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## Abstract

Corneal endothelial cells are responsible for removing fluid from the cornea through sodium/potassium-ATPase pumps, thus keeping the cornea relatively dehydrated and clear. Corneal edema occurs when excessive fluid is in the cornea, leading to a blue hue. Edema can occur focally from loss of the epithelial cell barrier or diffusely from pathology of the corneal endothelial cells. This article will discuss primary and secondary causes of corneal edema, including pathophysiology, diagnosis, and treatment. Proper management of the underlying disease can help prolong vision and comfort in affected eyes.

OPHTHALMOLOGY

# Corneal Edema: How to Approach a Blue Eye

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The cornea is the transparent outer fibrous tunic of the eye that protects the internal structures of the eye and transmits light to the retina to form an image. The canine cornea has 4 distinct "layers" from the outside in: multicellular epithelium, collagenous stroma, Descemet's membrane (a basement membrane of the endothelium), and single-layer endothelium.[1] The corneal epithelium and endothelium are important in preserving the clarity of the cornea. The epithelium provides an outer barrier that prevents fluid from the tears from infiltrating the stroma. The endothelium uses physiologic sodium/potassium ($Na^+/K^+$)-ATPase pumps to remove fluid (aqueous humor) from the stroma.

Any disruption to the epithelium and/or endothelium can result in fluid infiltrating the stroma, giving the eye a bluish, hazy appearance (**FIGURE 1**).[1] Any time a patient is presented with a "blue eye," a thorough history, physical exam, and ophthalmic exam are essential for diagnosing the cause of the edema.

## DIAGNOSTIC TESTS

### Tear Production and Fluorescein Stain

A Schirmer tear test should be performed to quantify the aqueous portion of the tears prior to

### Take-Home Points

- Glaucoma should be the first etiology ruled out in any eye with corneal edema because it poses the most immediate threat to vision and comfort.
- Next, other potentially painful and vision-threatening causes of corneal edema, including corneal ulcers, anterior uveitis, anterior lens luxations, or endotheliitis, should be ruled out.
- Endothelial dystrophy is a progressive and bilateral disease with treatment mostly aimed at preventing corneal ulcers secondary to severe corneal edema. However, newer treatments are being used to try to reduce the amount of corneal edema and help retain better vision at least for a short time.
- Endotheliitis is a poorly studied cause of corneal edema, although new studies are emerging regarding pathophysiology, clinical signs, and treatment for this disease.
- A good history and ophthalmic exam can usually provide a guide to the underlying diagnosis for corneal edema.
- Treatment is often aimed at treating the underlying cause and/or preventing painful sequelae of edema, such as corneal ulcers.

any drops being administered in the eye. Normal range for the test should be >15 mm/minute.[2] Values lower than this may be indicative of dry eye, which can predispose the eye to ulcers and neovascularization that can lead to focal corneal edema.[2] Corneal ulceration leads to secondary focal edema through influx of the aqueous portion of the tear film into the corneal stroma. Neovascularization leads to focal edema because new vessels leak serum into the cornea. On the other hand, significant corneal edema can result in secondary bullae ("blister") formation, which can rupture and lead to ulceration. Thus, any eye with corneal edema should be stained with fluorescein to evaluate for corneal ulcers. Fluorescein will adhere to any exposed stroma, thus allowing for the evaluation of breaks in the corneal epithelium.

### Intraocular Pressure

Intraocular pressure (IOP) measurement is the most important diagnostic tool for any eye with corneal edema as uveitis and glaucoma are both significant causes that can lead to blindness if left untreated. The IOP can be obtained using rebound tonometry (e.g., TonoVet [iCare, tonovet.com], Tono-Vera Vet [Reichert, reichert.com]) or applanation tonometry (e.g., Tono-Pen AVIA [Reichert, reichert.com]). One study found that the measurements read by TonoVet versus Tono-Pen vary between these devices with elevated pressures; therefore, consistently using the same device is necessary when monitoring individual patients.[3] This study also compared diseased portions of the cornea (e.g., pigmentation, vascularization, edema) to normal areas on the same eye.[3] The diseased portion of the cornea varied on average 2.1 mm Hg (–6 to +16 mm Hg) with the TonoVet and 3.2 mm Hg (–7 to +20 mm Hg) with the Tono-Pen.[3] Therefore, IOP measurements should be attempted on the most normal portion of the cornea.

**FIGURE 1.** The diffuse bluish, lacy appearance to the cornea depicts deep corneal edema secondary to moderate corneal endothelial dystrophy.

Normal canine IOP is in the range of 10 to 25 mm Hg.[4] Values above 25 mm Hg are consistent with glaucoma and should be taken seriously, as glaucoma can be devastating to intraocular structures and lead to blindness. Care should be taken to ensure that the values are not falsely elevated. Manual jugular pressure and eyelid manipulation can significantly increase IOP baseline values.[5] Skull shapes can also affect mean IOP, with brachycephalic breeds having a higher mean baseline (16.4 ± 2.9 mm Hg) compared to mesaticephalic (11.8 ± 3.7 mm Hg) and dolichocephalic (13.5 ± 1 mm Hg) breeds. Stress can also falsely elevate IOPs.[4] With overly stressed patients, gabapentin and/or trazodone can be used as they have not been shown to clinically affect the IOP.[6]

Low IOPs, especially in the single digits, may be indicative of uveitis. When low IOPs are seen concurrently with corneal edema, the eye should be examined closely for signs of inflammation (e.g., conjunctival hyperemia, miosis, hypopyon, hyphema, aqueous flare).[7] Corneal edema can make assessment of intraocular changes difficult. Working in a dark room and use of the focal slit beam on the ophthalmoscope can aid in visualizing these clinical signs.

## CAUSES OF CORNEAL EDEMA

### Glaucoma

Glaucoma is an optic neuropathy associated with an increase in IOP leading to vision loss from irreversible damage to the retinal ganglion cells and optic nerve. Some breeds predisposed to primary glaucoma include cocker spaniels, Boston terriers, basset hounds, and wire-haired fox terriers, along with a long list of other breeds in which it has been described. Females are overrepresented, and the average age of presentation is between 4 and 10 years of age.[4]

Secondary glaucoma results from a variety of causes, including uveitis, lens luxations, hypermature cataracts, retinal detachments, progressive retinal atrophy, neoplasia, and intraocular surgery.[4,8] Signalment, presentation, and the ocular exam may lead clinicians to suspect secondary glaucoma.[8] For example, which part of the exam is worse? If the uveitis is worse than

the pressure increase, or there are other changes in the eye as listed above, it is more likely to be secondary glaucoma.

Clinical signs of glaucoma depend on the severity of the pressures. Early stages may involve mild episcleral injection, mydriasis, and transient corneal edema. As the disease progresses and the pressures become higher, the corneal edema will be more severe and diffuse; additionally, significant mydriasis and episcleral injection, buphthalmia, and blindness can become apparent. Prolonged IOP >40 mm Hg is necessary to lead to corneal edema.[4] Diagnosis of glaucoma is based on an increased IOP, as described above. More advanced diagnostics, such as gonioscopy and ultrasound, may be used to evaluate the iridocorneal angle in the contralateral or "normal" eye to assess the risk of that eye developing glaucoma.

The pathogenesis behind corneal edema associated with glaucoma is multifactorial. One study found that glaucomatous eyes had lower corneal endothelial cell counts as compared to healthy eyes, which could be due to direct damage from the elevated IOP, congenital alterations of the endothelium in patients that develop glaucoma, glaucoma medication toxicity, or a combination of these causes.[9] Another study found an increased cyclooxygenase 2 (COX-2) expression in corneal epithelial and endothelial cells of glaucomatous eyes, which may play a role in aqueous production/removal or may be secondary to inflammation due to stretching of the tissues by the increased IOP.[10] Further studies are warranted to determine the significance of COX-2 in the pathogenesis of glaucoma and as a potential target for glaucoma therapy. Finally, during pressure elevations, the increased hydrostatic pressure in the anterior chamber decreases the normal flow of fluid from the cornea to the iridocorneal angle.[4]

Treatment for glaucoma is focused on lowering the IOP to safe levels (<20 mm Hg) to maintain the health of the optic nerve. Lowering the IOP also helps resolve or prevent further worsening of the corneal edema that has developed due to the aforementioned pathogenesis. If the pressure is controlled early enough, before the critical mass of endothelial cells is lost, the hydrostatic pressure is decreased and thus the endothelial cells can resume their normal function of removing fluid from the cornea. However, if too many endothelial cells are compromised, due to either chronic increased pressure or a severe pressure spike, corneal edema may be permanent despite proper pressure control.[4,10]

## Anterior Lens Luxation

Anterior lens luxation can be congenital, primary, or secondary:

- **Congenital lens luxation** is rare and involves the absence of zonules (the fibers that hold the lens in place).
- **Primary lens luxation** is most common in terrier breeds and has been associated with a genetic mutation that affects the zonules.
- **Secondary lens luxation** has been attributed to age-related degeneration, chronic uveitis, glaucoma, cataracts, and trauma.[11]

When the lens luxates anteriorly, acute glaucoma can result from the lens blocking normal flow of aqueous fluid through the pupil.[12] Corneal edema can develop due to the direct trauma of the lens hitting the endothelium or secondary glaucoma (**FIGURE 2**). A slit

**FIGURE 2.** The bluish, lacy appearance of corneal edema secondary to an anterior lens luxation. Note the equator of the lens anterior to the iris, especially dorsally in this image.

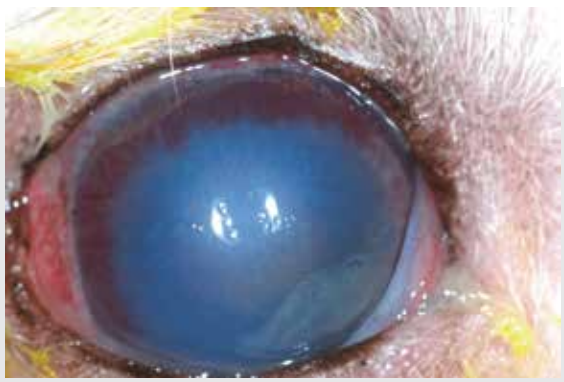

**FIGURE 3.** Corneal edema secondary to anterior uveitis. Note the deep neovascularization and conjunctival hyperemia, both additional clinical signs of anterior uveitis.

beam on the direct ophthalmoscope will show a shallow anterior chamber and the equator of the lens anterior to the iris due to the luxation of the lens. Treatments for anterior lens luxations include transcorneal reduction of the lens or intracapsular lens extraction.[12]

## Uveitis

Anterior uveitis is inflammation of the iris and/or ciliary body characterized by aqueous flare but can also encompass conjunctival hyperemia (**FIGURE 3**), miosis, hypopyon, or hyphema.[7] Uveitis can cause corneal edema due to an increase in endothelial permeability and a decrease in $Na^+/K^+$-ATPase pump site density.[7,13] In these cases, there is normal endothelial cell density, but the cells are edematous with disrupted intercellular junctions.[7] The damage to the endothelium may be due to prostaglandins, oxygen-free radicals, and hydrolytic enzymes from leukocytes.[7] Uveitis is managed through treatment of the underlying cause as well as topical and systemic anti-inflammatories. The corneal edema should dissipate with resolution of the uveitis. However, if keratic precipitates form or the endothelial cells are irreversibly damaged from the inflammation, edema may not resolve.

## Endothelial Dystrophy

Corneal endothelial dystrophy (CED) is a disease characterized by decreased endothelial cell density as well as abnormal morphology, including cell pleomorphism (variable size and shape of cells) and polymegathism (greater-than-normal variation in size), which results in increasing corneal edema.[14] It is a progressive and bilateral disease similar to a genetic disease in humans, Fuchs' dystrophy. Boston terriers, Chihuahuas, and dachshunds are overrepresented in the diagnosis of CED.[1,15] In addition, a study from the University of California, Davis, found that of large breeds, German shorthaired and wirehaired pointers were overrepresented.[16] Females are also 3 times more likely to develop this disease, which is also seen in Fuchs' dystrophy. The median age of onset is between 10 and 12 years of age,[14,15] with 92% of cases presenting over the age of 8 years.[15] These ages correlate with the average age of onset of Fuchs' dystrophy in humans at 50 to 60 years.[14] CED in Boston terriers is noted to typically start temporally then progress over 1 to 2 years to involvement of the entire cornea (**FIGURE 4**). The German shorthaired and wirehaired pointers were noted to have a more diffuse edema on presentation.[16] Although dogs are expected to be affected bilaterally, there can be an asymmetric onset and progression of the affected eyes.[14] Conjunctival hyperemia can range from absent to reportedly 69% of eyes affected by CED.[1,15] The Schirmer tear test and IOPs are reported to be unaffected by CED.[14]

The diffuse edema can result in formation of bullae that can rupture and lead to multiple tiny ulcerations, which then can progress to larger ulcers if the epithelium sloughs off. While CED itself is not painful, these ulcers are a source of pain and morbidity associated with this disease. At this time, treatment is mainly focused on preventing bullae and corneal ulcer formation to maintain comfort in these eyes. Palliative treatment includes topical 5% sodium chloride (NaCl) ointment, which helps reduce the development of bullae and subsequent ulcer formation. In normal corneas, treatment with 5% NaCl ointment was found to decrease central corneal thickness by 2% to 4%, but it is suspected that this percentage may be higher with diseased corneas.[17] However, significant corneal clearing should not be an expectation with topical 5% NaCl administration.[1] A new study found that a topical rho-associated kinase (ROCK) inhibitor, ripasudil, can show improvement or stabilization of the edema in up to 62% of dogs with endothelial dystrophy.[18] Further studies are warranted to better understand the efficacy, safety, and use of ROCK inhibitors in these cases.

Surgical options have also been used to help resolve some of the corneal edema. Thermokeratoplasty involves using thermal cautery to cause contraction of anterior stromal fibers multifocally, thus inducing scar tissue that physically prevents fluid from accumulating within the anterior stroma (**FIGURE 5**). This technique

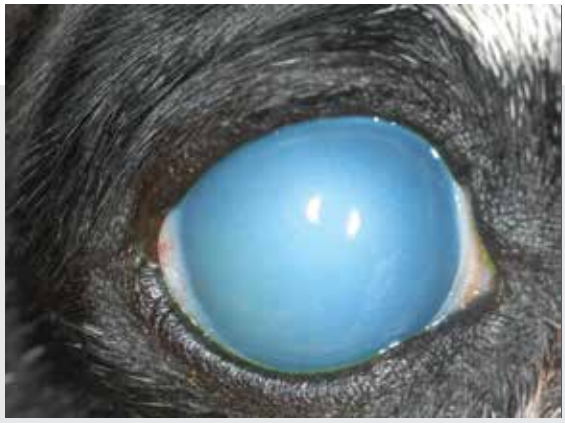

**FIGURE 4.** Diffuse corneal edema secondary to advanced endothelial dystrophy.

can only be performed over an ulcerated region but has been found to help resolve nonhealing corneal ulcers and reduce the incidence of developing recurrent ulcers.[19] Another procedure is a superficial keratectomy and conjunctival advancement hood flap (SKCAHF) (**FIGURE 6**). In 1 recent study, this procedure allowed for improvement of corneal edema for at least 1 year postoperatively and reduction of the frequency of topical 5% NaCl administration. The owners also reported an improvement in vision and corneal clarity.[20] SKCAHF has also been shown to decrease corneal thickness and ocular pain by decreasing the risk/rate of ulcer formation.[21] This procedure is thought to reduce edema because the conjunctiva provides an alternate route for fluid drainage.[20]

Procedures such as corneal collagen cross-linking and Descemet's stripping endothelial keratoplasty (DSEK) have been shown to decrease corneal thickness, with mixed results in corneal clarity[22,23]:

- **Corneal collagen cross-linking** has been described in humans for treatment of edema, but less success has been seen in canine patients. This surgery increases corneal clarity immediately postoperatively, but edema generally returns within 6 months.[23]
- **DSEK** is a partial corneal transplant in dogs that has been described in a recent pilot study.[22] Postoperative complications including corneal vascularization, ocular hypertension, and persistent uveitis occurred in 5 out of 6 patients. The procedure is still being refined to work well in dogs, but it has promise for the future.[22]

Complete corneal transplant is the most definitive treatment for CED. However, this procedure is rarely performed in dogs due to the high risk of complications.[15]

## Senile Endothelial Degeneration

Senile endothelial degeneration presents similarly to CED and causes diffuse corneal edema secondary to

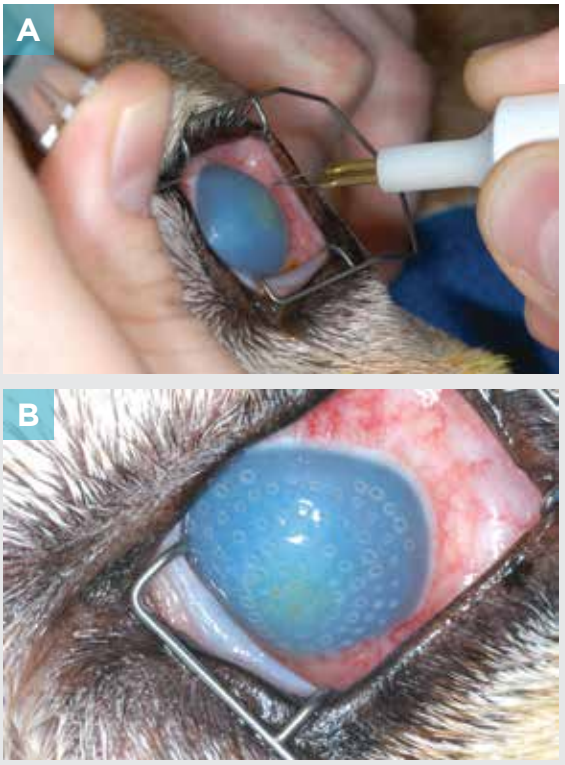


**FIGURE 5. (A)** Use of thermal cautery to create multifocal points of anterior stromal contraction. **(B)** Eye post-thermokeratoplasty procedure. Stromal scarring acts as a barrier to fluid flow, hopefully decreasing overall corneal edema.

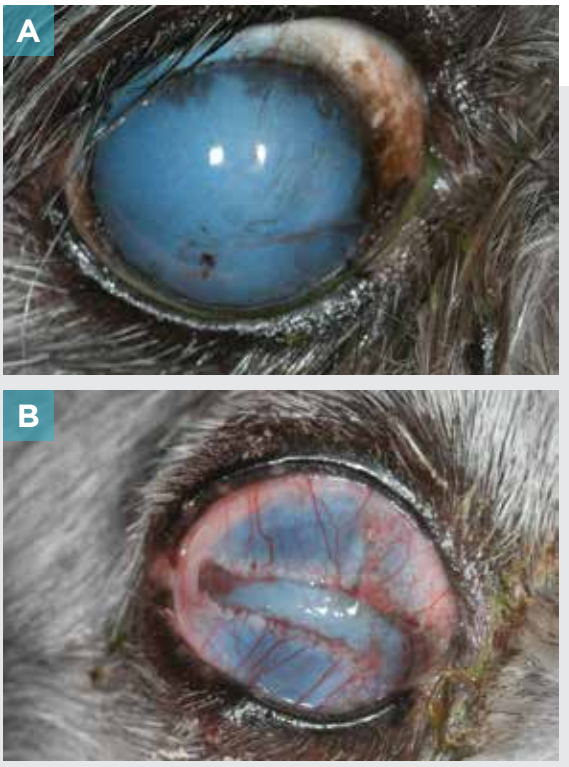


**FIGURE 6. (A)** Severe corneal edema due to corneal endothelial degeneration with pigmentation and corneal neovascularization. This patient was blind due to the severity of the edema. **(B)** The same patient after superficial keratectomy and conjunctival advancement hood flap was performed in the dorsal and ventral corneal. Conjunctival hood flaps act as fluid sinks to reduce edema and ulcer formation. Note that the conjunctival grafts are larger than in a patient that would have been taken to surgery earlier with less severe corneal edema.

the loss of endothelial cells. This disease process is presumed to be age related instead of inherited, and it can be seen in a variety of breeds.[24] However, this disease is poorly described in the literature and can be difficult to differentiate from CED. Diagnosis and treatment are similar to those for endothelial dystrophy, as described previously.

## Adenovirus Infection or Vaccination

Natural infection with, or modified-live vaccination against, canine adenovirus 1 is another cause of corneal edema. It has been recognized as a type III hypersensitivity from the release of the virus from corneal endothelial cells.[25,26] Immune complexes develop in the aqueous fluid; these immune complexes are then phagocytosed by neutrophils and macrophages, which may be cytotoxic to the endothelium.[26] The resulting damage to the endothelium leads to corneal edema approximately 2 to 3 weeks after infection in about 20% of affected animals.[26] The edema is usually transient over a few days and may affect 1 or both eyes.

Previously, this was a common diagnosis; however, vaccination with canine adenovirus 2 (instead of 1) has decreased the incidence of dogs developing corneal edema to less than 1%.[1] Therefore, systemic medical history as well as vaccine history are important to know when diagnosing acute corneal edema. Treatment with topical steroids is recommended due to the immune-mediated etiology of the edema in these cases.

## Endotheliitis

Endotheliitis is defined as primary inflammation of the

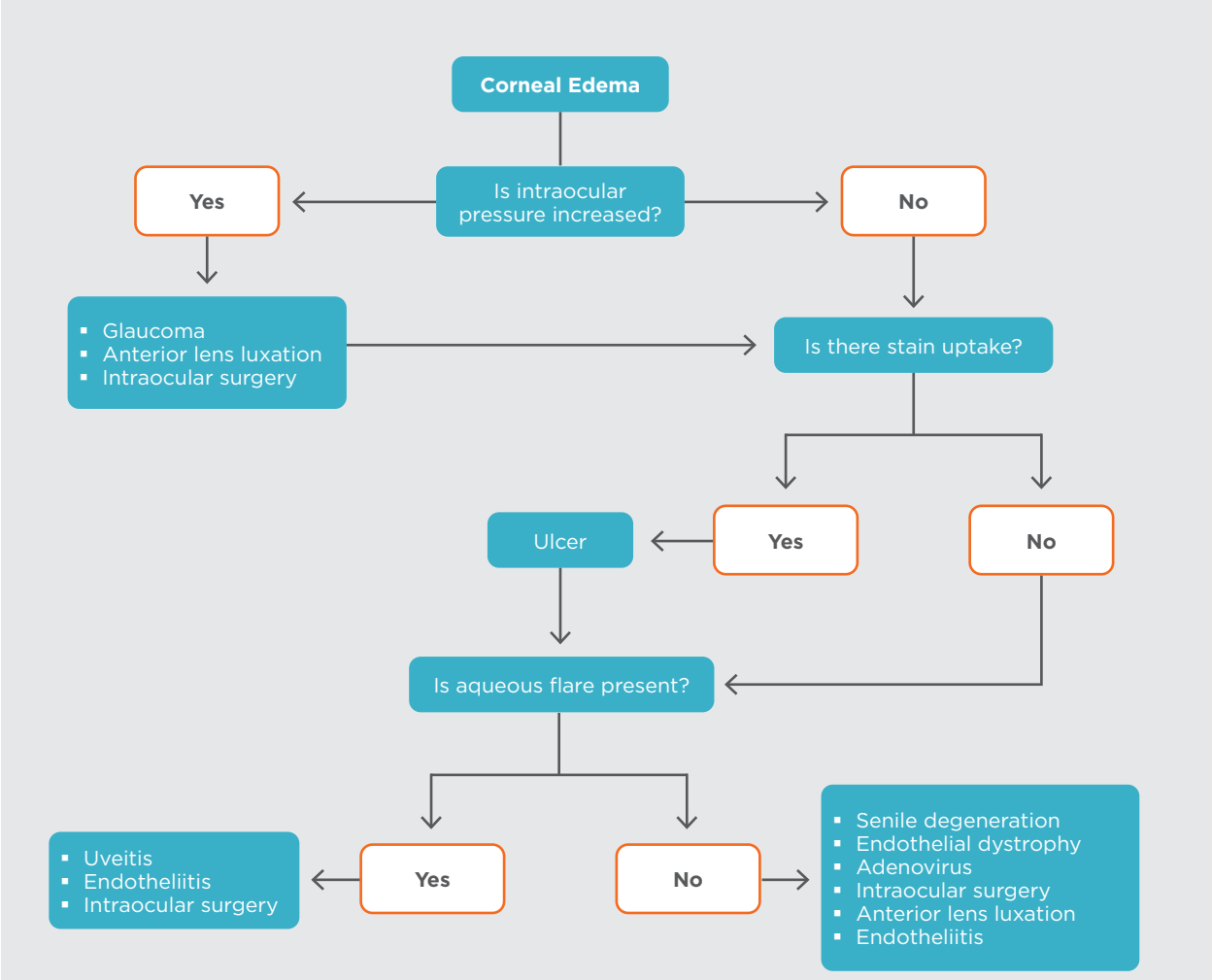


**FIGURE 7.** Flow chart of differentials based on the ophthalmic examination.

endothelial cells within the cornea which leads to corneal edema, but has not been well described in the literature and is thus likely underdiagnosed. A recent case series reports this disease and outlines the changes to the endothelium.[27] The edema was reported to be more severe than with uveitis alone and worse ventrally. Other clinical signs included conjunctival hyperemia, blepharospasm, and keratic precipitates (worse ventrally); some had aqueous flare. This study found changes to the endothelium—including pleomorphism, polymegathism, and deposits thought to be inflammatory in nature—using special imaging techniques.[27] These cases resolved with anti-inflammatory therapy; however, signs recurred when topical therapy was discontinued. Therefore, a low level of topical steroid treatment may be necessary to control the clinical signs in these patients.[27] This study also used a ROCK inhibitor (netarsudil) in 2 cases, with improvement in both, indicating another potential use for this class of medications.[27]

### Intraocular Surgery

Intraocular surgery, such as phacoemulsification or intracapsular lens extraction, has also been associated with corneal edema.[28] There is direct trauma and endothelial cell loss in the areas of the incision that will lead to focal short-term edema. Additionally, length of surgery, surgical technique, and intraocular solutions used (among others) contribute to endothelial damage and loss, leading to short-term or long-term diffuse edema.[28] It has been found that an average of 22% of endothelial cells are lost during phacoemulsification in the canine eye.[28] Edema simply from surgery should resolve over time; however, if enough cells are lost or other complications (such as uveitis or glaucoma) develop, the edema may remain or worsen over time.[28]

## THE OPHTHALMIC EXAM

A thorough history and physical exam are important parts of any ophthalmic examination as other systemic diseases can manifest as ocular abnormalities. If corneal edema is noted, specific history questions to ask may include:

1. Has the owner noticed any redness, squinting, and/or discharge from the affected eye(s)?
2. When did the owner notice the color change of the eye, and how has it progressed, if at all?
3. Has the dog been administered any recent vaccinations? If so, which one(s)?
4. What medications is the dog currently receiving?
5. Is there any history of other ophthalmic problems or previous surgeries?

See **FIGURE 7** for a flow chart of differentials based on the ophthalmic examination.

## SUMMARY

Corneal edema can be a sign of various causes, many of which need prompt identification and treatment. Often a good ocular exam and knowledge of the causes of corneal edema can provide a guide to proper diagnosis and treatment. Treatment is often aimed at managing the underlying cause, if possible, as well as preventing painful sequelae such as corneal ulcers. Newer treatments and surgeries are emerging to help reduce the amount of corneal edema in cases where the underlying cause may not be able to be resolved (e.g., CED). For any eye exhibiting corneal edema, early diagnosis and treatment are important to maintaining comfort and vision for as long as possible. TVP

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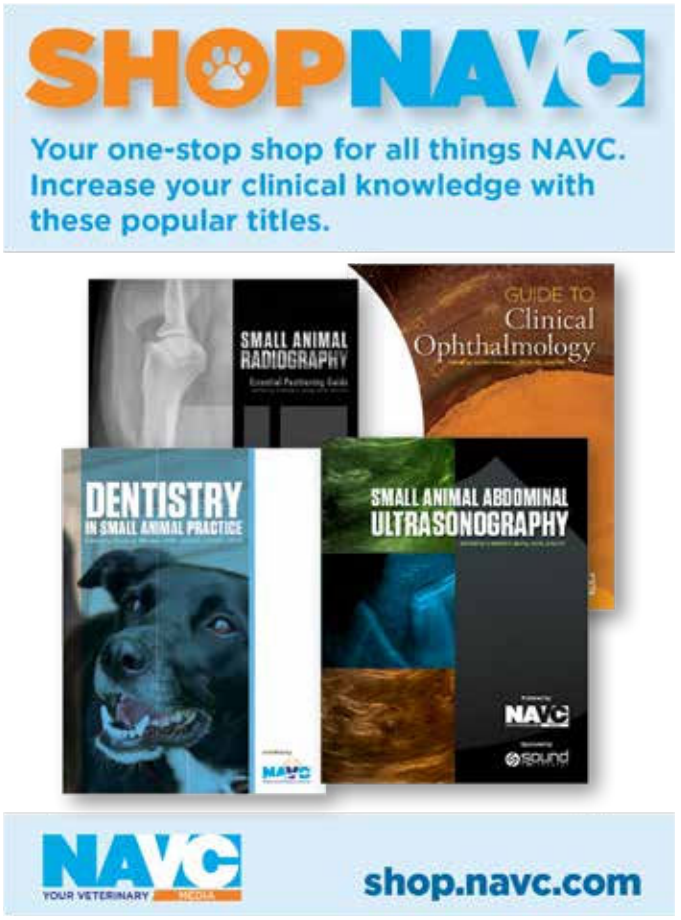




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