conjunctiva) developed 1–2 weeks, while SEIs (involving the visual axis) presented in 76% of the patients, with sub-corneal epithelial infiltrates presented for more than six months in 150 cases. Topical corticosteroids appeared to accelerate regression of SEIs, but keratitis did not present among patients under the age of ten. Patients with corneal involvement regained full vision, except for those acute superficial keratitis. (Abdelkader, 2014) Similar outbreaks were reported in Japan and China. (Yao et al., 2019; Wu et al., 2008)

2. Management

According to Dodge, et al., supportive care and whenever relevant immunosuppression is important management strategies. This includes medications to reduce discomfort, such as artificial tears and cool compresses, as well as topical non-steroidal anti-inflammatory agents. Conjunctival membranes should be removed carefully as and when they develop. At present, there are no approved antivirals for treating HAdV infections, but off-label broad-spectrum antivirals such as ganciclovir, ribavirin, and cidofovir are recommended. (Dodge et al., 2021; Kuwatsuka et al., 2020) Ribavirin has, however, been shown to have little, if any effect in the treatment of HAdV, and even if it were, minor amino acid changes in the virus may make viruses resistant. Off-label use of cidofovir for severe HAdV illnesses has demonstrated some clinical benefits even though the empirical evidence is inconclusive, but its poor bioavailability and rapid uptake (coupled with slow releases) is associated with severe nephrotoxicity. (Dodge et al., 2021)

Novel antivirals that attempt to overcome the limitations of cidofovir, such as *brincidofovir* have been developed. In common with *ganciclovir*, *brincidofovir* is activated by intracellular modification (cellular phospholipases coupled by phosphorylation by cell kinases). In vitro studies have shown *brincidofovir* to be effective against HAdVs at much lower concentrations compared to cidofovir. (Hartline et al., 2005) efficacy remains low and is unapproved for treating HAdV infections. It can also induce severe but reversible kidney injury. (Faure et al., 2016; Grimley et al., 2017)

Post-entry inhibitors have shown promise in preventing the entry and replication cycle of HAdVs. Topical corticosteroids significantly relieve acute symptoms of infection, even though data from animal trials show that corticosteroid use at acute phases of ocular HAdV infection increases viral shedding. (Romanowski et al., 2001) Other interventions include DNA replication inhibitors and host-directed therapies potentially cause toxicities and drug resistance may occur against some HDT agents. (Crenshaw et al., 2019; Dodge et al., 2021; Kumar et al., 2020) HAdV gene expression disruptors have been theoretically and in-vitro trials have been shown to have anti-HAdV properties but there no actual drugs that work this way. (Saha et al., 2019) Epigenetic regulator-based inhibitors can disrupt replication of HAdV through a number of mechanisms but can result in viral reactivation from tonsil tissue, which is indicative of the possibility that their activity may be different in in-vitro and in-vivo research. (Dodge et al., 2021; Lynch and Kajon, 2016; Saha et al., 2019) Protease-inhibitors involved in the onset of ocular pathologies like $\alpha 2$ -macroglobulin, metalloproteinase inhibitor, $\alpha 1$ -proteinase inhibitor, metalloproteinase inhibitor *maspin* and SERPINA3K potentially play a role in molecular remodeling leading to some ocular diseases. (Pescosolido et al., 2014) Other therapeutics include nuclear transport inhibitors and CDK inhibitors. (Dodge et al., 2021; Jonas et al., 2020) Emerging therapeutic approaches include T-cell immunotherapy, combination therapies,

synthetic lethality and drug repositioning to overcome viral mutations. (Dodge et al., 2021)

3. Summary

HAdVs are highly infectious agents that result in considerable morbidity and death, especially in at-risk populations. Epidemic outbreaks occur far too often, helped by, among others, the lack of effective antiviral interventions, diagnostic difficulties, high infectivity, and lack of early diagnosis. (Gonzalez et al., 2019) Even with the continual emergence of recombinant strains, (Lion, 2014; Jonas et al., 2020) robust knowledge about HAdVs and their ocular involvement already exists, (Ismail et al., 2016; Aljohani et al., 2021) except when such knowledge is a function of geography and Saudi Arabia's geopolitical/religious circumstances. (Abdelkader, 2014) The shortage of literature on EKC outbreaks, the nature of HAdV strains circulating in the country and neighbouring regions, as well as the extant management approaches and preparedness to manage future outbreaks presents both a challenge and research/policy opportunities. (Gonzalez et al., 2019; Tabbara et al., 2003) There is a realisation in the literature for safer and more effective antiviral drugs. (Jonas et al., 2020; Aoki et al., 2011)

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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