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REVIEW

Adenoviral Keratoconjunctivitis

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الْتِهابُ القَرْنِيَّةِ والمُلْتَحِمَة بالرواشح الغُدَّانيَّة

اليكساندر بيالاسويكز

الملخص: يعتقد أن معظم حالات التهاب القرنية والملتحمة يسببها الراشح الغداني. هذه المراجعة تركز على صفات أمراض العين التي يسببها الراشح الغداني، وطريقة الانتقال، والأعراض والعلامات، وكذلك التدخل المتاح، وطرق الوقاية. يمكن أن نستنتج بأن مُكَافَحَةُ الأَمْرَاضِ المُعْدِيَة تعتبر بشكل واسع الحجر الأساس في السيطرة على انتقال الراشح الغداني، وتقليل المعاناة والهدر الاقتصادي.

مفتاح الكلمات: الرواشح الغدانية، التهاب القرنية والملتحمة، العين، السيطرة على العدوى.

ABSTRACT Acute epibulbar infections in humans are one of the most frequently diagnosed eye diseases. The majority of these are thought to be caused by the adenovirus. This review focuses on the features of the human adenovirus eye diseases, mode of transmission, signs and symptoms, available interventions, and preventive measures. It is concluded that infection control is still widely accepted to be the key to the management of human adenovirus infection in order to prevent the spread, individual suffering and economic damage.

Key words: Adenovirus, Keratoconjunctivitis, Eye, Infection control

Acute epibulbar infections in humans are one of the most frequently diagnosed eye diseases, comprising 2.3-10% of all ophthalmological diagnoses, with a prevalence of 0.6-3.5 new cases per 1,000 patients in Oman. Although almost any microbe can elicit an inflammation in the outer eye, about 92% of these are thought on clinical grounds to be caused by adenovirus-associated epidemic keratoconjunctivitis. In healthy eyes, most of these infections are self-limited and without late sequelae, but in compromised surface conditions vision-threatening sequelae may result.[1, 2, 3]

The identification and notification of patients harbouring conditions and infections with a high morbidity (e.g. loss of workdays, high disability adjusted life years) and with nosocomial relevance is very important for the economy of a country.[3, 4, 5]

This overview will focus on the clinical ophthalmology of adenovirus infections, which plays a key role in this scenario. The ophthalmologist can make a focused differential diagnosis taking a detailed history (contacts, course), asking for symptoms and observing signs by biomicroscopy (localization, type and access of the inflammation). A clinical diagnosis can be established by a morphological examination and complemented by laboratory evidence of the infectious agent to identify the suspected organism.[6, 7] Close cooperation with infection control specialists may prevent potential harm to the healthy population as well as limit costly laboratory work-ups.

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epidemiology

Follicular epidemic keratoconjunctivitis (EKC):
Adenoviruses are the most important and most frequent cause of follicular epidemic keratoconjunctivitis (classification according to International Classification of Dieases 10: B 30.0: keratoconjunctivitis by adenovirus, B 30.1: conjunctivitis by adenovirus, B 30.2.: pharyngoconjunctival fever by adenovirus [Table 1].[3] Adenovirus infections are responsible for 92% of all keratoconjunctivitis cases, and appear mostly in late winter, spring and early summer.[8, 9, 3] The viruses implicated are adenovirus HAdV1-11, 14-17, 19-22, 26, 29 and 37. The most frequent types in Europe are HAdV 8>3>7>19/37, in Japan HAdV 8>81>4>19/37>3, and in USA 8, 19, and 37.[10, 9, 11, 12] Nosocomial infections have been reported to be associated more often with HAdV8, while HAdV 7, 19, 37 are more often associated with infections from the environment such as lakes and swimming pools.[9, 13, 14, 15] Adenovirus types responsible for nosocomial infections are defined by molecular epidemiologic methods such as genome and subgenome typing.[14] Virus shift, appearance of new virus types and simultaneous infections by several virus types can circumvent the type-specific acquired immunity in a population and may result in a new symptomatic outbreak.[16, 14, 12, 17, 18]

Acute hemorrhagic conjunctivitis:
Acute hemorrhagic conjunctivitis can be caused by HAdV8 and (rarely) HAdV11 in addition to enterovirus 70, 71 and coxsackievirus A24, B2.[3, 19] This adenoviral inflammation is also self-limited, as symptoms disappear after 6 days, faster than the non-hemorrhagic variant.

ARD-associated keratoconjunctitivis:
Adenovirus-associated acute respiratory disease (ARD) with conjunctivitis was first reported in military recruits during World War II. Epidemics of febrile disease with conjunctivitis can be due to waterborne transmission of HAdV4 and HAdV7 from inadequately chlorinated swimming pools and small lakes.[20] ARD is most often associated with adenovirus types HAdV4 and HAdV7.

transmission

Direct inoculation by fingers is to be considered a major mode of transmission when taking into account that the eyelids and tarsal conjunctiva are touched around 14 times per day involuntarily, and additionally voluntarily during make-up or application of facial cosmetics. Person-to-person transmission of adenovirus 8 is established to primarily occur through the hands of personnel and/or other persons in contact with patients. Outbreaks originating in health units can often be traced down to one or a few health care providers.[10, 21, 22, 23, 24]

In nosocomial infections inadequate hand washing by health-care personnel between patient contacts and inadequate disinfection of equipment is the main risk factor for an outbreak or an epidemic. In larger teaching hospitals (>500 beds), the attack rate of patients with EKC has been estimated at 4.7 per 1000 treatment cases. Transmission may also occur as smear droplet infection in crowded health institutions or in overpopulated areas with low personal hygiene and behaviour (HAdV 8, 19). Medical and paramedical staff mainly in ophthalmic units and hospitals are the most frequent sources of infections.[15, 6] In addition, the improper use of dropper bottles and vials with contaminated tips, tonometer tips and other inadequately disinfected contact instruments, inappropriate patching or multiple use of contact lenses are other important risk factors.

contagiosity

Adenoviruses are exceptionally stable to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body. Thus the high rate of transmission in an ophthalmic unit, e.g. the contagiosity of adenovirus-associated EKC, can be best understood when considering data of HAdV19 being viable up to 8 days on paper, 9 days on tonometer tips, 10 days on textiles and metal and up to 35 days on plastics.[25, 26] These results emphasize the need for proper selection and application of germicides for use in disinfecting non-critical surfaces and semi-critical medical devices, such as applanation tonometers, in order to prevent outbreaks of epidemic keratoconjunctivitis. The necessity for the implementation of infection control measures also seems to result from these data and the lack of effective medical treatment.[27, 28]

clinical picture - adults

Symptoms:
Patients diseased with the complex of "epidemic keratoconjunctivitis" complain about unilateral (right or left depending on handedness) itching, tearing, burning and foreign body sensation as well as photo-

Table 1: ***Ophthalmologically relevant adenovirus types in Europe***

Follicular conjunctivitis	Ad3, 4, 7
Epidemic keratoconjunctivitis	EKC Ad8,19, 37
Acute respiratory disease	ARD Ad1–3, 4, 6, 7, 14, 21
Pharyngoconjunctival fever	Ad3, 7, 14

phobia. In case of acute hemorrhagic conjunctivitis (AHC), extensive epibulbar and tarsal hemorrhages and precervical lymph node enlargement may manifest as early as 48 hours after the first symptoms in >90% of patients.

Signs:

Biomicroscopy reveals a serofibrinous, sometimes mucopurulent exudate, accompanied by chemosis, hyperemia and swelling of the plica [Fig.1]. Tarsal and epibulbar follicles (and petechial hemorrhages in case of HAdV3, 4) [Fig.2] appear. Corneal sensitivity is not affected. After a few days, multifocal non-vascularized, centrally located, nummular corneal infiltrates follow in 95% of cases. They consist of dendritic cells, lymphocytes, histiocytes and fibroblasts [Fig.3].[29] Rarely, a superficial punctate keratitis may present, particularly with HAdV8. An esthesiometry should be done in all cases of corneal signs, in order to differentiate potentially blinding herpetic disease from adenovirus infections. Tarsal pseudomembranes, which consist of necrotic tissue and fibrin on an intact epithelial surface (caveat: no hemorrhage when being removed), can be seen in acute fulminant disease [Fig. 4], and in association with immunodeficiency syndromes [Fig.5]. They tend to form conjunctival scars and mild symblephara.

Preauricular, submandibular and cervical lymph node swelling are typically associated with all adenovirus infections and can be seen and palpated in acute hemorrhagic conjunctivitis [Fig.6] 48 hours after onset of symptoms. Lid edema, secondary inflammatory ptosis, and an upper respiratory tract infection as well as severe malaise may accompany some cases. ARD is particularly pronounced in HAdV3 and HAdV4 infections of adults and in HAdV7 and HAdV8 infections in children.

Sequelae [Figs.7-8]:

The clinical symptoms of EKC and AHC are generally self-limiting after 2-3 weeks respectively 4-6 days, However, even after 2 years nummular corneal lesions (and a decrease in vision from 1.0 to 0.5) can be biomicroscopically documented for HAdV8 infections in 47% of patients.[30] Adenovirus can be isolated from the conjunctiva of a cohort of patients in a decreasing time pattern - about 50% of patients after 10 days are still infective, some remain infective for more than 2 years. In case of AHC, HAdV2, HAdV3, HAdV4, HAdV5, HAdV19 can also be isolated even several months after onset.

Any cytopathogenic agents infecting the ocular surface, including the adenovirus, result in a post infectious dry eye syndrome due to the loss of goblet cells. This event is clinically relevant in about one third of patients. This may sometimes be difficult to differentiate from an ongoing infection. The differential diagnosis can be made utilizing tests such as Schirmer's, Bengal rose stain, break-up time, tear film interference, and impression cytology.

Rarely, (sub)epithelial conjunctival scars can develop particularly in patients that had experienced fulminant and pseudomembraneous disease and lead to persisting corneal irritation and pain sensation [Fig. 9]. Also, as a sequel to the more serious dry eye syndromes with persistent infection and ongoing inflammation, mild symblephara can result.

Risk factors:

The adenovirus reservoir responsible for nosocomial ocular infections is the infected human. The mechanisms of transmission include contaminated skin, inorganic devices, secretions, aerosols, and droplets. The environmental ARD-associated adenovirus has a reservoir in pools and lakes. Humans infect themselves while bathing.

Clinical picture – neonates

Neonatal adenovirus infections involving the eye are rare compared to the frequent bacterial inflammations. Conjunctivitis has been reported in neonates surviving systemic disease.[31]

Symptoms:

Simultaneously bilateral "red eyes" and tearing can be easily differentiated from the mucopurulent exudate in bacterial infections.

Signs:

Lacrimal gland swelling, lid edema, conjunctival hyperemia, and conjunctival papillary reaction can be observed.

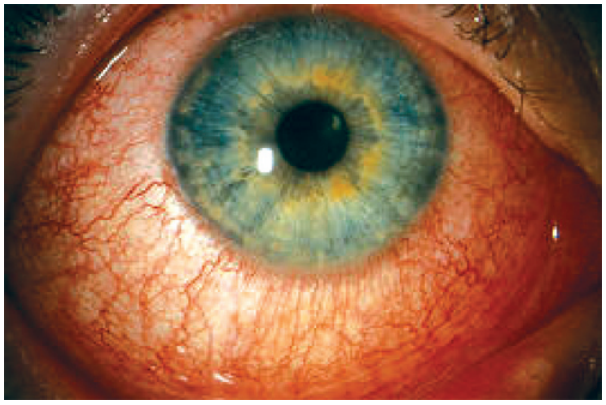

Figure 1: ***Epidemic keratoconjunctivitis: 20 year old patient featuring conjunctival hyperemia, chemosis, plica swelling and accompanying reactive tearing splenic rupture***

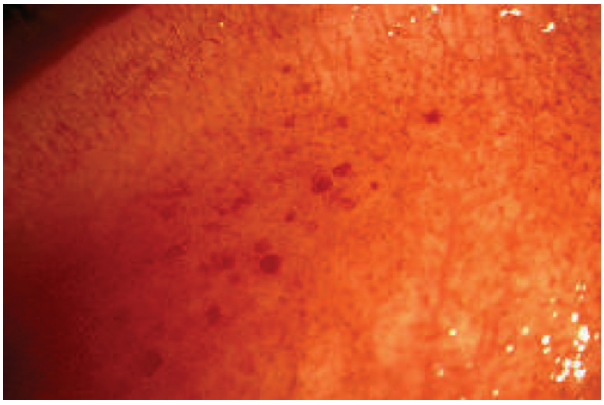

Figure 2: ***Epidemic keratoconjunctivitis: 16 year old patient with petechial hemorrhages on the subtarsal conjunctiva of the ectropionated upper eyelid (frequent cytopathogenic effect)***

Sequelae

The clinical symptoms are self-limited after less than 10 days, and compromising corneal disease and vision impairment have not been reported yet.

Risk factors

It has been documented in Heidelberg recently that the prior examination of neonates by ophthalmologists for screening of retinopathy of prematurity was the only significant risk factor for subsequent adenovirus conjunctivitis in the newborn.[15]

Laboratory diagnosis in ophthalmology

In the differential diagnosis of microbial conjunctivitis, particularly in immunocompromised patients, a laboratory diagnosis supporting and detailing the clinical impression is desirable. Since sometimes multiple types of adenovirus can contribute to an outbreak or epidemic, typing is of considerable epidemiologic relevance. A Dacron- or wood-tipped applicator for conjunctival swab should be inserted deep enough (caveat: use topical anesthetics and NaCl moisterization for applicators) to scrape epithelial cells. The material can be forwarded in commercially available virus transport media, e.g. VT8 for culture, which is still the reference method, however slow (5-33 days) and troublesome. The more practical method is the quantitative real-time polymerase chain reaction (PCR) to prove nucleic acid of HAdV3, 4, 6, 7, 8, 14, 19, 37, which are particularly important in Europe.[6, 7] Enzyme immunoassays are a cheaper and faster option with a high sensitivity of 91%; however, they bear a variable specificity depending on contaminations and false positive results. Even cheaper are direct immunofluorescence tests, which have a very variable sensitivity and specificity and are therefore currently not recommendable for a molecular epidemiologic investigation. For immune dot-blot tests, the sensitivity is 67-84%[32] compared to culture, and for the bedside immunochromatographic test it is 95%.[33]

Treatment

Prerequisites

In all self-limiting diseases the evaluation of treatment trials is difficult. Success concerning the disappearance of the infection is often measured by less organisms to be found at the site of infection, less subjective symptoms, amelioration of inflammatory signs (e.g. conjunctival hyperemia, exudate, corneal involvement) and decrease of morbidity (e.g. office presentations).

Medical - Curative

Experimental and clinical success has been reported for topical alpha-interferon, [34] cidofovir, [35] PVP-iodine 5%.[36] However, none of these agents could withstand the test of cost-effectiveness or freedom of limiting side-effects. As well, the most promising substance in vitro, cidofovir, has been doubted to be effective at all in clinical trials.[37]

Currently, N-chlorotaurin, which has been proven to be effective against adenovirus and adenovirus infection in vivo and in vitro and has been reported tolerable is entering a phase III clinical trial. However, data regarding the actual shortening of the disease, the duration of symptoms, and the effect on shedding of the virus in humans have not yet been reported and are difficult to obtain in a self-limiting disease

Figure 3: ***Epidemic keratoconjunctivitis: 26 year old patient with one paracentral subepithelial irregularly demarcated "dendritic" corneal infiltrate***

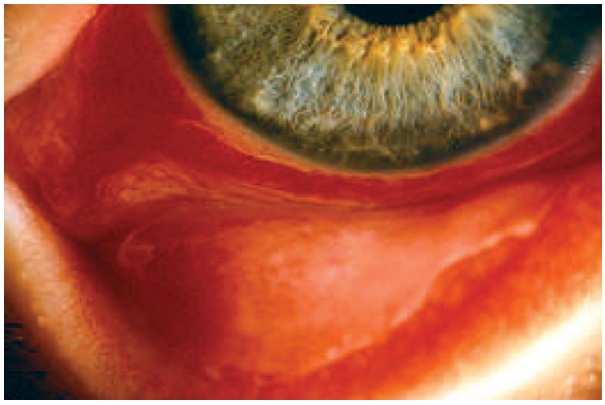

Figure 4: ***Epidemic keratoconjunctivitis: 28 year old immunocompetent patient with subconjunctival hemorrhages and tarsal pseudomembranes (no hemorrhage at removal)***

anyway.[38, 39, 40]

The use of antiherpetic medications such as arabinoside, [41] iodine-desoxyuridine, [42] or trifluorothymidine[43] has not been successful.

Medical - Symptomatic

Topical corticosteroids may mitigate the subjective symptoms and may delay or prevent the development of corneal infiltrates. After tapering the corticosteroids off, a recurrence rate of 30% has been reported.[30] It has been documented in animal experiments that the adenoviral replication may increase under the influence of corticosteroids.[44] Therefore, the application of corticosteroids may only be legitimate in massive fulminant infections with the intention to prevent symblephara, corneal scarring and permanent vision impairment. A consensus for the use or the dosing intervals for corticosteroids does not exist.

In only one study topical cyclosporin A has been reported beneficial with regard to the removal or disappearance of corneal infiltrates.[37]

Topical antihistaminics and physical supportive measures such as ice-cold bandages have also been advised.[18]

Topical combinations of tetracyclines and corticosteroids are frequently prescribed; however, there is no evidence to support a beneficial symptomatic or curative effect.

Medical - Prophylactic

Vaccines were developed for HAdV4 and HAdV7 infections (ARD associated conjunctivitis), but they were conceived only for preventing ARD among military recruits and were never relevant for ophthalmologists.[20]

Surgical

Late sequelae such as persisting scars, irregular shaping and irregular astigmatism after EKC may result in a compromised image quality or impairment of vision. In these cases a topography- or wavefront-guided phototherapeutic keratectomy may restore vision.[45]

Infection Control

General

Although the beneficial effect of infection control measures has recently been controversially discussed, the mainstream consensus is to pay strict attention to good infection-control practices that may be effective to stop nosocomial outbreaks of adenovirus-associated disease.[24, 6, 5]

Disinfecting agents proven to be active in vitro against the virus have been listed in the Environmental Protection Agency[46] and RKI/Berlin 4 lists of disinfectants. However, the in vitro conditions and interaction between test strains and germicides may not simulate in vivo conditions. For example, HAdV2 and HAdV7, is susceptible to alcohols after 10 minutes of contact time, [47] but adenovirus 8 is resistant to the action of 70% isopropyl alcohol.[48] Thus, research results concerning hygiene issues in adenovirus infections have often been confusing for the practicing clinician.

Maintaining adequate levels of chlorination is necessary and effective to prevent swimming pool-associated outbreaks of adenovirus conjunctivitis.[24, 20]

Ophthalmology – Medical staff

The main task of medical staff during an outbreak is strictly to adhere to hand disinfection to prevent

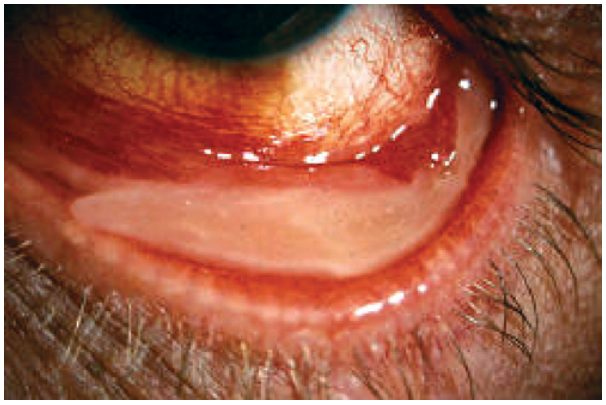

Figure 5: ***Epidemic keratoconjunctivitis: 35 year old AIDS patient with severe pain and pseudomembranes on the lower tarsal conjunctiva***

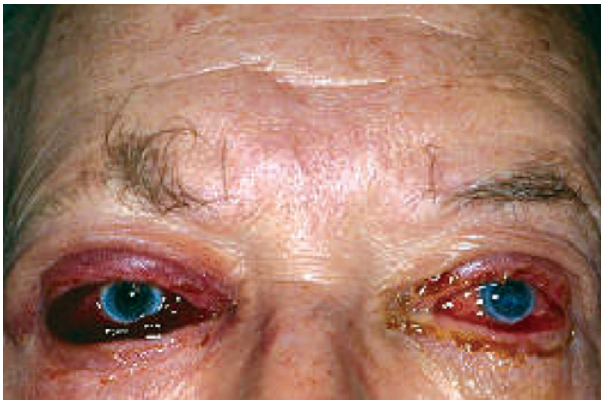

Figure 6: ***Acute hemorrhagic conjunctivitis: 81 year old patient 2 days after intraocular pressure profile for glaucoma, featuring bilateral massive (sub)conjunctival hemorrhages, lid edema and nonbacterial mucopurulent exudate***

person-to-person spread of infection using the recommended germicides and gloves for the handling of infectious patients or (potentially) contaminated materials. Of the germicides suitable for use as an antiseptic, 70% ethanol achieved a 3 log 10 reduction under four of the five test conditions.[49] These measures may limit the spread of EKC acutely and may achieve a long-term reduction of incidence rates.[50, 32, 9]

In a convincing comparative 6-year study employing enforced infection control measures in an ophthalmic unit, 0.54 outbreaks involving 5.66 infected patients per 10,000 patient examinations have been documented in contrast to 3.89 outbreaks involving 54.09 infected patients per 10,000 patient examinations without those measures ($p<0.005$ und $p<0.0005$).[13]

Physicians suffering from adenovirus conjunctivitis should in any case be restricted from working with patients. This results from a study in Canada when an outbreak of EKC could be traced back to 4 of 20 doctors of a health centre being responsible for 61% of the infections.[51]

Hand disinfection after glove removal should be performed using 80% ethanol for at least 5 minutes. or using tosylchloramide sodium 1% or 2% for at least 1 minute.[4] Hand washing with a detergent is not sufficient. Hand towels must be single use paper and not reusable cotton towels.

Ophthalmology – equipment etc:

Dropping bottles and eye ointment should only be used by one patient, and single-use units should be preferred.[52]

Patient-relevant areas, equipment, instruments, and other devices undergoing patient contact like slit lamp accessories must be disinfected with recommended germicides.[46, 4, 49]

Tonometry:

Contact tonometry with the Schitz tonometer or the applanation tonometer is a risk factor for EKC, and the pneumotonometer has also has been associated with nosocomial EKC outbreaks.[24, 53] Problems regarding disinfection or sterilization of the tonometers particularly the disassemblement have been elucidated.[54, 55] Tonometers vary in design and material composition; therefore, disinfection or sterilization procedures that are appropriate for one type of tonometer may not be suitable for another.[55, 56, 57] Adequate disinfection or sterilization cannot be achieved if the instruments are not initially cleaned thoroughly of any organic material that can impede contact between the disinfectant and the microorganism during the disinfection process.

In the absence of controlled studies, specifically on disinfection or sterilization of the pneumotonometer and other tonometers, the tips of such tonometers must be cleaned, then disinfected or sterilized after each patient use.

The irradiation of tonometer tips with ultraviolet light (maximal antiviral effectiveness: 253.7nm) has been proven effective in studies using HAdV2, but it has not been generally recommended due to the variable dosages in various adenovirus types (ID_{90} 20.0 to 50.0 mWs/cm^2) and undefined exposure times.[58, 54]

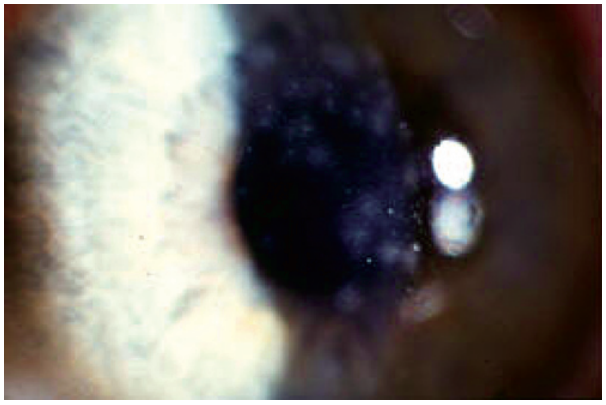

Figure 7: ***Epidemic keratoconjunctivitis – sequelae: 46 year old patient 7 days after start of clinical symptoms with persistent pronounced central subepithelial corneal infiltrates with a free zone towards the limbus. Photophobia, visual impairment***

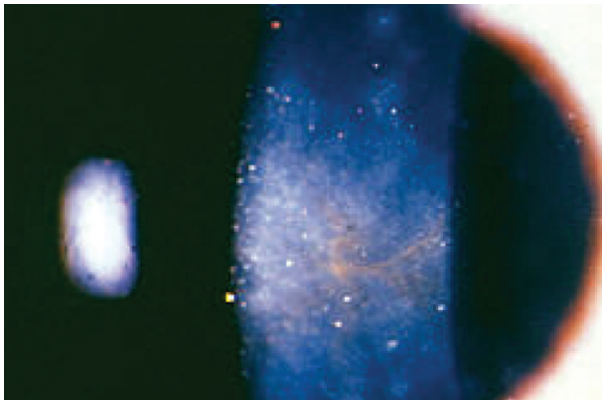

Figure 8: ***Epidemic keratoconjunctivitis – sequelae: 49 year old patient 5 months after start of clinical symptoms with pronounced central nonvascularized subepithelial corneal scars and a degenerative iron line. Vision OS cc 0.2, highly irregular astigmatism. A phototherapeutic keratectomy was successful, vision increased to 0.8***

Other contact instruments:
Thermal disinfection is preferred at 93°C 5 minutes in disinfection and cleansing machines, otherwise a virucidal 3% formaldehyde solution may be used for soaking (4 hours recommended contact), or a more practical 5% tosylchloramide sodium solution (10 minutes. recommended contact) can be applied, for example for three mirror lenses. Chlorhexidine has been tested on contact instruments (eye lid spatula) for screening of ROP patients and thermal disinfection was found to be superior to chlorhexidine, but chlorhexidine was found to be preferable with regard to 70% isopropyl alcohol. However, chlorhexidine is a weak disinfectant and highly irritating for the eye.[59]

Areas:
Patient contact areas such as slit lamp accessories must be treated with virucidal preparations or by meticulous cleansing with 70% ethanol for at least 5 minutes.[46, 5]

Textiles:
Contaminated textiles must be treated with a thermal (90°C, 10 min.) or chemothermal disinfection.[47]

Other:
Ancillary procedures are necessary to control nosocomial EKC outbreaks including, 1) cohorting of EKC-infected health-care personnel only with patients known to have EKC, 2) preventing infected personnel from having direct patient contact for up to 14 days following onset in affected personnel, and 3) using unit-dose eye solutions. Control of large epidemics or those that occur in association with a community outbreak require more stringent measures, such as triaging patients and assigning those suspected of being infected to waiting and examining rooms that are separate from those for uninfected patients and admitting into the clinic only emergency cases, while postponing examination and treatment of elective patients until after the outbreak.

NOTIFICATION

Notification of suspects and/or diagnosed cases of nosocomial adenovirus infections is requested by law in most Western countries. In Germany, the outbreak must be notified anonymously according to the Impfschutzgesetz (IfSG) § 6 (3.5). If laboratory evidence has been found, the notification must be by name according to IfSG § 7.[5] In the USA, patients must be reported through state health departments to the Epidemiology Branch, Center for Infectious Diseases, Atlanta.[20]

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