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REVIEW

A Review of Corneal Endotheliitis and Endotheliopathy: Differential Diagnosis, Evaluation, and Treatment

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ABSTRACT

The corneal endothelium plays an integral role in regulating corneal hydration and clarity. Endotheliitis, defined as inflammation of the corneal endothelium, may disrupt endothelial function and cause subsequent visual changes. Corneal endotheliitis is characterized by corneal edema, the presence of keratic precipitates, anterior chamber inflammation, and occasionally limbal injection, neovascularization, and co-existing or superimposed uveitis. The disorder is classified into four subgroups: linear, sectoral, disciform, and diffuse. Its etiology is extensive and, although commonly viral, may be medication-related, procedural, fungal, zoological, environmental, or systemic. Not all cases of endothelial dysfunction leading to corneal edema are inflammatory in nature. Therefore, it is imperative that practitioners consider a broad differential for patients presenting with possible endotheliitis, as well as familiarize themselves with appropriate diagnostic and therapeutic modalities.

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INTRODUCTION

The corneal endothelium, a monocellular layer lining the posterior cornea, plays an important role in regulating corneal hydration and clarity. This tissue is embryologically derived from neural crest cells which migrate from the neural plate to the optic disc around 40 days of gestation. By the eighth week of gestation, these cells thin to a single layer [1]. The endothelium serves to keep the corneal stroma in a relatively dehydrated state by pumping fluid from the hypo-osmotic stroma to the relatively hyperosmotic aqueous humor in the anterior chamber [1]. This process opposes osmotic water movement into the cornea and maintains corneal transparency. Endotheliitis, defined as inflammation of the corneal endothelium, can disrupt the normal function of these cells causing edema and subsequent visual changes. In this paper, we aim to review the history of endotheliitis, present various etiologies, and discuss current diagnostic criteria and treatment modalities. In this review, the authors discuss many causes of corneal edema due to endothelial dysfunction that may not be solely inflammatory in origin with the aim of aiding clinicians in determining a proper differential diagnosis for presumed corneal endotheliitis.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

HISTORY

The classic presentation of endotheliitis consists of corneal edema accompanied by keratic precipitates (KP). Nomenclature relative to this condition has undergone several revisions throughout history. One of the first recorded instances of the disease was described by Ernst Fuchs, who named the disease abscessus siccus corneae in 1870 [2]. In the seventh edition of his ophthalmology textbook, Fuchs himself changed course, describing disc-shaped lesions appearing in the stroma as disciform keratitis [3]. Other ophthalmologists of the time used separate, distinct terms to describe similar presentations including parenchymatous, sectoral, and deep keratitis [4]. These terms became incorporated as sub-classifications under the all-encompassing term endotheliitis.

Early case reports of endotheliitis revealed a diversity of etiologies. As early as 1923, Lundsgaard noted an association of corneal edema in patients with mumps [5]. In 1982, Khodadoust and Attarzadeh presented two cases of endotheliitis secondary to autoimmune corneal graft rejection that improved with corticosteroid administration [6]. These findings were followed by reported cases of patients unresponsive to treatment with corticosteroids, who later progressed to dendritic keratitis. Genomic analysis of aqueous humor using immunofluorescence and polymerase chain reaction has confirmed viral causes including herpes simplex virus (HSV) and cytomegalovirus (CMV) [7, 8]. These recent discoveries have shaped much of our current protocols and guidelines regarding diagnosis and treatment of this disease.

CLINICAL MANIFESTATIONS AND CLASSIFICATION

The most common symptoms reported by patients with endotheliitis include eye pain, photophobia, and visual disturbances. Clinically, endotheliitis is characterized by corneal edema, the presence of KP, and moderate anterior chamber inflammation [9], but occasionally may include limbal injection and neovascularization [10]. It is often complicated by co-existing or superimposed uveitis. In this review we will examine many diverse causes of corneal edema with the aim of aiding the clinician in determining the cause of endothelial dysfunction.

On the basis of the presentation of KP, endotheliitis has been classified into four subgroups: linear, sectoral, disciform, and diffuse [11]. As described by Alfawaz, linear

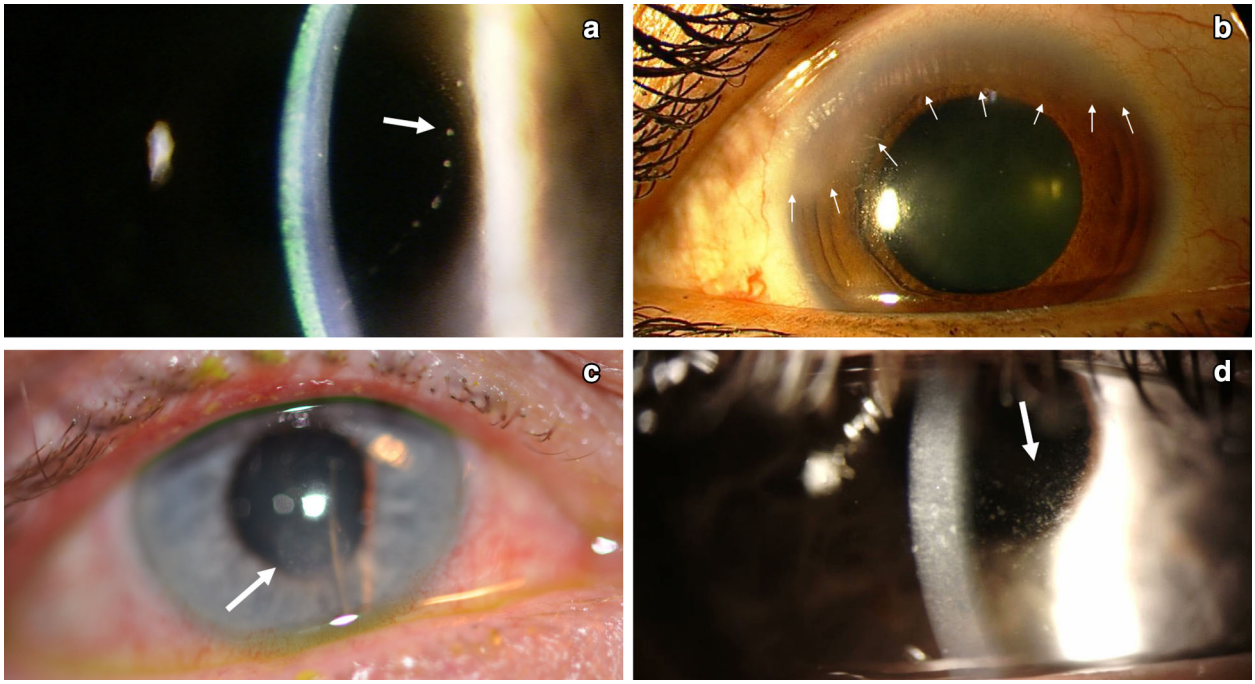

Fig. 1 Anterior segment photography demonstrating different patterns of endotheliitis. **a** Linear—fine KP (white arrow) in a linear pattern and overlying corneal edema. **b** Sectoral—HSV endotheliitis presenting with sectoral corneal edema (white arrows). **c** Disciform—CMV endotheliitis presenting in a disciform pattern (white arrow) with overlying edema. **d** Diffuse—endotheliitis presenting with diffuse KP (white arrow). KP keratic precipitates (Courtesy of Dr. Majid Moshirfar)

endotheliitis exhibits a linear distribution of KP (Fig. 1), while sectoral endotheliitis displays a disseminated arrangement of precipitates within the cornea. Disciform endotheliitis is distinguished by disc-shaped edematous lesions located centrally in the cornea with precipitates distributed throughout the affected area. Finally, diffuse endotheliitis presents with uniform distribution of both edema and precipitates throughout the entire cornea. Recently, a rare entity of "multiple-parallel-line" endotheliitis has also been described [12–15].

VIRAL ETIOLOGIES

Cytomegalovirus (CMV)

CMV-induced corneal endotheliitis can present with linear or circularly organized (often termed coin-shaped) KP in the presence or absence of local stromal edema (Fig. 1c) [11]. CMV-endotheliitis rarely results in diffuse distribution of KP. It is typically unilateral. One study by Koizumi et al. [16] reported that only 3 of 106 patients had bilateral involvement. Intraocular pressure (IOP) is often elevated at presentation. Co-existing anterior uveitis is not uncommon and may represent an alternate manifestation of the same disease [17]. This uveitis can progress to chronic anterior uveitis with either recurrent episodic iritis and raised IOP (resembling Posner–Schlossman syndrome) or the presence of anterior chamber cells and endothelial KP (resembling Fuchs' heterochromic iridocyclitis) [11]. However CMV may also present atypically as bullous keratopathy without KPs or elevated IOP [18]. Contrary to other viral etiologies of endotheliitis and CMV infections in general, CMV-related endotheliitis is more common in immunocompetent individuals [17].

Herpes Simplex Virus (HSV)

Herpetic endotheliitis typically presents with disciform KP but may also present with diffuse, linear, and sectoral KP (Fig. 1b) [10, 19]. Iritis and stromal edema are commonly seen, distinguishing this etiology from other causes of anterior uveitis. Elevated intraocular pressure is seen secondary to trabeculitis [20]. HSV endotheliitis is common in individuals who are immunocompromised and thorough history taking may elucidate prior or recurrent herpetic disease.

Myxovirus Parotitis (Mumps) Virus

Mumps virus commonly involves glandular structures, with lacrimal gland involvement being the most common ocular manifestation [21, 22]. However, on rare occasions this virus can involve the endothelium and stroma [22, 23]. Patients with mumps endotheliitis typically present with unilateral central corneal edema that spares the epithelium, KP in the area of edema, elevated IOP, decreased visual acuity, and ocular discomfort. Importantly, mumps may be differentiated from other causes of endotheliitis by the relative absence of uveitis and iritis [23].

Other Viral Causes

Other viruses, including those of the human herpes virus (HHV) family, have been reported as causing endotheliitis, albeit infrequently. Varicella zoster virus, of the herpes virus family, has been shown to cause disciform endotheliitis [24]. It has also been reported as a cause of endotheliitis after keratoplasty [25]. In addition Epstein–Barr Virus (EBV, Fig. 2), HHV-7, and HHV-8 have been implicated in endotheliitis [26, 27]. Coxsackie virus, while commonly known for its association with acute hemorrhagic conjunctivitis, may also cause endotheliitis [28]. Rhabdovirus has also been cited as a cause of unilateral endotheliitis [29].

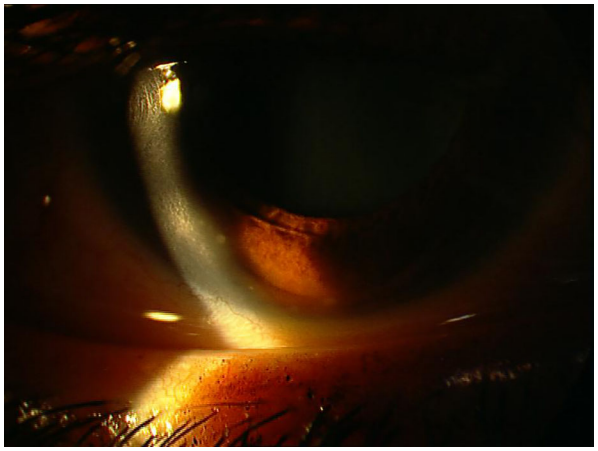

Fig. 2 Anterior segment photograph of a patient with EBV presenting with a subtle stromal reaction, KP of differing sizes and overlying corneal edema and haze (Courtesy of Dr. Majid Moshirfar, MD)

BACTERIAL ETIOLOGIES

The most common causes of bacterial keratitis are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, coagulase-negative *Streptococci*, and *Streptococcus pneumoniae* [30]. Although these bacteria may cause inflammation of both the corneal epithelium and endothelium, there are no reports in the literature of isolated endotheliitis of bacterial origin. Symptoms include erythema, discharge, photophobia, and decreased visual acuity. These patients present at slit-lamp exam with corneal thinning and edema, Descemet's folds, and anterior chamber reaction with rare posterior synechiae.

DRUG-INDUCED

Various pharmacological treatments may cause corneal toxicity and endothelial damage, with or without inflammatory contribution, and are included for completeness in an endotheliitis differential as well as a precaution for patients with existing endotheliitis/endothelial dysfunction.

Amantadine is an *N*-methyl-D-aspartate (NMDA) antagonist indicated for Parkinson's disease and drug-induced extrapyramidal symptoms. Its use has been associated with bilateral corneal edema and may lead to

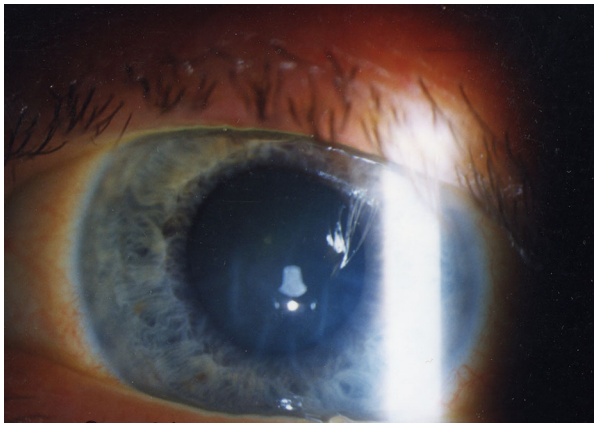

Fig. 3 Anterior segment photograph of amantadine-associated corneal edema with Descemet's folds (Courtesy of Dr. Dean Ouano, MD)

permanent endothelial damage (Fig. 3) [31]. While the underlying mechanism for corneal edema remains unclear, Lee et al. [32] showed a dose-dependent relationship between amantadine use and the risk of corneal edema in Parkinson's patients. Resolution of symptoms is dependent on complete cessation of treatment [31]. Similarly ketamine and memantine are NMDA receptor antagonists that can cause endothelial damage and corneal edema [33, 34]. Dopaminergic drugs, such as methylphenidate and ropinirole, and the capsaicin analogue resiniferatoxin have also been implicated in corneal edema and endothelial dysfunction [35, 36].

Amiodarone has an established association with vortex keratopathy of the corneal epithelium. However, amiodarone-induced endotheliopathy leading to corneal decompensation and edema has also been reported [37]. Menadione, a vitamin K supplement, is rarely used in developed countries but has also been linked to endothelial dysfunction [38]. The use of topical anesthetics, including proparacaine and high concentrations of lidocaine, was shown to cause structural changes in corneal endothelial cells and should be used minimally in patients with pre-existing endotheliopathy [39, 40]. Elevated systemic levels of digoxin can cause corneal edema with Descemet's folds likely due to the inhibition of the sodium–potassium pump in the corneal endothelium [41]. Zoledronate infusion used in treatment of osteoporosis has been reported as causing ocular inflammation including endotheliitis with extensive corneal edema and Descemet's folds [42].

Mitomycin C is used topically in several ophthalmic procedures to prevent scarring and corneal haze. Derick et al. first demonstrated its potential for endothelial toxicity in 1991 when injecting rabbit eyes with 50 μl of mitomycin C. Seventy-two hours after injection there was severe corneal edema and a complete loss of corneal endothelium [43]. Although associated with less corneal toxicity, 5-fluorouracil (5-FU) has also been associated with cases of both temporary and permanent endothelial dysfunction [44–46]. Perfluorodecalin and perfluoro-*n*-octane, fluorocarbons used in retinal detachment repair, have been associated with corneal dysfunction when accidentally retained after surgery [47–49]. Inadvertent intraoperative use of 1% methylene blue in place of 0.025% trypan blue in cataract surgery has been reported as causing permanent endothelial damage [50]. Other drugs, such as phenylephrine, have been shown to cause endotheliitis only in the case of epithelial compromise [51].

Benzalkonium chloride, a preservative in many eye drops, can cause toxic injury to the endothelium [52, 53]. In addition eye drops containing carbonic anhydrase inhibitors such as dorzolamide had been reported to cause endothelial dysfunction, particularly in patients with pre-existing endothelial problems. However, this effect may be secondary to preservatives contained in the drops [53–56].

Acute large volume intake of ethyl alcohol has also been shown to cause temporary endothelial cell dysfunction [57]. A 2017 study of the effects of long-term cannabinoid use on the corneal endothelium revealed decreased endothelial cell density in all of the patients participating [58].

PROCEDURAL CAUSES

Corneal Cross-Linking (CCL)

CCL strengthens the inter-fibrillar covalent bonds within the stroma and prevents the

progression of kerectasia [10]. One common method involves removal of the corneal epithelium and application of riboflavin solution which is later biochemically activated using ultraviolet A light.

Corneal endotheliitis presenting with hyperemia and photophobia has been reported after collagen cross-linking [59]. There may also be localized edema of the cornea containing coin-like KP [60]. However, the incidence of endotheliitis after CCL is relatively low. In a case study, Sharma et al. noted that only 10 of 350 patients (2.9%) presented with corneal endotheliitis after CCL with two patients eventually undergoing penetrating keratoplasty [61]. CCL was determined to be the cause due to lack of infectious or drug-induced etiologies. In the case presented by Gumus, treatment with topical steroids resulted in resolution of symptoms [60].

While the mechanism by which CCL causes endotheliitis remains undetermined, there are several likely contributing factors that should be considered [60]. An excessively thin cornea can allow the ultraviolet A (UV-A) treatment to penetrate to the endothelium and incite an inflammatory response. Yet, endotheliitis has been reported in corneas well above 400 μm of thickness, suggesting a host of other potential causes [62]. The use of riboflavin, which thins and dehydrates the cornea, may be a contributing factor. It has been theorized that riboflavin may incite inflammation but more investigation is needed to validate this claim [60, 63]. Another study assessing the long-term safety of CCL on the corneal endothelium found a significant decrease in endothelial cell density after CCL, which may contribute to the development of endotheliitis [64]. Pre-existing conditions such as Fuchs dystrophy, viral uveitis, and endotheliitis should also be considered prior to treatment of kerectasia with CCL.

Posterior Chamber Intraocular Lens Implantation

Corneal edema may occur in patients after cataract surgery for a variety of reasons including retained lens fragments, Descemet's membrane detachment, and Brown–McLean syndrome (BMS). The majority of postoperative corneal edema and endotheliopathy is associated with retained lens fragments. This typically presents 1–138 days postoperatively, but has been reported as late as 8.5 years postoperatively [65]. These complications can progress to corneal decompensation requiring Descemet stripping automated endothelial keratoplasty (DSAEK) or penetrating keratoplasty. BMS typically presents an average of 16 years after cataract surgery, with orange-brown pigment in the endothelium and peripheral corneal edema [10]. Confocal microscopy in some patients with BMS shows decreased endothelial cell density, while others show normal cell density, suggesting a multifactorial etiology [66–68]. Intraocular surgery has also been reported to trigger CMV endotheliitis [69, 70]. Vitreous incarceration is an additional cause of endotheliopathy and corneal decompensation after cataract surgery. McDonnell et al. [71] performed electron microscopy on the endothelium of vitreous incarcerated patients postmortem and discovered migration of corneal endothelium onto the vitreous causing endotheliopathy. If presenting with corneal edema and endothelial dysfunction 12–48 h after anterior segment surgery, acute toxic anterior segment syndrome (TASS) should be considered. This is by definition a non-infectious inflammatory reaction with many potential causes including ointments, preservatives, retention of sterilization detergent, abnormal pH or salt concentration, trypan blue, trace metal deposits, and denatured viscoelastic material [72–77]. These causes of corneal edema after posterior chamber intraocular lens implantation discussed above are not all true endotheliitis, yet should be considered in the differential of possible corneal endotheliitis.

Allograft Rejection

Endotheliitis has been seen in allograft rejection following penetrating keratoplasty. Khodadoust and Attarzadeh discovered that the epithelium, stroma, and endothelium can illicit the host response against donor tissue [6]. Of these, endothelial rejection is the most common and

is seen in up to 50% of graft rejections. More anterior procedures such as deep anterior lamellar keratoplasty (DALK) have led to the preservation of the host endothelium and subsequent decrease of endotheliitis caused by allograft rejection.

Other Procedural Causes

Dexamethasone implants are used for treatment of persistent macular edema refractory to anti-vascular endothelial growth factor (anti-VEGF) injections. These implants have been reported to occasionally migrate into the anterior chamber and cause temporary or even permanent endothelial damage even after removal of the implant [78–80]. In strabismus-correcting surgeries, simultaneous resection of three rectus muscles, or even two in patients with compromised blood flow, may result in anterior segment ischemia [81]. These patients can present initially with anterior chamber cell and flare, Descemet's folds, and mild uveitis, but may progress to severe corneal edema with or without striate keratopathy, hyphema, and posterior synechiae [82]. In retinal surgeries with silicone oil removal after a longer period (2–7 months), decreased corneal cell density and severe endothelial damage may occur, which does not improve even after removal of the oil [83]. Finally, patients may present with endothelial KPs, cells in the anterior chamber, and corneal edema after undergoing laser-assisted eyebrow epilation without proper eye protection [84].

OTHER CAUSES

Fungal Infection

Fungal infection is a well-documented cause of stromal and interstitial keratitis. In 2012, Garg [85] noted several fungal etiologies that infect the corneal epithelium which, if left untreated, have the potential to extend into the endothelium and cause decompensation and inflammation. In 2013, Zapata et al. [86] reported a case of infectious endotheliitis of suspected mycotic origin. Although no organisms were isolated, clinical improvement was seen after 5 days of antimycotic therapy. While rare, fungal origin should be considered in cases of infectious endotheliitis refractory to antiviral treatment.

Zoological Etiologies

Venom ophthalmia, a condition in which snake or frog venom has been excreted onto the eye, has been documented as causing marked corneal edema of the epithelium and endothelium [87]. Chu et al. [88] reviewed ten cases of venom ophthalmia in which corneal stromal edema with Descemet's folds was a major sequela. The cases presented involved ten different species of venomous snakes. Another source of zoological caused corneal edema is arachnids. When threatened, tarantulas expel a cloud of barbed hairs that can contact the eye directly or be transferred from hand to eye. These barbs can then migrate through the cornea and lodge in the endothelium causing corneal edema and mutton-fat KP, and can eventually migrate further to the retina (Fig. 4) [89]. In addition, decreased endothelial cell density and persistent corneal edema have been reported 1 year after corneal bee sting [90]. There have also been reports of caterpillar hair and coral aquarium causing corneal edema and endothelial attenuation, respectively [91].

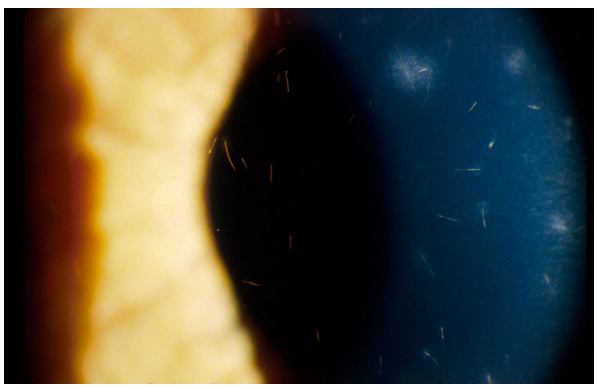

Fig. 4 Anterior segment photograph of endotheliitis secondary to tarantula hair exposure (Courtesy of James Gilman, Moran Eye Center)

Contact Lenses

The use of contact lenses has historically been the cause of localized endothelial cell loss and corneal edema. The causes of this endothelial insult are attributed to acidification of corneal endothelium by a reduction in carbon dioxide efflux (hypercapnia) and also an accumulation of lactic acid due to oxygen deprivation [92]. The advancements in oxygen-permeable contact lenses have greatly reduced these endothelial changes but improper maintenance and use of contact lenses can induce hypoxia and endothelial insult.

Environmental

Mustard gas keratopathy (MGK) is known to have diverse ocular manifestations including endothelial cell destruction. McNutt et al. studied MGK's effect on the corneal endothelium of rabbits and found significant destruction in a pattern described as centripetal, concentrated centrally with diffuse peripheral destruction [93]. There are cases of delayed MGK in the literature where corneal symptoms present up to a decade later [94]. This delayed type of MGK makes it a relevant differential diagnosis for citizens of war-torn countries where bioterrorism is prevalent.

Exposure to certain plants such as *Asclepias fruticosa* (milkweed) and *Calotropis procera* (Sodom apple) can cause endothelial toxicity [95, 96]. With *Asclepias fruticosa*, treatment typically resolves the dysfunction in 2–3 days, while *Calotropis procera* often causes a permanent decrease in endothelial cell count with average resolution of edema in 3–6 months. There are also rare reports of cadmium in a woman's eyeliner (khol) commonly used in the Middle East, Asia, and Africa causing severe corneal edema and endothelial dysfunction [97].

Exercise

High-intensity exercise (e.g., ultramarathon runners) has also been associated with bilateral corneal edema. This is likely due to an increase in lactic acid levels in the aqueous humor and the oxidative stress that causes endothelial injury (ultramarathon-induced bilateral corneal edema) [98, 99].

Systemic Diseases

Giant cell arteritis is an example where endothelial dysfunction is a sequela to the primary diagnosis [100]. A case study presented in June 2017 describes a woman who presented with unilateral corneal edema 1 day after uneventful cataract extraction. After 3 days, her presentation had progressed to bilateral corneal edema with ocular hypotony. Magnetic resonance angiography revealed stasis of the ophthalmic arteries and a tissue biopsy confirmed giant cell arteritis. A diagnosis of anterior segment ischemic syndrome was made and determined to be the cause of corneal decompensation [101].

Patients with sarcoidosis often present with pulmonary lymphadenopathy, elevated serum angiotensin converting enzyme (ACE), and granulomas in multiple organs. Ocular manifestations may include uveitis, macular edema, and endotheliitis. The endotheliitis is characterized by mutton-fat and granulomatous KP [102]. One case in the literature describes Crohn's disease with leukocytoclastic vasculitis with an associated progressive cicatrizing endotheliitis. Mitochondrial diseases including chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, and Pearson's syndrome cause acute corneal edema due to endothelial dysfunction [103–105].

Retinoblastoma

In 2016, Kelly et al. [106] reported a case of endotheliitis-like presentation in a 6-year-old diagnosed with retinoblastoma. The patient was unresponsive to corticosteroids and antivirals and aqueous humor was negative for any viral genomes.

Hypotony

Other cases of ocular hypotony inducing endothelial dysfunction have been reported including a case where the surgical correction of ocular hypotony cured the concomitant corneal edema [107].

Idiopathic

As mentioned earlier, "multiple-parallel-line" endotheliitis has been reported as a steroid-responsive non-infectious idiopathic cause of endothelial dysfunction [12]. Some have postulated that this may be a subtle form of aqueous negative but serological positive viral endotheliitis; however, more data is needed to support this claim [13]. Another idiopathic entity termed "zipper cell endotheliopathy" has been described as focal denudation of endothelial cells surrounded by endothelial cells with zipper-like extensions and overlapping neighboring cells. Immunohistochemistry suggested that epithelial metaplasia could be a possible cause for this case [108].

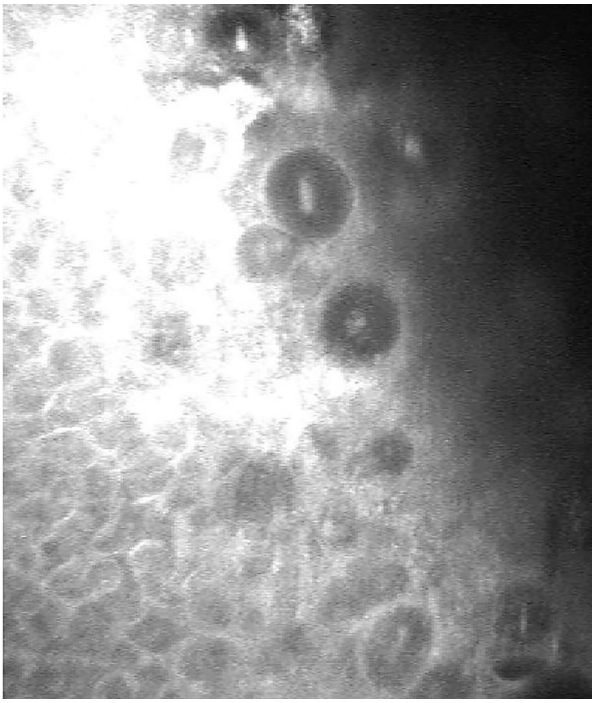

Fig. 5 Specular microscopy of a patient with CMV. The corneal endothelium shows polymorphism and polymegethism in the lower left corner as well as pseudoguttata (Courtesy of Dr. Majid Moshirfar)

DIAGNOSIS

Corneal endotheliitis is a clinical diagnosis. Once a diagnosis is made, testing for endothelial cell density with specular microscopy and further observation with in vivo confocal microscopy can be performed to support the diagnosis. Average endothelial cell density increases throughout childhood and adolescence, reaching its peak in early adulthood ranging from 2000 to 3300 cells/mm^2 and then declining as the individual ages past their second decade of life [109]. Injury to and inflammation of the endothelium will reveal polymegathism and intercellular gaps as well as pseudoguttata. These findings may be observed with specular microscopy, an additional method for evaluating the integrity of the corneal endothelium (Fig. 5).

The current standard for diagnosis of any viral etiology is viral genome polymerase chain reaction (PCR) analysis of anterior chamber aqueous. Because of the possible risk for endophthalmitis, wound leak, and sympathetic ophthalmia, anterior chamber paracentesis should only be performed in vision-threatened cases [11]. Immunoassay, often indicated as IgM and IgG seropositivity via enzyme-linked immunosorbent assay (ELISA), has proven effective at diagnosing these viral etiologies, but if negative, is not a substitute for anterior chamber paracentesis [16]. Because of the high sensitivity of PCR, contamination of the sample can occur [110]. Testing for HHVs (herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus, Epstein–Barr virus, CMV, HHV-6, HHV-7, and HHV-8) should be performed first, with Coxsackie and rhabdovirus testing later if needed. Isolating viral genome from the aqueous humor or serum suggests but does not definitively confirm the causative agent. HIV serologic testing should be included as part of the viral workup because of previously discussed association with HSV.

Corneal scrapings can be cultured to reveal bacterial infections which commonly colonize epithelial and endothelial tissue. If neither viral PCR nor bacterial culture return positive, further etiologies must be investigated. Fungal culture and/or a trial of antimycotic treatment may be warranted [86]. In vivo confocal microscopy can reveal KP and other lesions that might suggest another cause [111]. The presence of owl eye inclusion bodies and hyphae in the corneal endothelium on confocal microscopy are diagnostic of CMV and fungal infection, respectively [112].

A thorough medication review is necessary to rule out any of the possible medication-related etiologies discussed above. Review of the patient's procedural history may reveal prior cataract surgery or collagen cross-linking with riboflavin and UV-A, which may lead towards the diagnosis of iatrogenic endotheliitis. Diagnosis of environmental associated endotheliitis can be made by comparing a patient history of exposure to offending substances, such as zoological toxins or MGK, to the presentation of the disease. Patients with a history of contact lens use should be queried about proper maintenance and use. Patient history and presentation should be examined for systemic diseases such as sarcoidosis, giant cell arteritis, or mitochondrial disease. Of note, because elevated calcium levels and ACE are only elevated in 40% and 60% of patients with sarcoidosis, the gold standard for sarcoidosis diagnosis is tissue biopsy either of pulmonary or cutaneous lesions with pathology demonstrating non-caseating granuloma [113].

TREATMENT

Choice of treatment regimen for corneal endotheliitis depends on the underlying

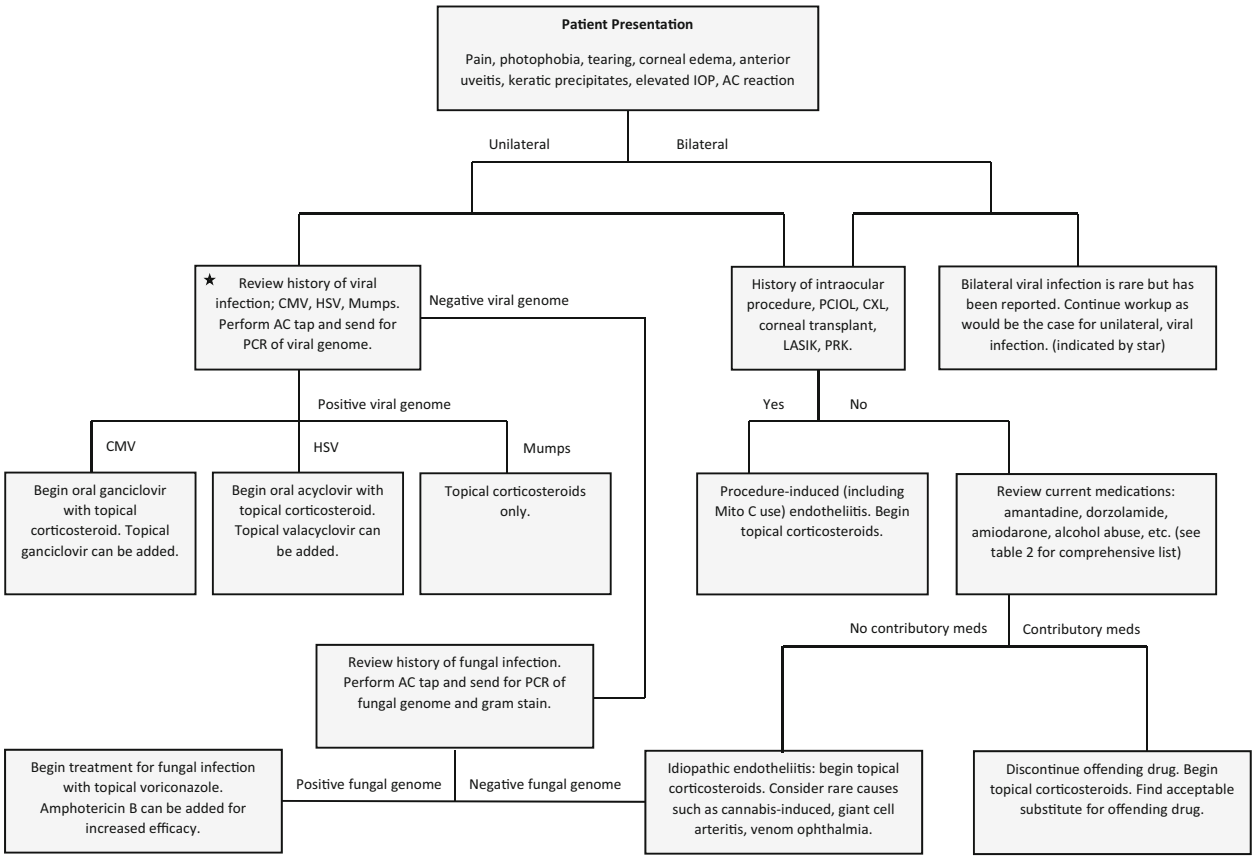

Fig. 6 Algorithm for Diagnosis and Treatment of Endotheliitis

Table 1 Presentation, diagnosis, and treatment of endotheliitis

Causative agent	Presentation	Diagnostic test	Treatment
Viral			
CMV	Unilateral, linear or coin-shaped KP, anterior uveitis, stromal edema, iritis, elevated IOP, patient is immunocompetent	PCR analysis of viral genome in sample of aqueous humor via AC tap is the gold standard; serum IgG and IgM have also demonstrated effectiveness	Oral (900–1800 mg daily) valganciclovir or IV (5–10 mg/kg) ganciclovir, can add topical ganciclovir (0.15%) for greater efficacy Topical corticosteroids or topical NSAIDs per clinical judgment
HSV	Unilateral, disciform KP, (can present with linear or diffuse KP), iritis, stromal edema, elevated IOP	PCR analysis of viral genome in sample of aqueous humor via AC tap is the gold standard; serum IgG and IgM have also demonstrated effectiveness	Oral acyclovir 400 mg 3–5 times daily and oral valaciclovir 500 mg 2 times daily Topical administration of acyclovir of is not indicated when confined to the endothelium Topical corticosteroids or topical NSAIDs per clinical judgment
Mumps	Unilateral, central corneal edema sparing the epithelium, KP in the area of edema, elevated IOP, decreased visual acuity, ocular discomfort, recent mumps infection, absence of uveitis and iritis	PCR analysis of viral genome in sample of aqueous humor via AC tap is the gold standard; serum IgG and IgM have also demonstrated effectiveness	Topical corticosteroids only
Bacterial			
Pseudomonas aeruginosa (most common)	Rapid onset pain, redness, photophobia, discharge, decreased visual acuity, commonly contact lens overuse	Corneal scrapings for smear and culture will reveal the causative agent	Consider 4th generation fluoroquinolone as first line of treatment with consideration of aminoglycosides for unresponsive cases

Table 1 continued

Causative agent	Presentation	Diagnostic test	Treatment
Staphylococcus aureus	Rapid onset pain, redness, photophobia, discharge, decreased visual acuity, commonly contact lens overuse	Corneal scrapings for smear and culture will reveal the causative agent	Consider 4th generation fluoroquinolone as first line of treatment with consideration of vancomycin for unresponsive cases
Other causes			
Giant cell arteritis	Bilateral or unilateral, corneal edema and decompensation, KP, elevated BP, retinopathy, initially low IOP	Magnetic resonance angiography revealing stasis of ophthalmic arteries, gold standard is temporal artery biopsy	High dose oral or IV corticosteroids
Sarcoidosis	Granulomas in multiple ocular and systemic tissues. Other ocular findings are that of mutton-fat KP, uveitis, and macular edema	Tissue biopsy of lung	Topical corticosteroids, cycloplegics, regional corticosteroid injections, systemic corticosteroids, and systemic immunosuppressive agents
Secondary to cannabinoid use	Corneal edema with endothelial dysfunction	Patient history of frequent cannabinoid use, decreased endothelial cell count in confocal microscopy	Topical corticosteroids
Drug-induced (amantadine, mitomycin C, ethyl alcohol)	Bilateral corneal edema, with endothelial dysfunction	Patient history of an offending drug (comprehensive list of drugs causing endothelial toxicity found in Table 2)	Discontinuation of offending drug, begin topical corticosteroids
Venom ophthalmia	Corneal edema, superficial keratitis, pain, photophobia, iritis, conjunctival injection, corneal opacity	Patient history of handling venomous animals: frogs and snakes	Wash eye with BSS, and palliative support with corticosteroids
Tarantula keratopathy	Corneal edema, superficial keratitis, pain, photophobia, mutton-fat KP, conjunctival injection	Patient history of handling tarantula	Removal of barbs and treat with topical corticosteroids

Table 1 continued

Causative agent	Presentation	Diagnostic test	Treatment
Allograft rejection, corneal cross-linking, retained lens fragments, and vitreous incarceration after cataract surgery	History of procedure	Corneal edema on slit lamp exam	Management based on the underlying etiology, topical or systemic corticosteroids per clinical judgment

AC anterior chamber, *BP* blood pressure, *BSS* balanced salt solution, *IOP* intraocular pressure, *KP* keratic precipitates, *PCR* polymerase chain reaction

etiology of the disease process. For the readers' convenience, a diagnostic and treatment algorithm has been proposed (Fig. 6). Topical steroids are used to help control the inflammation, and if viral infection is suspected, concomitant antivirals should be used.

For viral etiologies, identifying the infectious agent aids in properly treating the endotheliitis. Currently, there are no established guidelines for dosage of treatment for viral endotheliitis. Table 1 presents current published treatment regimens. Topical valacyclovir can be added if oral treatment alone does not resolve the symptoms. These same oral dosages should be continued once per day for at least a year as a prophylactic measure for viral infection. Foscarnet should also be considered in resistant cases of CMV or HSV endotheliitis. However, foscarnet penetration from the plasma to vitreous is modest. If PCR or serology confirms mumps-related endotheliitis, only topical steroids are used [23]. Patients placed on antivirals including foscarnet and ganciclovir should have frequent monitoring of their kidney function (blood urea nitrogen and creatinine) as well as CBC and platelet count for possible toxicity. Children and patients with renal impairment require more frequent monitoring [114]. All patients cited in the literature were placed on topical corticosteroids to reduce inflammation.

For fungal etiologies, the pathogen may not grow in culture or be discovered by PCR. However, coalescent circular endothelial lesions with a feathery and white appearance may be revealed by in vivo confocal microscopy. If these lesions are seen, or if there are other reasons in the patient's history to suggest a fungal infection, intravenous voriconazole 200 mg every 12 h for 5 days [86] and 0.15% topical amphotericin B prepared from fungizone may be initiated [115]. Some patients may require adjunct intracameral or intrastromal antimycotic injections [86, 116].

If infectious etiologies have been ruled out and it is medically possible, medications suspected of causing corneal edema should be discontinued and topical steroids initiated. Upon resolution of the inflammation and if medically possible, the offending medication should not be restarted. Notably, in patients that have chronic glaucomatous disease, alternative pressure control regimens that do not exacerbate the endotheliitis should be instituted. If no suitable alternative regimen is found, the patient should be notified of the risk of continued treatment and the medication dose should be titrated to minimize risk.

If further screening of patient contact with animals reveals venom ophthalmia, tarantula keratitis, bee sting corneal edema, or plant exposure, palliative medication with corticosteroids and removal of any offending foreign body is standard. Iatrogenic corneal endotheliitis is a risk inherent to cornea and refractive procedures and surgery, including collagen cross-linking treatments. If endotheliitis arises following a procedure, treatment with topical steroid and hypertonic saline solution is indicated.

Table 2 Common uses of drugs associated with endothelial dysfunction

Drug	Common use
Amantadine	Neuropsychiatric and antiviral drug that is routinely used in patients with depression, influenza A, and Parkinson's disease
Methylphenidate	ADHD and narcolepsy
Ropinirole	Parkinson's disease and restless leg syndrome
Resiniferatoxin	Analgesic
Memantine	Alzheimer's disease
Dorzolamide	Glaucoma and elevated IOP treatment
Amiodarone	Antiarrhythmic
Ethyl alcohol	Recreation
Intracameral lidocaine*	Intraoperative anesthetic
Phenylephrine*	Mydriatic (adrenergic agonist)
Benzalkonium chloride	Preservative in medicated eye drops
Mitomycin C	Antineoplastic, used in numerous intraocular surgeries
Menadione	Used as vitamin K supplement; not common in developed countries
Phenothiazines	Antipsychotic
Tetracaine*, proparacaine*	Topical anesthetic

*Toxicity and damage to the endothelium may be secondary to the carriers, preservatives, or high frequency usage of these medications

Systemic diseases should be treated according to established guidelines and coordinated with internal medicine or rheumatologic referral. Ocular sarcoidosis treatment consists of topical corticosteroids, cycloplegics, regional corticosteroid injections, systemic corticosteroids, and systemic immunosuppressive agents [117].

CONCLUSION

Endotheliitis has a vast range of etiologies which exceed the commonly known viral causes. The substantial knowledge of its symptomatology, disease course, and management can be overwhelming for some practitioners. Since there are many entities that can present with corneal edema, it is imperative that practitioners consider a broad differential to distinguish endotheliitis from other similar-appearing causes of corneal edema, as well as familiarize themselves with appropriate diagnostic and treatment methods.

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REFERENCES

1. Waring GO, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal and pathologic structure and function. Ophthalmology. 1982;89(6):531–90.

2. Müller A, McGhee CNJ. Professor Ernst Fuchs (1851-1930): a defining career in ophthalmology. Arch Ophthalmol. 2003;121(6):888–891.

3. Fuchs E. Text-book on ophthalmology. New York: Lippincott; 1923.

4. Doggart J. Superficial punctate. Br J Ophthalmol. 1933;17(2):65–82.

5. Lundsgaard K. Acute diffuse parenchymatous keratitis as a complication in parotitis epidemica. Acta Ophthalmol. 1923;1(1–2):185–8.

6. Khodadoust A, Attarzadeh A. Presumed autoimmune corneal endotheliopathy. Am J Ophthalmol. 1982;93(6):718–22.

7. Robin JB, Schanzlin DJ, Verity SM, et al. Peripheral corneal disorders. Surv Ophthalmol. 1986;31(1):1–36.

8. Ohashi Y, Yamamoto S, Nishida K, et al. Demonstration of herpes simplex virus DNA in idiopathic corneal endotheliopathy. Am J Ophthalmol. 1991;112(4):419–23.

9. Suzuki T, Ohashi Y. Corneal endotheliitis. Semin Ophthalmol. 2008;23(4):235–40.

10. Krachmer J, Mannis M, Holland E. Cornea e-book. Amsterdam: Elsevier; 2010. p. 967–8.

11. Alfawaz A. Cytomegalovirus-related corneal endotheliitis: a review article. Saudi J Ophthalmol. 2013;27:47–9.

12. Hori Y, Maeda N, Kosaki R, Inoue T, Tano Y. Three cases of idiopathic "multiple-parallel-line" endotheliitis. Cornea. 2008;27(1):103–6.

13. Oxley LA, Carrim ZI. Multiple parallel-line endotheliitis—a form of herpes simplex keratitis? Optom Vis Sci. 2012;89(3):E353–5.

14. Le Piane S, Hillenaar T, Remeijer L. Self-limiting corneal edema with multiple parallel lines on the endothelium (SCEMPLE). Int Ophthalmol. 2014;34(6):1279–84. https://doi.org/10.1007/s10792-014-9995-8.

15. Hamilton C, Seamone CD, Darvish M, Gupta RR. Multiple parallel-line endotheliitis: case report and literature review of an emerging entity. Can J Ophthalmol. 2016;51(3):e89–92.

16. Koizumi N, Inatomi T, Suzuki T, et al. Clinical features and management of cytomegalovirus corneal endotheliitis: analysis of 106 cases from the Japan corneal endotheliitis study. Br J Ophthalmol. 2015;99(1):54–8.

17. Inoue Y. Review of clinical and basic approaches to corneal endotheliitis. Cornea. 2014;33 Suppl 11:S3–8.

18. Chiang CC, Lin TH, Tien PT, Tsai YY. Atypical presentation of cytomegalovirus endotheliitis: a case report. Ocul Immunol Inflamm. 2011;19(1):69–71.

19. Baltatzis S, Romero-Rangel T, Foster CS. Sectorial keratitis and uveitis: differential diagnosis. Graefes Arch Clin Exp Ophthalmol. 2003;241:2–7.

20. Carrillo-Arroyo I, Gutierrez-Diaz E, Mencia-Gutierrez E, Gomez-Perez P, Montero-Rodriguez M. Herpetic endotheliitis and trabeculitis with delayed corneal involvement. Arch Soc Esp Oftalmol. 2012;87(2):47–9.

21. Galpine JF, Walkowski J. A case of mumps with involvement of the lacrimal glands. Br Med J. 1952;1(4767):1069–70.

22. Kawaguchi A. A case of fulminant comeal endotheliitis without parotitis suspected of mumps virus infection. Jpn J Clin Ophthalmol. 2013;67(7):1143–7.

23. Singh K, Sodhi PK. Mumps-induced corneal endotheliitis. Cornea. 2004;23(4):400–2.

24. Khodabande A. Varicella endotheliitis: a case report. Eur J Ophthalmol. 2009;19(6):1076–8.

25. Morishige N, Morita Y, Yamada N, Sonoda KH. Differential changes in intraocular pressure and corneal manifestations in individuals with viral

endotheliitis after keratoplasty. Cornea. 2016;35(5):602–6.

26. Lin TY, Hwang YS, Ma DHK. A method to prepare a Descemet's stripping automated endothelial keratoplasty (DSAEK) graft using donor corneas with narrow scleral rims: a case report. Medicine (Baltimore). 2015;94(39):e1597.

27. Inoue T, Kandori M, Takamatsu F, Hori Y, Maeda N. Corneal endotheliitis with quantitative polymerase chain reaction positive for human herpesvirus 7. Arch Ophthalmol. 2010;128(4):502–3.

28. Lim DH, Kim J, Lee JH, Chung ES, Chung TY. A case of corneal endothelial dysfunction due to coxsackievirus A24 corneal endotheliitis after cataract surgery. Cornea. 2014;33(5):533–5.

29. Madhavan H, Goldsmith C, Rao S, Al E. Isolation of a vesicular virus belonging to the family rhabdoviridae from the aqueous humor of a patient with bilateral corneal endotheliitis. Cornea. 2002;21:333–5.

30. Teweldemedhin M, Gebreyesus H, Atsbaha AH, Asgedom SW, Saravanan M. Bacterial profile of ocular infections: a systematic review. BMC Ophthalmol. 2017;17:212.

31. Yang Y, Teja S, Baig K. Bilateral corneal edema associated with amantadine. CMAJ. 2015;187(15):1155–8.

32. Lee PY, Tu HP, Lin CP, et al. Amantadine use as a risk factor for corneal edema: a nationwide cohort study in Taiwan. Am J Ophthalmol. 2016;171:122–9.

33. Starte JM, Tien-Chin Fung A, Kerdraon YA. Ketamine-associated corneal edema. Cornea. 2012;31(5):572–4.

34. Feng MT, Price FW, McKee Y, Price MO. Memantine-associated corneal endothelial dysfunction. JAMA Ophthalmol. 2015;133(10):1218–20.

35. Hadjikoutis S, Morgan JE, Wild JM, Smith PEM. Ocular complications of neurological therapy. Eur J Neurol. 2005;12:499–507.

36. Cui Y-B, Wu J. Research progress on the negative factors of corneal endothelial cells proliferation. Int J Ophthalmol. 2012;5(5):614–9.

37. Erdurmus M, Selcoki Y, Yagci R, Hepsen IF. Amiodarone-induced keratopathy: full-thickness corneal involvement. Eye Contact Lens. 2008;34(2):131–2.

38. Halilovic A, Schmedt T, Benischke A-S, et al. Menadione-induced DNA damage leads to mitochondrial dysfunction and fragmentation during rosette formation in Fuchs endothelial corneal dystrophy. Antioxid Redox Signal. 2016;24(18):1072–83.

39. Eggeling P, Pleyer U, Hartmann C, Rieck PW. Corneal endothelial toxicity of different lidocaine concentrations. J Cataract Refract Surg. 2000;26(9):1403–8.

40. Wen Q, Fan T, Bai S, Sui Y. Cytotoxicity of proparacaine to human corneal endothelial cells in vitro. J Toxicol Sci. 2015;40(4):427–36.

41. Madreperla S, Johnson M, O'Brien T. Corneal endothelial dysfunction in digoxin toxicity. Am J Ophthalmol. 1992;113(2):211–2.

42. Umunakwe O, Herren D, Kim S, Kohanim S. Diffuse ocular and orbital inflammation after zoledronate infusion-case report and review of the literature. Digit J Ophthalmol. 2017;23(4):18–21.

43. Derick R, Pasquale L, Quiqley H. Potential toxicity of mitomycin C. Arch Ophthalmol. 1991;109(12):1635.

44. Fu GL, Alexander JL, Saeedi OJ. Persistent corneal edema associated with subconjunctival 5-fluorouracil in an infant with primary congenital glaucoma. J Pediatr Ophthalmol Strabismus. 2016;53:e54–7.

45. Hirji N, Griffiths M. Snailtrack corneal changes following subconjunctival injection of 5-fluorouracil. Eye (London). 2012;26:1495–6.

46. Jalil A, Au L, Khan I, Ashworth J, Lloyd IC, Biswas S. Combined trabeculotomy-trabeculectomy augmented with 5-fluorouracil in paediatric glaucoma. Clin Exp Ophthalmol. 2011;39(3):207–14.

47. Scott IU, Murray TG, Flynn HW, Feuer WJ, Schiffman JC. Outcomes and complications associated with giant retinal tear management using perfluoro-*n*-octane. Ophthalmology. 2002;109(10):1828–33.

48. Alharbi SS, Asiri MS. Reversible corneal toxicity of retained intracameral perfluoro-*n*-octane. Middle East Afr J Ophthalmol. 2016;23(3):277–9.

49. Wilbanks GA, Apel AJG, Jolly SS, Devenyi RG, Rootman DS. Perfluorodecalin corneal toxicity: five case reports. Cornea. 1996;15(3):329–34.

50. Timucin OB, Karadag MF, Aslanci ME, Baykara M. Methylene blue-related corneal edema and iris discoloration. Arq Bras Oftalmol. 2015;79(2):121–2.

51. Edelhauser HF. The resiliency of the corneal endothelium to refractive and intraocular surgery. Cornea. 2000;19:263–73.

52. Kwon J, Heo JH, Kim HM, Song JS. Comparison of cytotoxic effects on rabbit corneal endothelium between preservative-free and preservative-containing dorzolamide/timolol. Korean J Ophthalmol. 2015;29(5):1011–8942.

53. Hughes EH, Pretorius M, Eleftheriadis H, Liu CSC. Long-term recovery of the human corneal endothelium after toxic injury by benzalkonium chloride. Br J Ophthalmol. 2007;91(11):1460–3.

54. Wirtitsch MG, Findl O, Heinzl H, Drexler W. Effect of dorzolamide hydrochloride on central corneal thickness in humans with cornea guttata. Arch Ophthalmol. 2007;125(10):1345–50.

55. Konowal A, Morrison JC, Brown SVL, et al. Irreversible corneal decompensation in patients treated with topical dorzolamide. Am J Ophthalmol. 1999;127(4):403–6.

56. Inoue K, Okugawa K, Oshika T, Amano S. Influence of dorzolamide on corneal endothelium. Jpn J Ophthalmol. 2003;47(2):129–33.

57. Shiono T, Asano Y, Hashimoto T, Mizuno K. Temporary corneal oedema after acute intake of alcohol. Br J Ophthalmol. 1987;71(6):462–5.

58. Polat N, Cumurcu B, Cumurcu T, Tuncer İ. Corneal endothelial changes in long-term cannabinoid users. Cutan Ocul Toxicol. 2018;37(1):19–23.

59. Bagga B, Pahuja S, Murthy S, Sangwan VS. Endothelial failure after collagen cross-linking with riboflavin and UV-A: case report with literature review. Cornea. 2012;31(10):1197–200.

60. Gumus K. Acute idiopathic endotheliitis early after corneal cross-linking with riboflavin and ultraviolet-A. Cornea. 2014;33:630–3.

61. Sharma A, Nottage J, Mirchia K, Al E. Persistent corneal edema after collagen cross-linking for keratoconus. Am J Ophthalmol. 2012;154:922–6.

62. Gokhale NS. Corneal endothelial damage after collagen cross-linking treatment. Cornea. 2011;30(12):1495–8.

63. Holopainen JM, Krootila K. Transient corneal thinning in eyes undergoing corneal cross-linking. Am J Ophthalmol. 2011;152(4):533–6.

64. Razmjoo H, Al E. Comparison of the findings of endothelial specular microscopy before and after corneal cross-linking. Adv Biomed Res. 2015;17(4):52.

65. Hui JI, Fishler J, Karp CL, Shuler MF, Gedde SJ. Retained nuclear fragments in the anterior chamber after phacoemulsification with an intact posterior capsule. Ophthalmology. 2006;113(11):1949–53.

66. Lim L, Tarafdar S, Collins C, Ramamurthi S, Ramaesh K. Corneal endothelium in Brown–McLean syndrome: in vivo confocal microscopy finding. Semin Ophthalmol. 2012;27(1–2):6–7.

67. Kam K, Jhanji V, Young A. Brown–McLean syndrome. BMJ Case Rep. 2013;1:2. https://doi.org/10.1136/bcr-2013-201280.

68. Sun B, He Y, Zhong P, Wang R. Peripheral corneal oedema following cataract extraction. Zhonghua Yan Ke Za Zhi. 1998;34(1):31–3.

69. Anshu A, Chee SP, Mehta JS, Tan DTH. Cytomegalovirus endotheliitis in Descemet's stripping endothelial keratoplasty. Ophthalmology. 2009;116(4):624–30.

70. Ghauri A, Williams G, Shah S, Murray P, Rauz S. Post-phacoemulsification cytomegalovirus corneal endotheliitis diagnosis and management. JRSM Short Rep. 2012;3(6):42.

71. McDonnell PJ, de la Cruz ZC, Green WR. Vitreous incarceration complicating cataract surgery: a light and electron microscopic study. Ophthalmology. 1986;93(2):247–53.

72. Mamalis N, Edelhauser H, Dawson D, Chew J, LeBoyer R, Werner L. Toxic anterior segment syndrome. J Cataract Refract Surg. 2006;32(2):324–33.

73. Altıntaş AK, Ciritoğlu MY, BeyazyıldıZ Ö, Can ÇÜ, Polat S. Toxic anterior segment syndrome outbreak after cataract surgery triggered by viscoelastic substance. Middle East Afr J Ophthalmol. 2017;24(1):43–7.

74. Matsou A, Tzamalis A, Chalvatzis N, Mataftsi A, Tsinopoulos I, Brazitikos P. Generic trypan blue as possible cause of a cluster of toxic anterior segment syndrome cases after uneventful cataract surgery. J Cataract Refract Surg. 2017;43(6):848–52.

75. Baradaran-Rafii A, Asl NS, Ebrahimi M, et al. The role of amniotic membrane extract eye drop (AMEED) in in vivo cultivation of limbal stem cells. Ocul Surf. 2017;16:146–53.

76. Lim CHL, Wong NJY, Ng CH, Meusemann RA, Daniell MD, Symons RA. Toxic anterior segment syndrome in a tertiary Australian healthcare institution. Clin Exp Ophthalmol. 2017;45:750–2.

77. Sorenson AL, Sorenson RL, Evans DJ. Toxic anterior segment syndrome caused by autoclave reservoir wall biofilms and their residual toxins. J Cataract Refract Surg. 2016;42(11):1602–14.

78. Madi HA, Morgan SJ, Ghosh S. Corneal graft failure due to migration of OzurdexTM implant into the anterior chamber. Am J Ophthalmol Case Reports. 2017;8:25–7.

79. Pacella F, Agostinelli E, Carlesimo SC, et al. Management of anterior chamber dislocation of a dexamethasone intravitreal implant: a case report. J Med Case Rep. 2016;10(1):282.

80. Bernal L, Estévez B. Corneal toxicity after Ozurdex® migration into anterior chamber. Arch Soc Esp Oftalmol. 2016;91(6):292–4.

81. Saunders R, Bluestein E, Wilson M, Berland J. Anterior segment ischemia after strabismus surgery. Surv Ophthalmol. 1994;38(5):456–66.

82. Pineles SL, Chang MY, Oltra EL, et al. Anterior segment ischemia: etiology, assessment, and management. Eye. 2018;32(2):173–8.

83. Gurelik G, Safak N, Koksal M, Bilgihan K, Hasanreisoglu B. Acute corneal decompensation after silicone oil removal. Int Ophthalmol. 2001;23(3):131–5.

84. Gunes A, Yasar C, Tok L, Tok O. Two cases of anterior uveitis after laser eyebrow epilation. Cornea. 2015;34(1):101–2.

85. Garg P. Fungal, mycobacterial, and nocardia infections and the eye: an update. Eye. 2012;26:245–51.

86. Zapata LF, Paulo JD, Restrepo CA, Velásquez LF, Montoya AET, Zapata MA. Infectious endotheliitis: a rare case of presumed mycotic origin. Clin Ophthalmol. 2013;7:1459–61.

87. Chen YC, Yen DHT, Chen YW, Huang MS, Huang CI, Chen MH. Toxin ophthalmia caused by nuchal gland secretion of the Taiwan tiger keelback (Rhabdophis tigrinus formosanus). J Formos Med Assoc. 2014;113(10):750–3.

88. Chu ER, Weinstein SA, White J, Warrell DA. Venom ophthalmia caused by venoms of spitting elapid and other snakes: report of ten cases with review of epidemiology, clinical features, pathophysiology and management. Toxicon. 2010;56:259–72.

89. Shrum K, Robertson D, Baratz K, Casperson T, Rostvold J. Keratitis and retinitis secondary to tarantula hair. Arch Ophthalmol. 1999;117(8):1096–7.

90. Gürlü VP, Erda N. Corneal bee sting-induced endothelial changes. Cornea. 2006;25(8):981–3.

91. Jullienne R, He Z, Manoli P, et al. In vivo confocal microscopy of pine processionary caterpillar hair-induced keratitis. Cornea. 2015;34(3):350–2.

92. Efron N. Contact lens-induced changes in the anterior eye as observed in vivo with the confocal microscope. Prog Retin Eye Res. 2007;26(4):398–436.

93. McNutt P, Tuznik K, Nelson M, et al. Structural, morphological, and functional correlates of corneal endothelial toxicity following corneal exposure to sulfur mustard vapor. Investig Ophthalmol Vis Sci. 2013;54(10):6735–44.

94. Pleyer U, Sherif Z, Baatz H, Hartmann C. Delayed mustard gas keratopathy: clinical findings and confocal microscopy. Am J Ophthalmol. 1999;128:506–7.

95. Amiran MD, Lang Y, Yeung SN. Corneal endothelial toxicity secondary to *Asclepias fruticosa*. Eye. 2011;25:961–3.

96. Basak SK, Bhaumik A, Mohanta A, Singhal P. Ocular toxicity by latex of *Calotropis procera* (Sodom apple). Indian J Ophthalmol. 2009;57(3):232–4.

97. Amry MA, Al-Saikhan F, Ayoubi A. Toxic effect of cadmium found in eyeliner to the eye of a 21 year old Saudi woman: a case report. Saudi Pharm J. 2011;19(4):269–72.

98. Moshirfar M, Ding Y, Ronquillo Y, Birdsong OC. Ultramarathon-induced bilateral corneal edema : a case report and a review of the literature. Ophthalmol Ther. 2018. https://doi.org/10.1007/s40123-018-0125-y.

99. Khodaee M, Torres DR. Corneal opacity in a participant of a 161-km mountain bike race at high altitude. Wilderness Environ Med. 2016;27(2):274–6. https://doi.org/10.1016/j.wem.2016.02.002.

100. Bayar SA, Gokmen O, Pinarci EY, Altinors DD, Gedik Ş. Corneal endothelial decompansation and ocular hypotony in a case with temporal arteritis. J Neuro-Ophthalmol. 2012;32:385.

101. Pellegrini F, Prosdocimo G, Bonsanto D, Machin P, Foroozan R. Thick corneas, large pupils, and a giant problem. Surv Ophthalmol. 2017;63:595–9.

102. Ambiya V, Singh HP, Mandal S, Radhakrishnan AP. A case of systemic sarcoidosis with ocular presentation. Med J: Armed Forces India; 2015. p. 71.

103. Kasbekar SA, Gonzalez-Martin JA, Shafiq AE, Chandna A, Willoughby CE. Corneal endothelial dysfunction in Pearson syndrome. Ophthalmic Genet. 2013;34(1–2):55–7.

104. Colyer M, Bower K, Ward T, Hidayat A, Subramanian P. Mitochondrial myopathy presenting with

segmental corneal oedema and retrocorneal membrane. Br J Ophthalmol. 2007;91(5):696–7.

105. Momont AC, Trobe JD. Transient corneal edema and left hemisphere dysfunction in Pearson syndrome. J Neuro-Ophthalmol. 2009;29:158–9.

106. Kelly A, Kaufman SC, Ali R, Grajewski A, Anderson J. Rare anterior segment retinoblastoma masquerading as corneal endotheliitis. Eye Contact Lens. 2016;42(1):e1–3.

107. Sriram A, Tania Tai T. Resolution of chronic corneal edema after surgical treatment for ocular hypotony. J Glaucoma. 2017;26(6):187–9.

108. Hillenaar T, Mooy CM, Verjans GMGM, Remeijer L. Zipper cell endotheliopathy: a new subset of idiopathic corneal edema. Ophthalmology. 2010;117(12):2255–62.

109. Duman R, Tok Çevik M, Görkem Çevik S, Duman R, Perente İ. Corneal endothelial cell density in healthy Caucasian population. Saudi J Ophthalmol. 2016;30(4):236–9.

110. Bacich DJ, Sobek KM, Cummings JL, Atwood AA, O'Keefe DS. False negative results from using common PCR reagents. BMC Res Notes. 2011;4(1):457.

111. Tavakoli M, Hossain P, Malik RA. Clinical applications of corneal confocal microscopy. Clin Ophthalmol. 2008;2(2):435–45.

112. Shiraishi A, Hara Y, Takahashi M, et al. Demonstration of "Owl's Eye" morphology by confocal microscopy in a patient with presumed cytomegalovirus corneal endotheliitis. Am J Ophthalmol. 2007;143(4):715–7.

113. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21):2153–65.

114. UCSF Medical Center. Foscarnet dosing and monitoring. https://idmp.ucsf.edu/ucsf-medical-center-foscarnet-dosing-and-monitoring.

115. Müller GG, Kara-José N, De Castro RS. Antifungals in eye infections: drugs and routes of administration. Rev Bras Oftalmol. 2013;72(2):132–41.

116. Mittal V, Mittal R. Intracameral and topical voriconazole for fungal corneal endoexudates. Cornea. 2012;31(4):366–70.

117. Pasadhika S, Rosenbaum JT. Ocular sarcoidosis. Clin Chest Med. 2015;36:669–83.