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
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
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 with orange-brown pigment in the endothelium and peripheral corneal edema [10]. Confo-cal 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 striae 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 antifungal 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 cicatriz ing 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].

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/mm² 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 antifungal 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

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**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                | 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          |
| (amantadine, mitomycin C, ethyl alcohol) |                                                                              |                                                                                  |                                                                          |
| 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                   |
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 antymyotic 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 glucomatous 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 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
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].

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

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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