Restoring Brilliance: Update on Dry Eye Disease

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Introduction

As veterinarians, we are pretty familiar with our run of the mill aqueous tear deficiency even though we sometimes forget about the tear film and its importance. Most of us regularly perform the Schirmer tear test (STT) in dogs, however, there are times in which keratitis and conjunctivitis may seem like dry eye, but the STT is normal. There are many underused tear film tests that we should think about! We will review the importance of the tear film, quantitative and qualitative dry eye disease, and therapy in dogs, as well as recent advances in feline dry eye disease.

The Tear Film

The tear film is composed of three parts- mucin, aqueous, and lipid. Mucin, which sticks the tear film to the cornea and fills any corneal epithelial irregularities, is mixed with the aqueous portion of the tear film (which is the part we have concentrated on for so many years by performing STTs). The aqueous portion of the tear film contains many nutrients that are required by the superficial cornea and provides a flushing action. The lipid layer that is produced from the meibomian glands prevents evaporation of the tear film.

If the tear film is healthy, many other ocular problems, such as corneal pigmentation, vascularization, and scarring, corneal ulcers, and discomfort can be avoided. Aqueous tear production is very important, but there are several other features of the eyes and periocular structures that contribute to a good tear film.[1]

Blinking and Corneal Sensitivity

Tear distribution is initiated by a complete blinking action. The mechanism for tear distribution starts when the eyelids touch each other. The lipid layer then follows the moving eyelid margins and distributes the tear film evenly over the corneal surface. Then the lipid starts to thin, and the aqueous and mucin layers evaporate; once evaporation reaches a critical level, corneal epithelium is exposed and the nerve endings in the corneal epithelium detect the drying which triggers blinking and reflex tearing. If a patient is brachycephalic, has facial nerve paralysis, or is exophthalmic, this reflex is incomplete.[1,2] Corneal sensitivity can also play a role in proper blinking and production of tears. If corneal sensitivity is decreased due to trigeminal nerve dysfunction or breed (brachycephalic), tear production can decrease and neurotrophic factors important for corneal health can also decrease, leading to keratitis.

Canine Dry Eye Disease

Quantitative

When the aqueous layer of the tear film is decreased, mucus and lipid accumulate on the surface of the eye.[1,2] Patients often present with excessive white or ropy discharge on their eyelids. Clinical signs of decreased aqueous tear production include conjunctival hyperemia, corneal edema, lackluster surface of cornea, corneal vessel ingrowth, corneal pigmentation, and corneal ulceration. In chronic KCS cases, the corneal epithelium becomes thickened and keratinized. If left untreated, these clinical signs of KCS can result in loss of vision.

Diagnosis

Diagnosis of quantitative tear film disorders is made based on clinical signs and a Schirmer tear test <15 mm/min.

Etiologies

There are several etiologies of dry eye disease in dogs with the **most common being immune-mediated and breed-related.** For this presentation, we will focus on lesser-known causes of dry eye disease in dogs**.**

Neurogenic KCS

Damage to the parasympathetic innervation of the lacrimal glands (runs with CN VII) results in neurogenic KCS.[3] Neurogenic KCS is often unilateral and has a severe/acute onset. ***The nares on the unilateral side will appear dry if the parasympathetic innervation is damaged proximal to the pterygopalatine ganglion (xeromycteria)***. Neurogenic KCS can occur following trauma to the nerve (blunt trauma, proptosis, or ear canal surgery). It can also be idiopathic and is seen in middle-aged female dogs more often. Sometimes this disease is permanent, but neurogenic KCS can improve if the underlying cause is addressed, and the tear film is supported. Idiopathic neurogenic KCS has been reported to often resolve within a couple of months and sometimes medications can be stopped.

Endocrine Diseases

Three endocrine diseases have been associated with dry eye signs in dogs.[4,5] These are hyperadrenocorticism, hypothyroidism and diabetes mellitus. The underlying cause is unknown for hypothyroidism and Cushing's disease, but is thought to be due to decreased corneal sensitivity in diabetes mellitus.[5]

Congenital (lacrimal gland aplasia/hypoplasia)

Congenital acinar hypoplasia is often the cause of KCS in young dogs with severe clinical signs. Miniature breed dogs are predisposed, including Yorkshire terrier, miniature pinscher, pug, and Chihuahua.[6,7] This type of dry eye can be difficult to treat and often is non-responsive to medical therapy. A parotid duct transposition may be necessary to improve ocular lubrication in these dogs.

Qualitative

Qualitative tear film dysfunction is caused by a decrease in lipid or mucin and is not completely understood.[8] Lipid deficiency can be associated with chronic blepharitis, scarring of the eyelids, previous treatments for distichiasis that may have damaged the meibomian glands, or lack of complete blinking (lagophthalmos). Mucin deficiency has also been associated with decreased goblet cell density caused by chronic conjunctival inflammation secondary to infectious or immune-mediated diseases. Sometimes when the STT is performed, it is normal even if tear quality is poor. These cases usually have red, itchy eyes or mild non-ulcerative keratitis. It can affect one or both eyes.

Tear Film Break Up Time (TFBUT)

TFBUT is an indirect evaluation of the mucin or lipid layers of the tear film. It measures the time it takes for the tears to evaporate from the corneal surface. TFBUT is performed with magnification, such as a magnifying head loupe or slit lamp biomicroscope. To perform, wet the fluorescein strip with 1 drop of eyewash, touch to the bulbar conjunctivae of each eye. Do not rinse. Manually blink the eye and hold open while observing the dorsolateral portion of the cornea with magnification and the cobalt filter for dark spots to appear in the fluorescein stain, indicating drying. The TFBUT is the time it takes for the drying to occur. Reports of normal values for dogs and cats vary, but most texts agree that normal is between 10-20 seconds.

Treatment of Dry Eye Disease- General

Tear Stimulants

There are two main categories of tear stimulants: **T-cell modulators** increase tear production by controlling glandular inflammation and dysfunction, and **cholinergic agents** stimulate lacrimal secretion via parasympathetic fibers for the treatment of neurogenic KCS.

Treatment (Immune-mediated)-T-cell modulators

Cyclosporine A (topical)- available commercially as Optimmune® (cyclosporine 0.2%) and can be compounded into a 1-2% oil or aqueous-based solution. The oil formulations are more bioavailable than the aqueous-based solutions.[1]

Tacrolimus (topical)- must be compounded into a solution for use in the eyes. It can be compounded from 0.01%-1% solutions, but the author is most familiar with 0.01-0.02%. Tacrolimus has been shown to be effective in some cases that are non-responsive to cyclosporine. It has also been thought anecdotally to decrease corneal pigmentation better than cyclosporine. [1]

Treatment with either drug is usually 2-3 times per day. These drugs are the mainstay of immune-mediated dry eye therapy but are also used for other types of dry eye disease (including qualitative) because they improve mucin quality and increase tear production locally at the lacrimal glands. In most cases, tear production improves within 30-45 days.

Cyclosporine episcleral implants have recently been evaluated for control of immune mediated dry eye disease. They have been found to be useful and can last up to 18 months. This implant may be a good choice for dogs that are difficult to treat topically. They have not been used in cats.[10]

Treatment (neurogenic)-cholinergic agents

Neurogenic KCS may not respond well to tacrolimus or cyclosporine alone. This lack of response could even be the reason you are suspecting neurogenic KCS. Most of the time, these medications are still given as adjunctive therapy for their local effects on the tear gland.

The mainstay of treating neurogenic KCS is a direct acting parasympathomimetic drug-***pilocarpine***. This is an eye drop but is usually used *systemically* for the effects on the tear gland and nasal mucosa. It is given on the food to decrease side effect and taste aversion. At the 1-2% commercially available concentration, it usually causes uveitis when used topically.

Pilocarpine 1-2% drops: 1 drop/10 kg PO q 12 h in food (it tastes bitter). After 2 weeks, if the initial dose is insufficient, I increase by 1 drop/day every 5 days, watching for toxicity. (i.e., salivation, vomiting, diarrhea, bradycardia). This is available commercially but can be compounded into an oral solution at some compounding pharmacies. Depending on size of patient, I usually stop increasing if I reach 5-7 drops BID or if toxicity seen. If gastrointestinal signs occur, decrease dose back to level where medication was tolerated. If commercial drops are unavailable, some compounding pharmacies make an oral solution that ranges in concentrations that can be purchased.

Another option for treatment is compounded **Pilocarpine 0.1 % eye drops** into the affected eye 1-2 times daily. Systemic side effects are less and because it is diluted, topical side effects are minimal.

Tear Substitutes

Ointments, gels, and viscous drops are available, and some are preservative free. The viscosity of a drop/gel is the most important factor when choosing a tear replacement.

The preferred tear substitute in veterinary medicine is an aqueous solution modified by the addition of agents to bind the solution to the corneal epithelium and/or increase viscosity. In the normal tear film, this function is performed by the mucin layer of the healthy tear film. Solutions modified to be like mucin (termed mucinomimetic), have longer contact time and offer more lubrication than traditional saline solutions. Regardless of the type of artificial tear chosen, there is value in choosing a non-preservative tear because the preservatives can cause inflammation or worsening of primary disease.

Of the mucinomimetic tear replacement agents, hyaluronate is particularly useful.[11] Hyaluronic acid is present in normal tears, and it becomes less viscous during blinking to aid tear dispersion and more viscous between blinks to provide good lubrication. Hyaluronates are also helpful for chronic conjunctivitis, corneal ulceration, and corneal sequestration in cats (thought to possibly be related to feline dry eye disease) because they support mucin and may help with goblet cell regeneration. Hyaluronic acid is a common ingredient in many artificial tears (veterinary and human products; preservative and preservative-free).

Antibacterial Agents

Broad-spectrum topical antibiotics may need to be administered in the early stages of treatment, usually at a frequency of 3–4 times daily. Use of topical antibiotics would also be necessary if a corneal ulcer is present. Because the flushing action of normal tears is absent, bacterial conjunctivitis is commonly seen secondary to dry eye disease. Conjunctival cytology can be helpful in choosing an appropriate topical antibiotic. As the tear levels improve and ocular surface inflammation subsides, these antibiotics can be reduced and eventually stopped.

Anti-inflammatories

Dry eye disease is inflammatory in dogs. Topical and oral anti-inflammatories are useful in reducing ocular surface inflammation, improving comfort, and diminishing corneal opacities and vascularization. Due to the propensity for corneal ulceration formation with KCS, the author does not use topical steroids. Topical NSAIDs may be useful to help with inflammation if an ulcer is not present. Systemic NSAIDs, such as carprofen, meloxicam, or robenacoxib (cats) are often used early in the course of disease.

Feline Dry Eye Disease

KCS is rare in cats and for a long time was thought not to exist. Recent studies and case reports have suggested that cats do suffer from dry eye disease, but their clinical signs can be different than dogs.[11-15] Decreased tear production can occur temporarily in patients with chronic infectious conjunctivitis or keratitis. In contrast to canine KCS with marked corneal vascularization, pigmentation, and ocular discharge, feline KCS is characterized by variable conjunctival hyperemia, non-healing corneal ulceration, corneal sequestra formation and mild diffuse corneal opacification resulting from epithelial hyperplasia. Excessive mucus discharge is rarely a component. It may affect one or both eyes. Dry eye in cats is thought to commonly be neurogenic in origin.

Diagnosis

In the past, the STT was not usually recommended for cats because it was thought to be unreliable. It was thought that stress could temporarily reduce STT values in cats, but recent studies have shown this phenomenon to be false.[14] In cats with dry eye disease, presence of clinical signs is an important part of making the diagnosis. Also, Schirmer tear test values are consistently less than 9 mm/minute in cats with dry eye disease and TFBUT values are also less than 9 seconds.

Treatment

Response to cyclosporine is usually poor owing to the underlying causes of tear film dysfunction in cats. Supportive care with hyaluronic acid artificial tears, possible treatment with anti-viral medications, and sometimes therapy with pilocarpine (either compounded 0.1% drops or oral administration of the 1% drops) has been advocated in the few case studies that are published. However, cats may be more sensitive to the side effects of pilocarpine. It is not recommended to use topical steroids in these cases due to risks of reactivation of FHV-1 and because corneal ulceration is often a component of this disease process in cats.

Key Take Home Points

1. Having good tear production and quality can prevent many ocular surface diseases.
2. Tear quality is important and may be affected by eyelid abnormalities, skull conformation, and eye position.
3. There are several lesser-known causes of dry eye disease.
4. There is no harm in supporting the tear film- it will help manage and prevent other ocular surface diseases.
5. Cats get dry eye disease!

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