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Topical Review

Glaucomas

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Canine and feline glaucomas are commonly presented as ocular emergencies. Glaucoma is a common cause of vision loss and a frustrating disorder in terms of medical and surgical treatment. Increased intraocular pressure (IOP) is a significant risk factor in the disease, leading to damage of the retina and optic nerve head. IOP measurement and gonioscopic and fundic examinations provide the instruments for diagnosis of glaucoma. The primary goal in glaucoma therapy is aimed at vision preservation. Medical treatment provides temporary relief, but alone it fails to control IOP in the long term, and surgical intervention is recommended. Surgical patient selection depends on several factors, from type and stage of glaucoma to the presence of or potential for vision. Available surgical procedures to decrease IOP consist of cyclodestructive techniques to decrease aqueous humor production and filtering techniques to increase its drainage. Even with recent surgical and medical advances, pain and blindness are still common occurrences in the disease: end-stage procedures such as enucleation, evisceration with intrascleral prosthesis, and pharmacologic ablation of ciliary bodies are then recommended to address chronic discomfort for buphthalmic and blind globes.

Introduction

Canine and feline glaucomas represent one of the most common emergencies in veterinary ophthalmology and veterinary practice.

The glaucomas are a group of diseases characterized by the neurodegenerative disorder of retinal ganglion cells and optic nerve, leading to blindness. Despite the increased complexity in the etiopathogenesis of the disease, increase in intraocular pressure (IOP) is still regarded as the main risk factor in the development of glaucoma in veterinary patients. IOP management is the main target of glaucoma treatment; however, medical and surgical therapies vary according to the cause and stage of the disease.

Owing to their common acute presentation and rapid progression, canine and feline glaucomas are one of the true ophthalmic emergencies, and prompt medical and surgical treatment is warranted.

Anatomy and Physiology

Normal IOP in dogs and cats varies according to different studies and testing devices. Currently, mean normal values for IOP in dogs are estimated at 19.2 $\pm$ 5.5 mmHg[1] and 12.9 $\pm$ 2.7 mmHg[2] (by applanation tonometry) and 10.8 $\pm$ 3.1 mmHg[2] and 9.1 $\pm$ 3.4 mmHg[3] (by rebound tonometry). In cats, mean reported values of normal IOP are 18.4 $\pm$ 0.67 mmHg (by applanation tonometry) and 20 $\pm$ 0.48 mmHg[4] (by rebound tonometry).

The value of IOP results from a balance between aqueous humor production and its outflow. Aqueous humor (AH) is secreted by the nonpigmented epithelium of the ciliary bodies through 3 basic mechanisms: diffusion, ultrafiltration, and active secretion. Carbonic anhydrase is the isoenzyme within the nonpigmented epithelial cells responsible for the formation of bicarbonate and its active transport across the ciliary epithelium. It catalyzes the following reaction: $H_2O + CO_2 \leftrightarrow HCO_3^- + H^+$. Na^+ ion is the major constituent actively transported from blood to AH by the enzyme complex Na^+, K^+-ATPase, located along the lateral intedigitations of the nonpigmented epithelium cells. The osmotic gradient of solutes resulting from their active transport across the ciliary epithelium favors the movement of water by diffusion and ultrafiltration, with the formation of AH. Carbonic anhydrase can account for up to 60% of AH production,[5] and even 75% in dogs.[6] This is especially important in the medical management of glaucoma, as carbonic anhydrase inhibitors (CAIs) are among the most effective medications in decreasing IOP.

The AH then flows from the posterior chamber through the pupil, to leave the eye through 2 main pathways, the conventional outflow and the uveoscleral or nonconventional outflow. The anatomic site of the former is the iridocorneal angle (ICA), where slender strands of pigmented tissue (pectinate ligaments) connect the base of the iris to the inner peripheral cornea. The AH flows through the pectinate ligaments and into the trabecular meshwork and from there into the aqueous angular plexus and the episcleral veins.[7] The uveoscleral outflow allows the drainage of AH posteriorly along the supraciliary-suprachoroidal spaces and into the adjacent sclera. This pathway accounts for only 3% of the total AH drainage in cats and 15% in dogs and it is influenced by the contraction of the ciliary body muscle and by the difference in hydrostatic pressure between the anterior chamber and the suprachoroidal spaces.[8] Glaucoma is caused by a pathologic increase in IOP, due to the impairment of aqueous humor outflow. IOP increase is still considered to be the major risk factor in optic nerve damage and subsequent blindness in cats and dogs.

Types of Glaucomas and Etiopathogenesis

Glaucoma is a multifactorial disease with many different phenotypes and etiologies, and consequently its classification is quite complex. According to their etiology, stage of disease, and

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Fig. 1. Severe congenital glaucoma in a young kitten.

ICA morphology, glaucomas can be primary, secondary, or congenital; early noncongestive, acute congestive, and chronic; open-angle, narrow- to closed-angle, and with goniodysgenesis, respectively.

Congenital glaucoma in dogs and cats develops at birth or a few weeks to months later (Fig 1); it is quite rare and usually caused by genetic defects leading to the abnormal development of the anterior chamber and the trabecular outflow pathways.[9] Primary glaucoma is the most common presentation in dogs.[10] In primary glaucoma, the increase in IOP is unrelated to any other concurrent ocular disorder; the disease is bilateral, although it does not usually develop simultaneously in both the eyes, and it has a known hereditary predisposition in several breeds (Table 1). The most common type of primary disorder in dogs is represented by closed angle glaucoma (PCAG), with American Cocker Spaniels and Basset Hounds being overrepresented in North America.[11] The pathogenesis and pathophysiology of PCAG are still largely unknown; however, several predisposing factors have been identified. Aging, gender, and genetics all play a role in the incidence of primary glaucoma. The onset of the disease is more common between 4 and 10 years of age and is usually characterized by abrupt and severe clinical signs; female dogs appear to be twice as likely to develop glaucoma as males.[11,12] Goniodysgenesis is a genetic defect in the development of the pectinate ligaments, which may be malformed and associated with decreased angle width. Several breeds predisposed to glaucoma show a high incidence of pectinate ligament dysplasia. However the incidence of glaucoma does not seem to be directly related to the severity of goniodysgenesis; other factors are clearly at play in the manifestation of the disease.[13] It has been suggested that changes in the ocular anatomy, with bowing of the iris, reverse pupillary block, and age-related increase in lens thickness are responsible for the increase in IOP.[14,15] These changes would result in increased apposition of the peripheral iris and cornea, with collapse of the filtration angle and impairment of outflow. More current theories have focused on the importance of age-related pigment dispersion with tissue remodeling and subtle but relentless inflammation and fibrosis, which are eventually responsible for modification of the trabecular meshwork extracellular matrix and of the outflow pathways.[16] The common final event to all types of glaucoma is the eventual degeneration of the optic nerve head, or glaucoma optic neuropathy (GON). Although the increase in IOP is still considered a main risk factor in dogs, other components are suspected in the progression of GON, from defects in the microcirculation of the optic nerve head and oxidative stress, to liberation of excitotoxic amino acids and mechanical stretching of the lamina cribrosa, with eventual axonal damage to the retinal ganglion cells.

Inherited primary open-angle glaucoma (POAG) is far less common than primary angle closure glaucoma, and is usually described in Beagles and Norwegian Elkhounds. In this disorder, representing the animal model of the most common type of glaucoma in people, the collapse of the ICA is apparent only in the advanced stages of the disease. At the origin of the disorder is a progressive accumulation of basement membrane-like material in the extracellular spaces of the trabecular meshwork, with impairment and eventual suppression of aqueous outflow.[17]

Secondary glaucoma is caused by preexistent intraocular disorders and tends to be unilateral. It is seen in all species, but represents the most common type of glaucoma in cats. Several ocular conditions can cause secondary glaucoma, from inflammatory and degenerative to neoplastic and traumatic (Table 2). The clinical onset is usually more slowly progressive than in primary glaucoma, although it may vary according to the nature of the primary disorder. Anterior and posterior synechiae, formation of preiridal fibrovascular membranes, lens dislocation and pupillary block, and cellular infiltrations (neoplastic or inflammatory) of the trabecular meshwork are all involved in the pathogenesis of secondary glaucoma. Treatment is directed toward the resolution, if possible, of the primary disease affecting the eye, but specific glaucoma therapy is also usually required. An uncommon type of secondary glaucoma is associated with the presence of diabetic, intumescent cataracts in dogs: phacomorphic glaucoma is caused by the anterior displacement of the iris, due to the increased size of the cataractous lens, with narrowing of ICA and anterior chamber (Fig 2). The only possible treatment is phacoemulsification of the lens.

Classification of glaucoma according to its stage is less relevant on the basis of investigative research, but quite pragmatic for its therapeutic approach. Early noncongestive glaucoma characterizes the early stages of both POAG and narrow-angle glaucoma. The clinical signs are insidious and often undetected, with values of IOP approximately at 25-30 mmHg. Sudden and severe spikes in IOP, at times approximating 50-70 mmHg, are typical of acute

Table 1
Canine Breeds Predisposed to Primary Glaucoma

American Cocker Spaniel	Akita
Basset Hound	Jack Russell Terrier
Chow Chow	English Cocker Spaniel
Shar-Pei	Lhasa Apso
Boston Terrier	Bouvier des Flandres
Fox Terrier, Wire	Pekingese
Norwegian Elkhound	Poodle, Toy
Siberian Husky	Beagle
Cairn Terrier	Brittany Spaniel
Poodle, Miniature	Saint Bernard
Samoyed	English Springer Spaniel
Bichon Frise	Poodle, Standard
Shih Tzu	Dalmatian
Australian Cattle Dog	

Table 2
Causes of Secondary Glaucoma in Cats and Dogs

Anterior uveitis
Lens—associated
Cataract
Lens luxation or subluxation
Intraocular neoplasms
Hyphema
Melanocytic (dog)
Aphakic or pseudophakic
Aqueous humor misdirection syndrome (cat)
Malignant

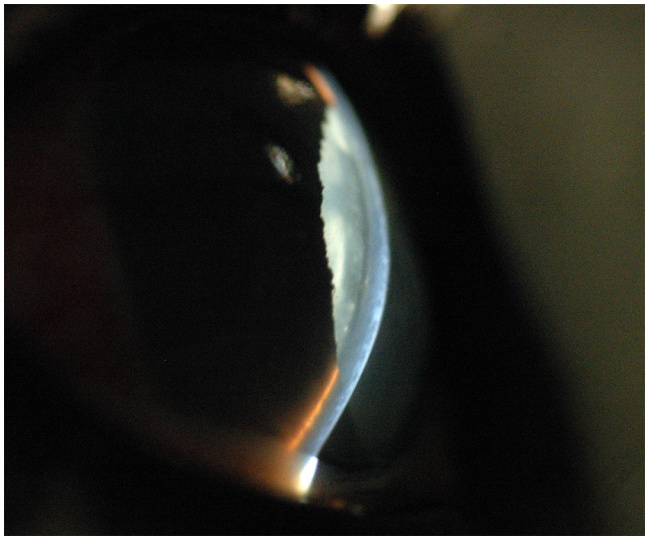


Fig. 2. Slit lamp biomicroscopy of phacomorphic glaucoma in a dog with diabetes mellitus. The enlarged and cataractous lens has displaced the iris forward, with collapse of the anterior chamber and iridocorneal angle.

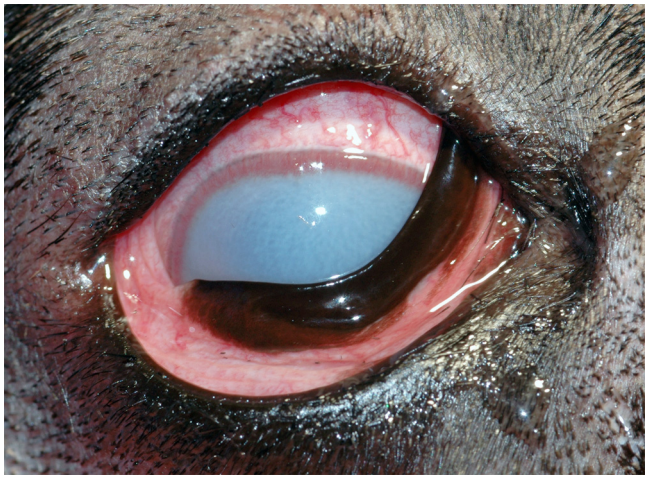


Fig. 3. Acute congestive glaucoma of the right eye in a dog. Severe conjunctival hyperemia and scleral injection are present, in addition to perilimbal corneal neovascularization of unknown origin. Severe corneal edema and third eyelid protrusion are also present.

congestive glaucoma (ACG); this presentation is common for PCAG, and it is responsible for the most dramatic clinical signs in affected patients. Chronic glaucoma is described in the advanced stages of the disease, when the extensive ocular damage almost invariably results in blindness. Specific clinical signs are characteristic of each described stage of glaucoma, and their identification aids in the choice of treatment and in offering a correct prognosis.

Clinical Signs

Clinical signs of glaucoma can differ according to the species, and with the stage and type of glaucoma.

Primary glaucoma is most commonly described in dogs, often affecting specific predisposed breeds. It is a bilateral disorder, although both the eyes may not be simultaneously affected. POAG is defined by a very slow progression, with subtle and often undetected clinical signs. Mild mydriasis, with a variable degree of episcleral injection and transient corneal edema, may be present in animals as young as 2 years of age, but they are often overlooked by the owners and patients often present only in the late stages of the disease, when vision is already compromised. PCAG is by far the most common type of primary glaucoma in dogs, and the clinical signs vary according to the stage. In the prodromal phases of the disease, moderate and transient spikes in IOP are experienced by the patient; however, compensatory changes in aqueous secretion and outflow tend to bring the IOP back toward baseline values.[18] Unfortunately, this mechanism is eventually overcome and abrupt permanent increases in IOP, around 40-70 mmHg, lead to the dramatic clinical signs of ACG. The affected dog is often presented as an emergency, owing to severe ocular pain and increased ocular redness, most commonly unilateral. Blepharospasm, epiphora, conjunctival hyperemia, and scleral injection are common clinical signs; the patient may appear lethargic and may resist ocular manipulation. Examination of the eye is often difficult, due to protrusion of the third eyelid and discomfort experienced by the patient. Diffuse corneal edema is evident, and it can sometimes hinder the assessment of the anterior chamber and posterior segment (Fig 3); when visible, the pupil is mid-range to moderately dilated and usually unresponsive. Visual testing may be difficult to perform on the affected eye; in this case, the evaluation of a consensual pupillary light reflex (PLR) in the healthy contralateral eye may help assess the presence or absence of vision. According to the severity and duration of the spike, vision may already be compromised. Fundic examination is not always possible, owing to the cloudiness of the ocular media. Occasionally, in cases of extreme elevation of IOP to more than 50-60 mmHg, mild papilledema may be detected, due to enlargement of the optic nerve fibers owing to impaired axoplasmic flow.[10] Infarction of select short posterior ciliary arteries may also result in ischemia, with formation of wedge-shaped peripapillary areas of chorioretinal degeneration.

Chronic glaucoma is not usually a reason for emergency presentation, but it may occasionally be detected in the contralateral eye of a patient presented for ACG. The clinical presentation is usually less dramatic than in patients with ACG. A dull, chronic discomfort is still present, as confirmed by the evident relief manifested by affected patients after globe removal; however, all of the signs of acute pain are absent (blepharospasm and third eyelid protrusion). Ocular redness is also decreased, due to the absence of conjunctival hyperemia. Almost pathognomonic, though, is the persistency of severe episcleral vessels injection, which is permanent. Corneal edema is moderate to absent, and the eye shows evident buphthalmos, with or without Haab's striae. Both buphthalmos and Haab's striae are caused by the stretching and chronic enlargement of the eye, in response to the persistent increase in IOP: the latter are pathognomonic for chronic glaucoma and secondary to rupture of Descemet's membrane. Vision is absent and the pupil is dilated and unresponsive. Not infrequently, the enlargement of the globe causes lens displacement and often its complete luxation in the anterior chamber or posterior segment (Fig 4). Diffuse retinal degeneration, with tapetal hyperreflectivity and fading or absent retinal vessels, and optic nerve head cupping are common fundic findings.

Clinical signs of secondary glaucoma are usually associated to the signs of the primary disorder; however, they may vary from acute to progressive or chronic, according to the etiopathogenesis of the disease.

Owing to differences in the anatomy and physiology of the feline eye, glaucoma in cats shows slightly different clinical signs. The increase in IOP is usually slow and progressive, and no signs of evident conjunctival hyperemia or corneal edema are initially present. Vision is also maintained for a much longer time than in dogs. For these reasons, the patient is usually presented when glaucoma has reached a chronic stage, when mild to moderate

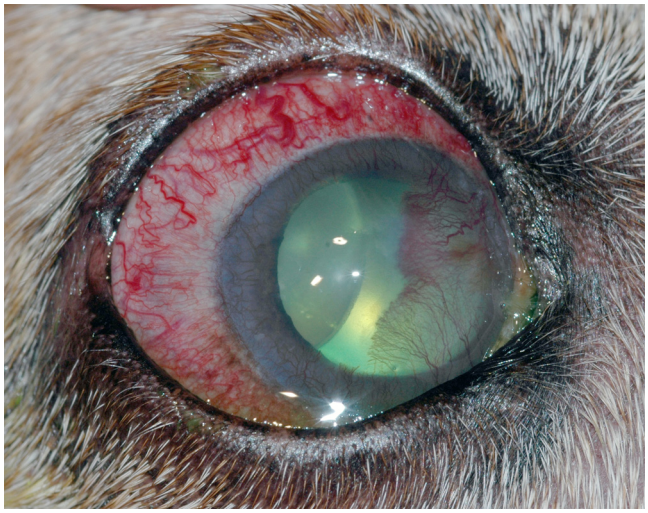


Fig. 4. Advanced chronic glaucoma in a dog. Episcleral injection and buphthalmos are visible, with superficial keratitis from corneal exposure. The pupil is dilated and secondary lens subluxation is present with a wide medial aphakic crescent.

corneal edema and buphthalmos are present. Mydriasis, mild episcleral vessels injection, lens luxation or subluxation, and retinal degeneration with blindness complete the clinical picture of chronic feline glaucoma.

Diagnostics

The diagnosis of glaucoma relies on clinical signs, signalment of the affected patient, and on 3 basic procedures: tonometry, gonioscopy, and ophthalmoscopy.

IOP measurement (tonometry) is pivotal in the diagnosis of glaucoma, and in clinical practice it is usually performed by applanation or rebound tonometry. In applanation tonometry the IOP is inferred from the force required to flatten (applanate) a constant area of the cornea. As it is needed for the probe to contact the corneal surface, topical anesthetic is required before the test. The current most common applanation tonometers in veterinary medicine are the Tono-Pen® XL and Tono-Pen Vet™. Rebound tonometers (TonoVet® Rebound Tonometer) measure IOP by bouncing a magnetized small plastic-tipped metal probe (1.4 mm in diameter) against the cornea. The velocity at which the probe bounces back into the device is converted into electrical signals, from which the IOP is calculated. Owing to the small size of the tip, no topical anesthetic is needed, making this instrument extremely useful for serial IOP curves, as often required after endoscopic cyclophotocoagulation (ECPC) procedures. In addition, the effect of the light-weight probe is regulated automatically by the instrument, and thus IOP readings are less influenced by the examiners and their experience. Both instruments are very reliable; however, recent studies have highlighted the tendency of applanation tonometers to underestimate IOP levels as they increase, whereas the rebound tonometer appears to be superiorly accurate in both dogs and cats.[19–21] IOP readings can be affected by excessive restraint (pressure on jugulars or eyelids), patient's distress, corneal health, and time of the day with both instruments.[10,20] Repeated IOP readings should be performed always with the same instrument, at the same time of the day, and with minimal restraint on both dogs and cats. Although tonometry is essential in the diagnosis of acute and chronic glaucoma, its validity as a predictive tool for PCAG in IOP screening of high-risk patients is poor.[22]

Gonioscopy allows direct or indirect visualization of the ICA angle, pectinate ligaments, and anterior portion of the ciliary cleft. After application of topical anesthesia and minimal restraint, a specific lens is applied on the corneal surface and the intended area is inspected by use of a magnifying instrument, usually a biomicroscope, but also a direct ophthalmoscope or a PanOptic ophthalmoscope could suffice. This is a more sophisticated procedure, requiring training and specific knowledge of the anterior chamber anatomy, and it is here only briefly discussed. It is particularly useful in the assessment of the degree of goniodysgenesis and narrowing of the ICA in predisposed patients, especially if performed serially. However, gonioscopic findings are not a direct indication of aqueous humor outflow and IOP values: it is not unusual for patients with moderate to severe goniodysgenesis or narrow angles to show normal IOP values. Gonioscopic assessment should always be interpreted in association with clinical signs and IOP measurements.

Direct and indirect ophthalmoscopies are not always possible in the patient with glaucoma, owing to the opacity of the ocular media. When assessable, the fundus should be examined for signs of optic nerve head degeneration and cupping, peripapillary areas of chorioretinal atrophy, and diffuse retinal degeneration, especially in comparison to the contralateral healthy eye if applicable. These findings are signs of chronic glaucomatous changes, and they are always present with more overt clinical signs, such as buphthalmos, corneal edema, or Haab's striae. Earlier signs, such as the occasional early mild papilledema in patients with very high IOP values, are less common and more difficult to detect by the private practitioner.

Sophisticated and advanced diagnostic tools for the investigation of glaucoma, such as high-resolution ultrasound, ultrasound biomicroscopy, and optical coherence tomography, have also recently been used, but their description goes beyond the purpose of this article.

Treatment Goals

Glaucoma treatment varies according to the stage of the disease, its etiology, and presence or absence of vision. If vision can be maintained or recovered, the main treatment goal is focused on IOP control and neuroprotection. Once vision is lost, the goal shifts toward pain and corneal complications management to improve the quality of life for the patient.

Other important factors to consider are also the patient's species, breed, and age, and last but not the least, client's expectations, compliance, and financial resources.

The goal of glaucoma treatment is to decrease the IOP to values assumed to be "safe," where "safe" is intended for values that would stop or reduce the loss of retinal ganglion cells (RGCs) and slow down further vision impairment. Unfortunately, several factors make this "safe" or "target" IOP quite elusive. The first consideration is that our IOP assessment is usually expressed by one single and random tonometric measurement, whereas IOP may present wild variations throughout the day. The second consideration reflects our inability to accurately determine a specific IOP value below which GON can be prevented or limited. It is usually assumed that the more severe the preexisting or possible glaucoma damage, the lower the "target" IOP should be set. It is generally accepted that a safe IOP in dogs with overt glaucoma and on medical treatment should not exceed 19-20 mmHg.[10]

Eventually medical treatment alone is destined to fail in the management of PCAG, owing to the progressive nature of the disease. Although medical treatment is the mainstay for any newly diagnosed cases, glaucoma is ultimately a surgical disease.

The most common clinical scenario in canine primary glaucoma includes patients that are presented with severe or irreversible damage in one eye. Although salvage procedures may be

Table 3
Commonly Used Glaucoma Medications

Carbonic anhydrase inhibitor	2% Dorzolamide 1% Brinzolamide
B-blocker	Timolol 0.5%
Parasympathomimetic	0.125% Demecarium bromide 0.25 Demecarium bromide
Prostaglandin analogs	0.005% Latanoprost 0.03% Bimatoprost 0.004% Travoprost
Hyperosmotic	20% Mannitol

appropriate for these globes to prevent or control ocular pain, prophylactic medical treatment in the contralateral visual eye must be instituted immediately, and surgery recommended at the early indications of ocular hypertension. It has been suggested that earlier surgical timing may improve the outcome of glaucoma surgery in dogs.[23]

Management of secondary glaucoma varies according to the primary disorder affecting the eye and to the species.

Medical Therapy

Medical treatment is aimed at controlling the increase in IOP by decreasing the AH inflow, increasing its outflow, or both. Many different classes of medications are currently used for glaucoma treatment, including CAIs, β-blockers, parasympathomimetics, prostaglandin analogs (PGAs), and osmotic agents. The most common glaucoma medications are listed in Table 3.

CAIs lower IOP by decreasing the production of AH. They act on the enzyme carbonic anhydrase, which is present in several tissues and considerably in the pigmented and nonpigmented ciliary body epithelial cells. CAIs block the catalyzed formation of bicarbonate ions and the subsequent movement of water by osmosis from the ciliary stroma to the posterior chamber. Carbonic anhydrase is responsible for only 60%-75% of AH formation[5,6]; therefore, although effective, CAIs may not sufficiently control increased levels of IOP. Both systemic and topical CAIs are available; however, the use of topical CAIs has almost completely replaced the systemic medications. Several side effects and complications have been associated with the use of systemic CAIs, from metabolic acidosis to gastrointestinal tract disturbances (anorexia, vomiting, and diarrhea), panting, lethargy, and hypokalemia,[10] with cats being especially sensitive. As a consequence, systemic CAIs have been progressively abandoned. Topical CAIs, specifically 2% dorzolamide and 1% brinzolamide, are very effective in lowering IOP and can be used in every type of glaucoma both in cats and dogs. They are usually applied topically q8-q12hrs, and they reach the maximum effect at the 5th day of treatment in dogs.[24] Both medications are effective, although brinzolamide to a lesser degree than dorzolamide in the feline population.[25-27] Side effects are usually minimal and mostly associated with ocular discomfort at application, which appears to be more common with dorzolamide than brinzolamide; for this reason brinzolamide is usually preferred in sensitive patients. However, recent reports have showed that both medications can cause severe perilimbal ulcerative and nonulcerative keratitis in select dogs, progressive and unresponsive to topical anti-inflammatory or immunomodulatory treatment.[28] The disorder is likely caused by a hypersensitivity response to the medication, and it resolves rapidly following drug cessation.

Timolol is an adrenergic antagonist β-blocker, and its action on the decrease of AH formation is still not perfectly known. It is classically believed to alter the adrenergic neuronal control of AH formation, by acting on the β-receptors in the ciliary body processes (CPs).[29] Timolol is the most common medication in human glaucoma, where it causes a decrease in IOP between 13% and 48%.[30] In dogs and cats its effect on IOP reduction is quite meager, 16% and 22%, respectively.[31,32] It is available at 0.25% and 0.5% concentrations, and it can be used in all types of glaucoma. It also has a miotic effect, bilateral in dogs and on the treated eye only in cats. Its systemic absorption may cause significant cardiorespiratory effects, with bradycardia, hypotension, and bronchospasm, and its use is contraindicated in patients with cardiac and respiratory disorders. For this reason, it should never be applied more than twice daily, especially in small-sized patients. Owing to its minimal effect in our patients and the potential for severe side effects, it is not a popular glaucoma medication in veterinary ophthalmology, although it may be more effective when combined with 2% dorzolamide.[33]

Demecarium bromide is an indirectly acting parasympathomimetic drug that acts by increasing the conventional AH outflow, and it is used mainly for treatment of POAG in dogs. Its use has not been evaluated in cats. It causes a contraction of the pupil sphincter and ciliary body muscles, with significant and long-term secondary miosis. Unfortunately, it has been associated with breakdown of the blood-ocular barrier, and its use is contraindicated in patients with secondary glaucoma from uveitis.[10] It is available only in compounded formulations at concentrations of 0.125% and 0.25%, and it is applied twice daily. Owing to its suppression of acetylcholinesterase and the potential systemic side effects, its use should be strictly monitored.[34]

The PGAs latanoprost, bimatoprost, and travoprost are the most effective glaucoma medications in humans and dogs. Through their high affinity for the prostanoid FP receptors in the eye, they are responsible for the MMP-mediated remodeling of the extracellular matrix of the ciliary body muscle.[35] They are known for increasing the AH outflow through the uveoscleral and conventional pathways, although a recent study in dogs showed that latanoprost can also significantly decrease AH production.[36] The action of PGAs on FP receptors in the iris is also responsible for the significant pupillary constriction present in both dogs and cats treated with latanoprost. Unfortunately, in cats the IOP-lowering effects of PGAs is mediated by EP receptors, not FP receptors.[37] Owing to their FP-receptor selectivity, the commercially available PGAs are not effective in decreasing IOP in cats, although they are responsible for pupil constriction in this species, too.[38]

The topical application of 0.005% latanoprost once to twice daily causes a decrease in IOP of approximately 25% in healthy dogs and up to 60% in glaucomatous dogs.[38,39] Similar results are observed with topical application of 0.03% bimatoprost and 0.004% travoprost. Twice daily application is usually recommended to avoid daily IOP fluctuations; however, the medication should be applied at nighttime if administered once daily, to better address the circadian fluctuations of IOP in dogs. Latanoprost is effective in every type of canine primary glaucoma, but it may also be used in select cases of secondary glaucomas. Recent studies have shown that the use of concurrent topical anti-inflammatory medications may significantly inhibit the IOP-lowering effect of latanoprost,[40,41] which should be taken into consideration when steroidal or nonsteroidal anti-inflammatory drugs are administered to patients with glaucoma.

The most common side effects of PGAs include conjunctival hyperemia and miosis. Owing to their miotic effect, PGAs should never be administered to patients with glaucoma secondary to anterior lens luxation, to avoid pupillary block. PGAs also have the potential to affect the blood-ocular barrier, and therefore they should be used with caution in patients with overt uveitis.

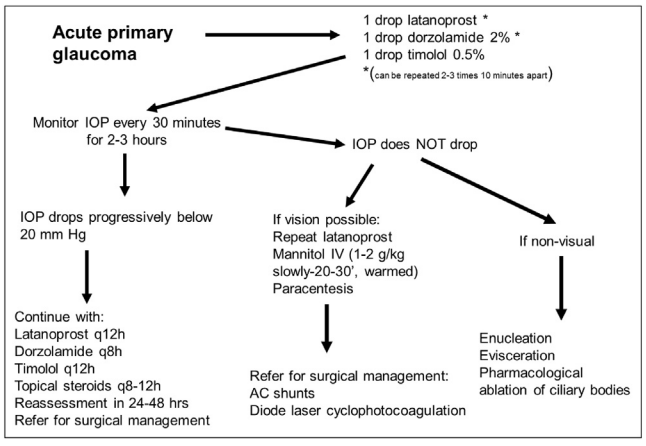
Mannitol, the most common osmotic agent, is used on an emergency basis only. It decreases IOP by increasing the osmolality of the extracellular fluids, thus inhibiting the ultrafiltration

process and shrinking the vitreous body. Because of its considerable molecular weight, mannitol is less likely to penetrate the eye if the blood-ocular barrier is compromised. However, in case of severe intraocular inflammation, its osmotic effects may be decreased. It is administered through intravenous infusion, at the dose of 1.1-2.2 g/kg over the course of 20-40 minutes. Maximum IOP decrease is reached within 1-2 hours, and water must be withheld from the patient for at least 4 hours. Its effect lasts approximately 6 hours, but it can be repeated in 24 hours. For its effect on the cardiovascular system and the potential for cardiac overload, it is contraindicated in patients with cardiac or renal disorders. With the introduction of PGAs, far more effective in rapidly decreasing IOP, its use has become less common in emergency treatment of ACG. However, mannitol administration can be added to the protocol in severe refractory cases.

Treatment Guidelines

ACG is considered to be a true ophthalmic emergency in dogs; timely and effective treatment is warranted. The main goal is to decrease the IOP to values less than 20 mmHg as soon as possible. Intravenous administration of mannitol was considered to be the go-to management protocol of acute primary glaucoma before PGAs medications were available. The rapid and effective drop in IOP provided by latanoprost has now changed the typical emergency approach. PGAs are administered in combination with CAIs, and both can be repeated 2-3 times every 10 minutes (Table 4); β-blockers are administered once every 12 hours only. Hospitalization of the patient is often required to monitor the IOP curve. If treatment is successful, the patient is discharged with the medical directions reported in Table 4, and referral to a specialist for future management an possible surgical intervention should be recommended within a few days. The presence of or potential for vision is usually the discriminating factor to determine the best course of action, when medical treatment fails to decrease the IOP. If a menace response is absent in the affected eye, both dazzle reflexes on the affected eye or a consensual PLR from the affected to the contralateral healthy eye need to be assessed. If either one is present or there is good certainty that the increase in IOP is acute and fairly recent, vision could be possible and additional procedures should be pursued. Both intravenous mannitol injection and AH paracentesis are employed for short-term control of IOP. Paracentesis is far more effective and consistent than mannitol administration in rapidly lowering IOP and it is the Author's preferred procedure; however, specific training and experience are required.

Table 4
Emergency Treatment of Acute Primary Glaucoma



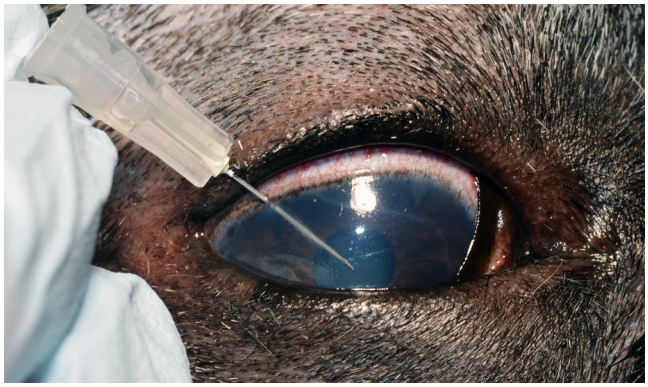


Fig. 5. Aqueous humor paracentesis in a dog with chronic glaucoma. A Haab's stria is visible along the dorsal or dorsomedial corneal quadrant.

For the trained professional and in cooperative patients, topical anesthesia provides adequate analgesia; however, sedation may be required. A sterile 27G needle is slowly but steadily inserted at the limbus and progressed into the anterior chamber, avoiding any contact with the intraocular tissues (Fig 5). The needle is withdrawn as soon as the fluid fills the hub, or when one drop exits the hub, according to the severity of IOP increase. IOP is then assessed. The eye should never be allowed to collapse, and ideally IOP in the low teens to high one-digit values is desirable.

Regardless of the outcome of either procedure, if vision preservation is still the main goal, patients should be immediately referred to the specialist for possible surgical treatment. When vision is no longer an option or in cases of chronic uncontrolled glaucoma, salvage procedures to control ocular discomfort are recommended.

Once primary glaucoma has been diagnosed in one eye, prophylactic treatment should be immediately started on the contralateral eye. Several studies have showed a significant increase in time interval from starting of therapy to the onset of overt glaucoma, when prophylactic antiglaucoma medications are started in the predisposed eye.[12,42] Recently, a new study has also showed that in addition to glaucoma medications, topical anti-inflammatory drugs may be beneficial in prophylactic glaucoma treatment.[43] Several protocols are available, but the Author's preferred choice of medications is 2% dorzolamide and dexamethasone alcohol or prednisolone acetate 1% suspension twice daily. Periodic IOP monitoring (every 3-4 months) is usually recommended, although acute and unpredictable IOP spikes may occur at any time on the predisposed eye. As already discussed, the progressive nature of glaucoma eventually requires the addition of medications, usually PGAs, or their increase in dosing. Eventually any medical treatment of PACG fails, and glaucoma surgery should be considered in the early stages of primary glaucoma.

In cases of secondary glaucoma, treatment is directed at removing the primary cause, when possible. In all cases of glaucoma secondary to uveitis, topical or oral anti-inflammatory medications are added to antiglaucoma drugs. Intraocular inflammation is the most commonly reported cause of glaucoma in cats and topical 0.1% dexamethasone alcohol or 1% prednisolone acetate is usually indicated for its management. However, cats share with human patients a predisposition to steroid-induced ocular hypertension, with increases in IOP of approximately 5-10 mmHg after topical application.[44,45] A change in route of administration or in the choice of medication should be considered in patients at risk.

In all other cases of secondary glaucoma, from glaucoma associated with lens disorders (cataract and luxation or subluxation) or caused by intraocular neoplasms to pseudophakic or

aphakic glaucomas, surgical treatment is most commonly recommended.

Surgical Management of Glaucoma

Etiology, clinical stage, and vision status affect the choice of the proper surgical treatment of glaucoma. Owing to the high rate of postsurgical failure associated with earlier surgical techniques, a conservative approach to glaucoma management has relied on chronic long-term medical treatment in the past, followed by surgery only in cases of advanced damage and uncontrolled IOP. Selection criteria for surgical procedures in glaucomatous dogs have now changed because a successful surgical outcome is more likely owing to the refinement of surgical techniques and early intervention.[10] Other important considerations guiding the choice of surgical treatment include surgeon's experience and skills, available instrumentation, and the patient's species, breed, age, and general health.

The main goal of surgical intervention in visual patients is still aimed at decreasing IOP in the affected eyes. This can be attained through techniques that modulate the AH flow, by decreasing its production or increasing its drainage (Table 5). Typically, the most common candidates are patients with primary glaucoma or glaucoma secondary to lens disorders; in the latter case, extracapsular or intracapsular lens extraction procedures, implantation of lens stabilization devices (capsular tension ring), and anterior vitrectomy are usually associated with the selected glaucoma procedures.

Most of the surgical procedures for visual patients involve the use of sophisticated techniques, with variable but usually significant financial effect for the owners. Demanding postsurgery follow-up and owner's expectations are also important factors to add to the general picture. Glaucoma is arguably among the most frustrating and difficult disorders in veterinary ophthalmology and surgical treatment can still often result in failure. Financial constraints and poor owner compliance may often direct the choice toward more conservative and less demanding options.

When vision is no longer present, the main goal shifts toward quality of life for the patient; ocular discomfort and corneal complications from buphthalmos are managed through salvage procedures (Table 6). Cases of secondary glaucoma from intraocular tumors or chronic inflammatory and traumatic conditions associated with blindness are usually addressed by globe removal.

Visual Patients

Both cyclodestructive procedures and filtering techniques are employed to control IOP in visual patients. The former procedures consist of selective damage to the ciliary body epithelia, most commonly through delivery of diode laser energy. The latter techniques increase the AH outflow through the implantation of glaucoma drainage devices (GDDs). The 2 techniques can be combined to improve success rate.

Melanin present in the ciliary body epithelium and stroma is the target of diode laser energy. Absorption of this energy results in photocoagulation and destruction of the ciliary bodies, with decrease of IOP production. Currently, the available procedures for cyclophotocoagulation in veterinary ophthalmology are transscleral cyclophotocoagulation (TSCPC) and ECPC.

Table 5
Available Surgical Techniques for Visual Eyes

Cyclodestructive techniques	Transscleral cyclophotocoagulation
	Endoscopic cyclophotocoagulation
Filtering techniques	Subconjunctival
	Frontal sinus
	Intrascleral
	Suprachoroidal
Combined procedures	Gonioimplants + TSCPC/ECPC

Table 6
Salvage Procedures for Blind Eyes

Enucleation
Evisceration with intrascleral prosthetic
Chemical ablation of ciliary bodies
Gentamicin
Cidofovir

TSCPC is performed via contact mode application, where scleral indentation by a handpiece probe enhances laser delivery and absorption by the target tissues. The procedure is performed with the patients under general anesthesia and in lateral recumbency. The probe is placed 3-4 mm posterior to the limbus over 30-35 different spots on the ventral and dorsal quadrants (Fig 6). The 3- and 9-o'clock positions must be avoided to spare the posterior ciliary arteries. The energy is transmitted to the ciliary bodies through conjunctiva and sclera. Higher energy delivery is associated with increased efficacy, but also with more severe complications.[46] As the target tissues cannot be directly visualized, an audible "pop" provides the measure of effective laser treatment. Currently, it is recommended that the laser energy be adjusted to levels where the "pop" is heard in approximately 20%-33% of the treatment sites.[46,47] However, the "pop" is produced by the shock wave resulting from cellular destruction and tissue vaporization, which is associated with increased tissue necrosis and a more severe inflammatory response. Although it has been historically reported that TSCPC may be less effective in subalbinotic patients,[46] recent investigations have showed that the distribution of pigment in the CPs of blue- and brown-eyed dogs is similar.[48]

Spikes in IOP, up to 50-60 mmHg, are a common occurrence immediately after TSCPC and the globe should be treated by paracentesis until the pressure is safely decreased to values inferior to 20 mmHg. Topical anti-inflammatory and glaucoma treatment is recommended in the postoperative period and the IOP needs to be frequently monitored.

Various surgical parameters have been described in canine patients. In an early study on 176 canine eyes, a protocol using high-power and short-duration parameters (1500 mW/1500 /ms/ 35 spots) reported control of IOP at 1 year in 53% of the cases; however, vision was preserved in only 22% of the treated

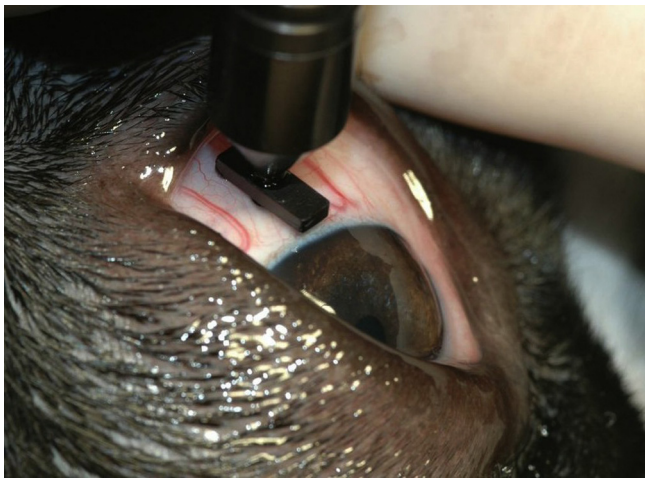


Fig. 6. Transscleral cyclophotocoagulation. The contact probe is slightly indenting the sclera.

patients.[47] In a smaller study, a low-power and long-duration (1000 mW/5000 ms/24 spots) yielded a 92% success in IOP control at 1 year postoperatively, with a better outcome at vision preservation, present in 50% of the potentially sighted dogs.[49] TSCPC in cats has yielded far less effective results and it is not currently recommended in this species.[50] The most common complications in dogs include uveitis, intraocular hemorrhage, retinal detachment, cataracts, corneal ulceration, and relapsing glaucoma.[46]

ECPC, which is relatively recent in veterinary ophthalmology, allows direct visualization of the target tissues through an endoscopic approach. Energy delivery is optimal, as it can be titrated to reach the desired tissue blanching and destruction, which is visible during the procedure. The laser unit (E2 console, Endo Optiks, Little Silver, NJ, USA) includes an 810-nm diode laser, a 175-W xenon light source, a helium-neon laser aiming beam, and video camera imaging. All these components are transmitted via fiber optics to 18- or 20-gauge endoscopic probes, and the energy delivery is controlled by a footswitch pedal. An integrated endoscopy system can be combined with an existing diode laser (E4 console). The endoprobes, straight or curved (Fig 7), allow 110°-140° field of view and they are connected to the console and a video monitor. The surgical procedure is surveyed on the monitor, not through the operating microscope.

All patients are premedicated with topical and systemic anti-inflammatories and antibiotics for 24-48 hours before surgery, and all miotic medications are discontinued 24 hours before surgery. With the patient under general anesthesia and nondepolarizing neuromuscular block, the endoprobe is inserted into the globe through a limbal or, less commonly, a pars-plana approach. ECPC in canine and feline glaucoma is usually performed in combination with phacoemulsification and intraocular lens implantation, and the patient is positioned in dorsal recumbency under the operating microscope. Phacoemulsification is performed first, and ECPC is performed before intraocular lens implantation. The probe is inserted through a 2-3-mm limbal incision at 12-o'clock and progressed behind the dilated iris to a distance that allows visualization of at least 4-6 CPs (Fig 8). The curved probe is usually preferred, owing to its ability to access 300° of ciliary bodies through a single entry; however, a second incision at 6-o' clock is often necessary. The ideal goal is to treat the CPs through their whole length, but this may not always be attainable. The energy is delivered through a "painting" or "sweeping" motion, addressing both CPs tips and valleys. The technique varies according to species, breed, severity of IOP increase, and lens status; however, at least 270°-330° of ciliary bodies should be treated. Sulcus inflation by sodium hyaluronate viscoelastic is indispensable for correct exposure of the CPs. The energy settings vary from 100-500 mW in continuous (or 9000 ms) mode, according to the desired effect. The ability to directly monitor the effect of the laser provides the advantage of avoiding overtreatment ("pops") and minimizing inflammation. Once treatment is completed, the cornea is closed following routine intraocular surgery procedure. Postoperative anti-inflammatory, antibiotic, and glaucoma treatment is started immediately after surgery, as IOP control is crucial and can be challenging during the first 1-2 weeks after surgery. Monitoring of IOP and inflammation must be aggressive during this time period, and paracentesis may be required.

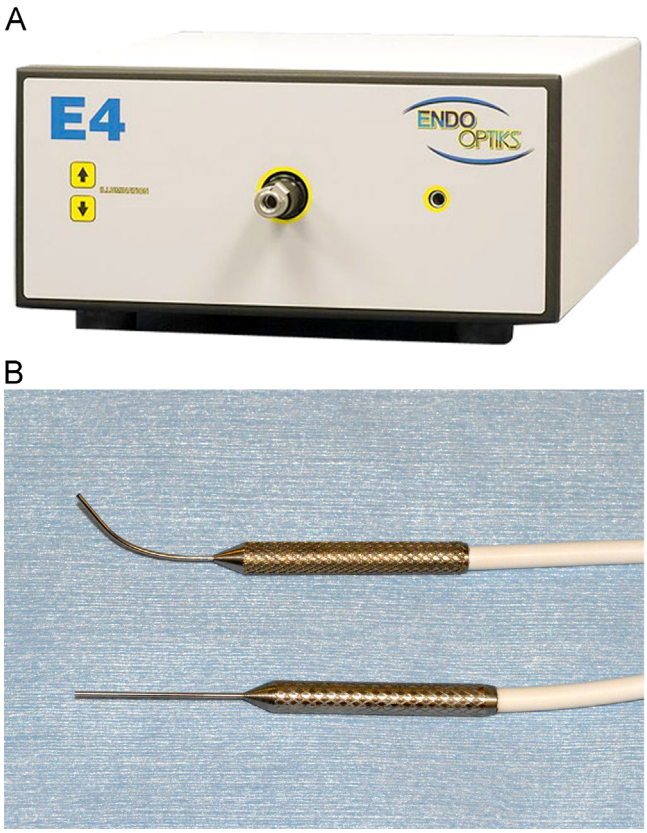


Fig. 7. (A) E4 console, Endo Optiks. (B) Straight and curved probes for endoscopic cyclophotocoagulation.

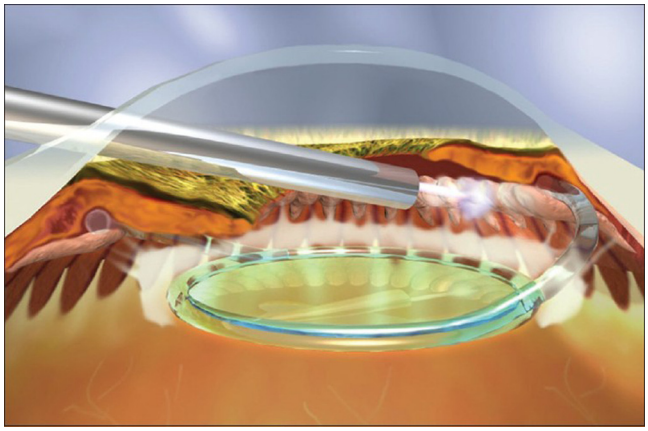


Fig. 8. Limbal approach during endoscopic cyclophotocoagulation. The sulcus is deepened with cohesive viscoelastic, the probe tip is positioned just beneath the pupillary border, and laser energy is applied to the ciliary processes.

ECPC has shown promising results for treatment of both primary and secondary glaucoma in cats and dogs. In contrast with TSCPC, ECPC in feline glaucoma has showed more than 90% success rate in long-term control of IOP and vision preservation.[51] In a study of 292 eyes affected by primary and secondary canine glaucoma and treated by ECPC, 80% of patients showed IOP control at 1 year postoperatively, with vision preservation in 70%. A decrease in the amount and frequency of glaucoma medications is also reported, following successful ECPC.

Reported postoperative complications range from moderate to severe uveitis, ectropion uveae, corneal ulceration, relapsing of glaucoma, and phthisis bulbi.[52]

Filtering procedures employ the use of gonioimplants or GDDs, allowing the AH to be diverted from the anterior chamber to different venues, most commonly the subconjunctival space. The predominant general design is similar across devices and generally consists of a silicone tube connected to a plate, also made of silicone, polypropylene, or, more recently, polyethylene. The tubular portion, inserted into the anterior chamber, drains the AH to the platform, located subconjunctivally. The AH is thus

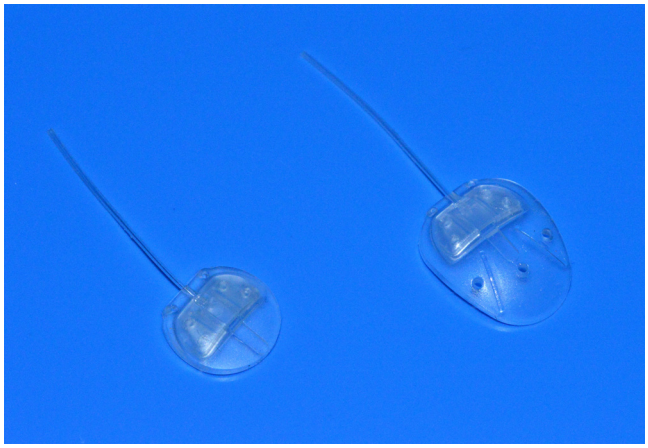


Fig. 9. Silicone Ahmed valves, VFP7 (on the right) and VFP8 (on the left).

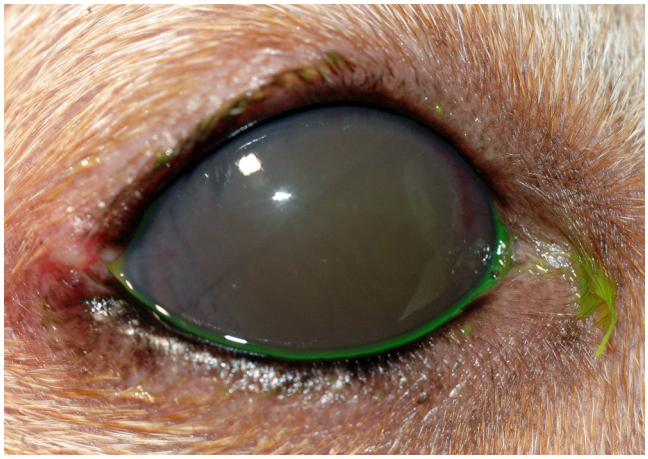


Fig. 10. Intrascleral prosthetic in a dog.

diverted from the anterior chamber into a filtering bleb that surrounds the plate, and from there it is absorbed by the local vasculature. Several models are available, from nonvalved Molteno and Baerveldt to valved Ahmed implants. Currently, the most commonly used GDDs in filtering canine glaucoma surgery are the silicone Ahmed valves VFP7 and VFP8, and polypropylene Ahmed valves S2 and S3, with a surface area of 184.00 and 96.00 mm^2, respectively (Fig 9). In the Ahmed models the presence of a valve provides a unidirectional flow, preventing postsurgical hypotony, secondary uveitis, and potential retinal detachment. Unfortunately, bleb failure may occur within a few weeks to few months after surgery and is more common in animals than in humans.[53,54] Other common complications include implant failure or extrusion, late onset corneal decompensation, and filtration failure due to intracameral tube occlusion by fibrin. The success rate has improved in more recent studies: a recent 9 case series of Ahmed implantation in glaucomatous dogs has showed an impressive success, with 8 of 9 eyes visual at 1-year follow-up.[55] A less popular drainage implant, aimed at diverting the AH to the frontal sinus in dogs, has been investigated and reported by Grahn and Cullen.[56,57] The aim of this type of shunting procedure is to prevent bleb fibrosis and implant failure by diverting the AH to an epithelium-lined, air-filled space such as the frontal sinus.

Currently, the combination of cyclodestructive and filtering techniques offers attractive advantages, namely the additional control of potential IOP spikes after cyclophotoablation, while allowing more extensive cyclodestruction and long-term sight preservation. In 2 separate studies, glaucomatous eyes underwent both gonioimplantation with Ahmed devices and either cyclocryoablation or TSCP. Bentley et al.[58] reported IOP control in 73% and vision preservation in 58% of treated eyes 1 year after the operation. Similar results have been reported by Sapienza and van der Woerdt,[59] with IOP control in 76% and vision preservation in 41% of patients at 1 year. Further advantage is offered by ECPC, which allows optimal laser energy delivery, with decrease in intraocular inflammation when compared with TSCPC.[60] Combination treatment involving the use of ECPC and GDDs may improve long-term success rate, while minimizing inflammation and the complication of IOP spikes in the postoperative period.

Nonvisual Patients

Unfortunately, medical and surgical failures are still common in canine and feline glaucoma, and end-stage surgical procedures are recommended for treatment of blind, buphthalmic, and painful globes.

Enucleation is commonly performed in chronic glaucoma cases and in cases where glaucoma is secondary to intraocular tumors. The description of the technique can be found elsewhere.[61] To improve cosmetic results, intraorbital polymethylmethacrylate or silicone prosthetics may be inserted in the orbit after globe removal. Evisceration with intrascleral prosthesis provides a cosmetic solution in cases of primary and secondary non-neoplastic glaucoma (Fig 10), provided that the ocular surface is healthy and intact. In this procedure the intraocular tissues are removed through a dorsal scleral incision, performed approximately 4-5 mm from the limbus; the prosthesis is then inserted into the scleral shell. In a recent study, 8.21% of evisceration samples and 38.75% of scleral shells from previously eviscerated canine globes showed evidence of intraocular tumors.[62] For this reason, ocular ultrasound is always recommended before evisceration and prosthesis. The same study also highlighted a high percentage of severe corneal disease (46%) among the canine scleral shells, confirming corneal ulceration and perforation among the most common complications of this procedure.

Intravitreal injections of both gentamicin and cidofovir are known to cause irreversible damage to the ciliary bodies with decrease or suppression of AH production. Chemical ablation is an option when potential anesthetic risks for the patient or financial constraints for the client are present. Sedation is usually required; however, in cooperative patients, topical proparacaine solution and subconjunctival injection of 0.2-0.4 mL of 2% lidocaine in the dorsolateral quadrant may provide adequate analgesia. The dose of intravitreal gentamicin varies according to the surgeon's preference (25-40 mg), but it is recommended that the total daily dose for the specific patient (6-8 mg/kg) not be exceeded.[63] Dexamethasone sodium phosphate (1 mg) may be added to control intraocular inflammation. A 20-22-gage needle is inserted 8 mm posterior to the dorsolateral limbus, directed toward the central vitreous space (Fig 11). If possible, 0.5-0.6 mLs of vitreous are aspirated. When the vitreous is too dense and cannot be aspirated, an aqueocentesis is performed. The selected dose of gentamicin is then injected in the vitreal cavity. Recent reports show an improved success rate with this procedure, ranging from 86.4%-100%,[63,64] mostly due to increased doses of injected gentamicin. A negative correlation between success and patient weight is suggestive of a dose-dependent effect of gentamicin, with doses $<$ 20-25 mg associated with failure to adequately control IOP after the procedure. The most common complications of chemical ablation include intraocular inflammation or hemorrhage, corneal opacity, cataracts, phthisis bulbi, and inadequate control of IOP.[23,65,66] Recently, intraocular tumors have been identified by histopathology in 40% of enucleated eyes previously treated with

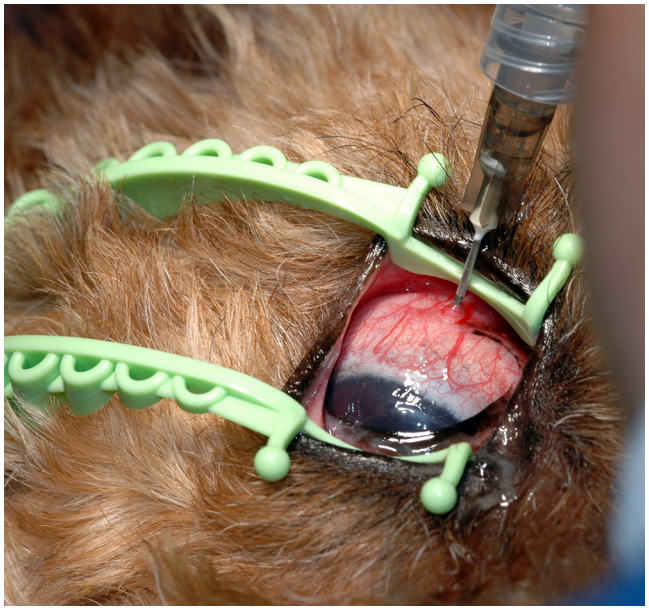


Fig. 11. Intravitreal gentamicin injection in a dog with chronic glaucoma.

intravitreal gentamicin injection (IGI)[67]; it is of concern that a large portion of those tumors exhibited unusually malignant behavior. Thorough ocular examination, including ocular ultrasonography, should always be performed before proceeding for IGI in dogs.

Recently, a study has reported the results of intravitreal cidofovir injection for the treatment of chronic canine glaucoma.[68] Cidofovir (562.5 μg, 0.15 mLs) is injected 5 mm posterior to the limbus with a 30-gauge needle, in a manner similar to that of IGI. Triamcinolone (1 mg) is then injected subconjunctivally. Owing to the minimal volume of injected agent, delivered through a small-gauge needle, this procedure does not require sedation or anesthesia. Intravitreal cidofovir injection may prove to be effective in high-risk anesthesia patients and in patients in which renal disease prevents the use of gentamicin. Despite the high success rate of 85% at 2 weeks after the procedure, the incidence of phthisis bulbi is quite elevated (70% at 6 months). Reported complications are similar to the complications secondary to IGI.

Conclusions

Glaucoma still represents a common and frustrating cause of blindness in the canine and feline population, with frequent failure of medical management. Surgical treatment is frequently required to provide IOP control, by increasing AH outflow or decreasing its production or both. Recent improvements in techniques, materials, postoperative management, and patient selection have resulted in better long-term outcome of surgical procedures. Currently, the combination of cyclodestructive and filtering techniques offers the advantage of posttreatment IOP spikes control, in addition to more extensive cyclodestruction and vision preservation.

However, surgical failure with relapsing glaucoma or irreversible ocular damage is still a common occurrence; end-stage procedures such as enucleation, evisceration with intrascleral prosthesis, and pharmacologic ablation of the ciliary bodies are available to provide relief to blind and painful globes.

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