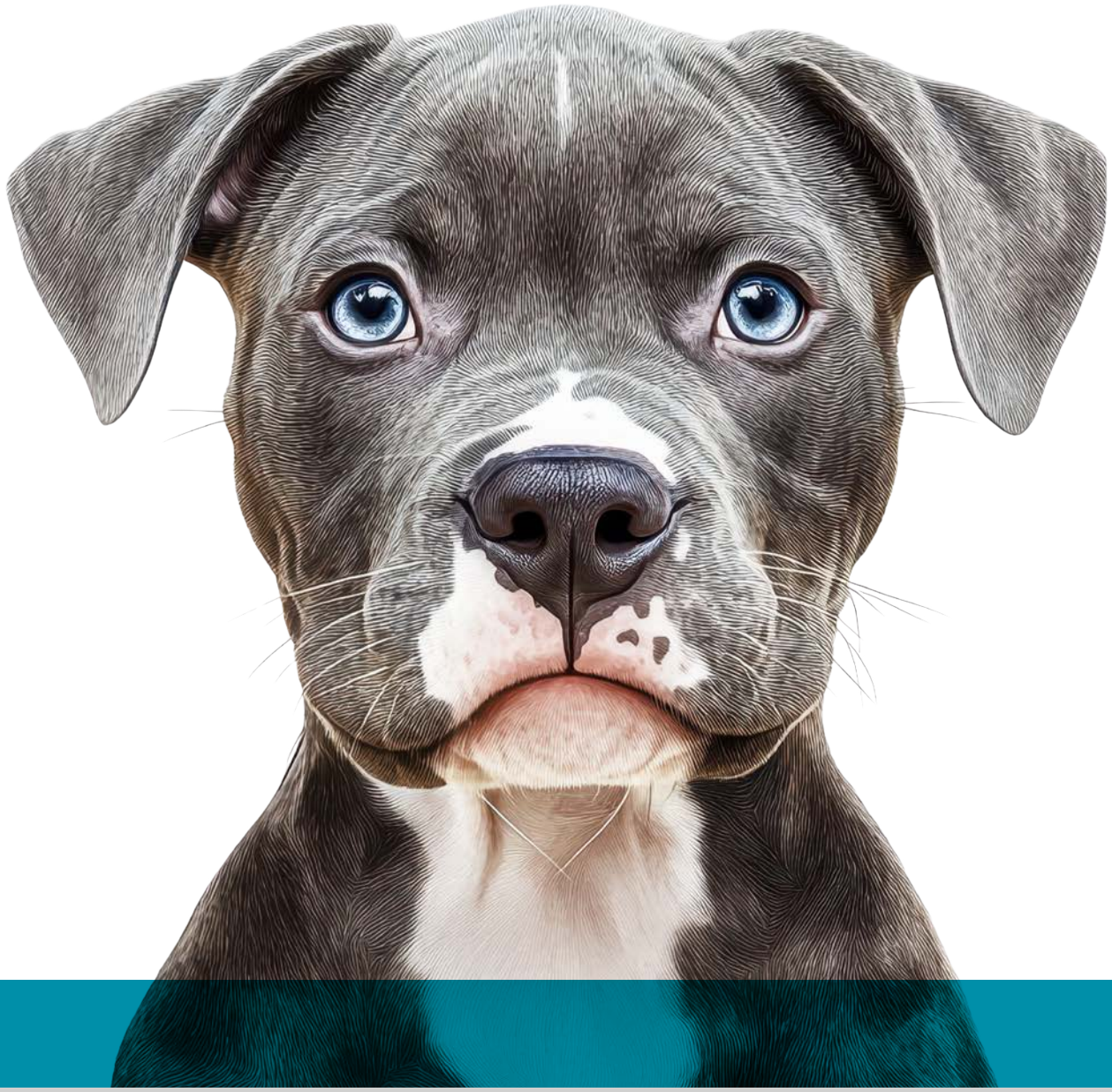
MANAGING
DRY EYE DISEASE

IN DOGS AND CATS



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DÔMES PHARMA

1 INTRODUCTION TO **DRY EYE DISEASE**

Dry eye disease (DED, keratoconjunctivitis sicca/KCS) is a disease syndrome of the ocular surface arising from dysfunction of the integrated functional system of lacrimal glands, ocular surface, eyelids and/or the motor and sensory nerve supply, which create and distribute the composite preocular tear film. There is accompanying ocular surface inflammation, discomfort, and damage, which can be very mild to very severe.

We tend to place DED into one of three main camps:
- **Quantitative (reduced aqueous tear production)**
- **Qualitative (issues with the mucin or lipid layers of the tear film)**
- **Distributive (issues with the eyelids)**

Modified from *(Tear Film and Ocular Surface Society 2007)*.

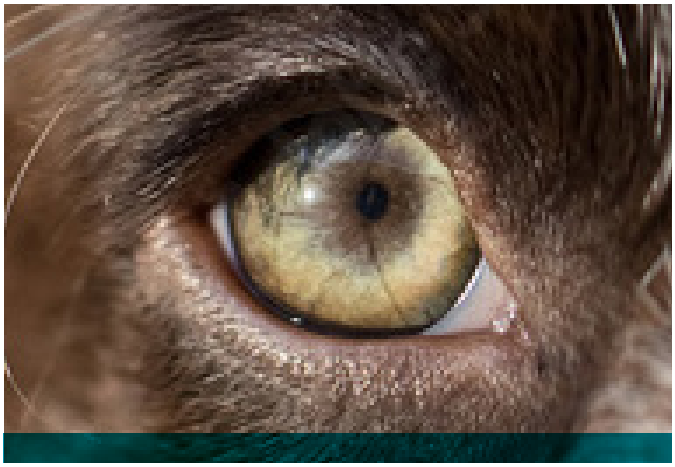
2 THE **NORMAL EYE**

Before digging into diagnosing and treating dry eye disease, it is necessary to distinguish normal from abnormal in canine and feline ophthalmology.

The cornea is the transparent, anterior one-fifth of the fibrous tunic of the globe. The functions of the cornea include support of intraocular contents, refraction and transmission of light. The healthy cornea is clear, smooth, avascular, and refracts light. The cornea relies on both the aqueous humour and the tear film for nourishment and cleansing, and on the eyelids, tear film and nictitating membrane for protection from the external environment.

The conjunctiva is the most exposed of all the mucous membranes. Its primary functions are to prevent desiccation of the cornea, to increase mobility of the eyelids and the globe, and to provide a physical and physiologic barrier against microorganisms and foreign bodies.

An adequate supply of **tears** covering the partially exposed anterior segment of the globe and associated adnexa is necessary for the maintenance of a healthy cornea and of the visual function.



The precorneal tear film serves several functions, including:

- Maintenance of an optically uniform corneal surface
- Lubricant between the lids and ocular surface
- Removal of foreign material and debris from the cornea and conjunctival sac
- Passage of oxygen and provision of other nutritional requirements to the cornea
- Protection against microbial insults.

Tears are present over the surface of the eye as a **triple-layered film**.

The **outer, thin, superficial oily layer** is provided by the meibomian (or tarsal) glands, located in the eyelid epidermis, and flows over the corneal surface through the openings of the tarsal glands in edge of the eyelids. It delays tear evaporation and evens out the surface of the tear film.

The second layer is the **aqueous tear fluid layer**, which is mainly secreted by the lacrimal gland and the gland of the third eyelid. It is the thickest layer of the tear film, and provides nutrients, oxygen and microbial protection to the ocular surface. It is also responsible for hydration of, and the smooth movement of the eyelids over the cornea.

The third, innermost layer is the **mucin layer**, which is produced largely by the conjunctival goblet cells. The mucins it contains are largely responsible for the adhesion of the tear film to the ocular surfaces.

The composite secretion of tears is continuously spread over the surface of the eye in a uniform, thin layer by the constant action of the eyelids (and nictitans) during blinking.

The normal blinking of the eyelids maintains the physiologic thickness of the preocular tear film, aids movement of the tears both to and within the nasolacrimal system, and helps eliminate small particles from the corneal and conjunctival surfaces. The frequency of blinking in a dog eye is **approximately 3–5 times/min**. In cats, complete blinks are infrequent, occurring at a rate of approximately **1 to 5 times/5min**.

Excess fluid collects in the lower conjunctival sac by gravity and is mechanically "pumped" through the openings, the upper and lower lacrimal puncta. These structures mark the beginning of the nasolacrimal drainage apparatus.

The tear film, lacrimal glands, and eyelids act together with the ocular surface as a functional unit to preserve the quality of the refractive surface of the eye and to protect the globe from injury.

Abnormalities in either the quantity or quality of any tear component (lipid, aqueous, mucus) may alter tear fluid dynamics and compromise tear function. Hypertonicity and dehydration of conjunctival and corneal epithelia are initial pathophysiologic events associated with tear deficiency. Lack of appropriate lubrication results in frictional irritation of the ocular surface by the eyelids and third eyelid. Potentially toxic tissue metabolites may accumulate on the ocular surface as well. In tear-deficient patients, microorganisms more readily colonize affected eyes, thereby resulting in an increased incidence of ocular surface infections.

Figure 1 below presents the fail points and causes that can lead to dry eye disease.

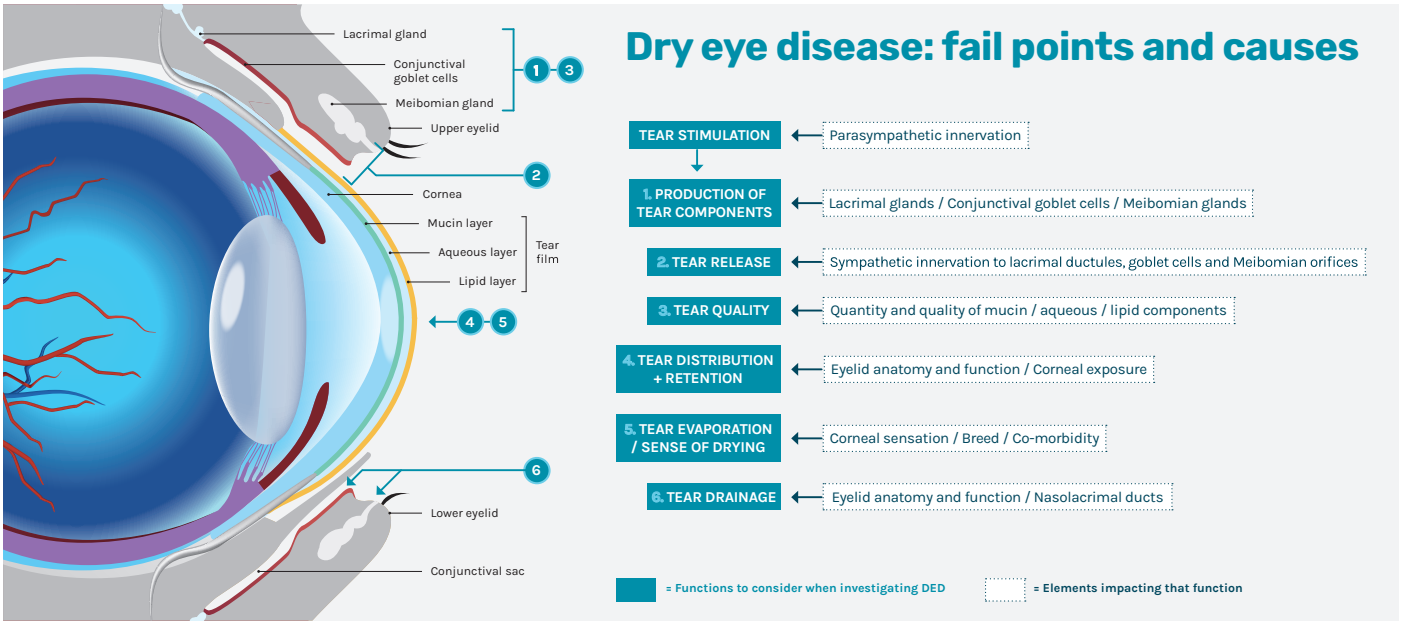


Figure 1: *Structures and functions involved in normal tear production and drainage. Damage to or failure of any of these structures or functions can lead to dry eye disease*

TAKE HOME MESSAGE:

The normal tear production and drainage involves a variety of structures and physiological functions. It both requires and preserves the integrity of the ocular surfaces (cornea, conjunctiva).

Single or combined dysfunctions or injuries of either of the structures and functions involved in tear production and drainage can alter the quality or quantity of the tear film and potentially lead to dry eye disease.

3 AETIOLOGY AND EPIDEMIOLOGY OF DED

The aetiology of DED is complex and can be either poor performance of multiple components of the functional tear system creating an overall failure of the preocular tear film, or complete failure of an individual component. All components of the tear film system are reliant on each other for a functional outcome.

Various aetiologies have been described in dogs *(Peiffer and Petersen-Jones 2009; Miller 2008)* and the **DAMNIT list can be used systematically to investigate the causes of reduced aqueous production**:

- **Developmental:** Glandular aplasia or hypoplasia
- **Autoimmune adenitis of glandular tissue:** the majority of cases of canine DED probably fall into this category. Histopathologic examination of the lacrimal gland reveals break-up of glandular structure with duct dilatation and epithelial cell loss, mononuclear cell infiltration, and fibrosis.
- **Metabolic:** Diabetes mellitus, hypothyroidism, Cushing's disease
- **Neoplastic:** Adenoma or adenocarcinoma of the lacrimal gland
- **Neurologic:** loss of parasympathetic innervation to lacrimal glands, loss of sensory innervation to the ocular surface
- **Infectious:** Distemper virus and Feline Herpesvirus can cause a dacryoadenitis with resultant destruction of the glandular tissue.
- **Iatrogenic:** Surgical gland removal, general anaesthesia and sedation
- **Traumatic:** Damage to the gland or nerve supply
- **Toxic:** Sulpha drugs, paracetamol, atropine, topical drugs/ preservatives

One should note that the DAMNIT list does not rank causes in order of severity or frequency.

The dysfunctional factors can be compounded by environmental conditions (such as pollens, wind) and trigger clinical signs in animals that were compensating until then.

Figure 2 below shows how external and internal factors can contribute to dry eye disease.

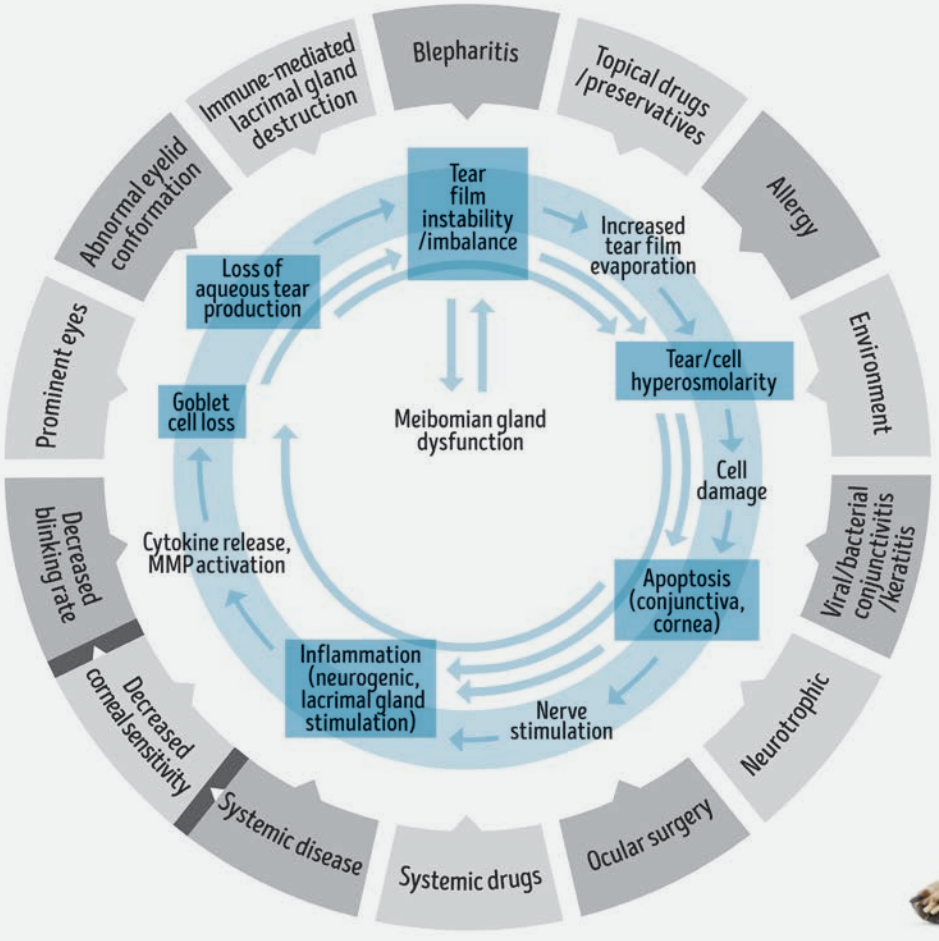


Figure 2: *Cycle and interactions contributing to dry eye disease in dogs and cats. Adapted from https://www.dryeye-society.com/resources/dry-eye-disease-complex-interactions-vicious-cycles. Accessed February 2025*

A dysfunction of any of these points can cause dry eye disease, however the clinical disease most often occurs when several points are involved.

The true prevalence of DED is hard to ascertain because of underdiagnosing. However, some risk factors have been clearly identified as connected to DED, and should be seen by GP vets as **red flags prompting them to further investigate the possibility of DED**.

Those **risk factors** can be categorized as follows:

Breed

Predominantly those with:

- Decreased corneal sensitivity
- Decreased blink rate
- Increased corneal exposure: altered distribution of the tear film
- Anatomical risk factors
  - Head shape: brachycephalic dogs
  - Prominent eyes: pugs, other brachycephalic dogs
  - Reduced globe protection: lagophthalmos, entropion, ectropion

Age

Systemic diseases

In the study by *(O'Neill et al. 2021)*, a predisposition was found in the following breeds:

- **American Cocker Spaniel**
- **English Bulldog**
- **Pug**
- **Lhasa Apso**
- **Cavalier King Charles Spaniel**
- **English Bull Terrier**
- **English Cocker Spaniel**
- **Basset Hound**
- **West Highland White Terrier**
- **Shih-Tzu**
- **King Charles Spaniel**

If earlier studies by *(Sansom and Barnett 1985; Kaswan and Salisbury 1990; Helper 1996; and Sanchez et al. 2007)*, are included, the **English Cocker Spaniel**, the **American Cocker Spaniel**, the **Pug**, the **English Bulldog**, the **Cavalier King Charles Spaniel** and the **West Highland White Terrier** are particularly overrepresented in canine DED populations.

Some breeds such as **Pugs** and **Shih-Tzus** have been shown to have reduced corneal sensitivity and blinking rates *(Sebbag et al. 2023)*. In addition, brachycephalic head shapes with prominent eyes and large palpebral fissures exacerbate the effects of DED and often lead to corneal ulceration from exposure *(Sanchez et al. 2007; O'Neill et al. 2017)*.

Pugs have a predisposition to DED and have been shown to have reduced corneal sensitivity and blinking rate.

It has been demonstrated that KCS also becomes more frequent in dogs **with increasing age** *(Hartley et al. 2006; O'Neill et al. 2021)*. Most dogs diagnosed with DED are **5.5 years or older** *(Sanchez et al. 2007; O'Neill et al. 2021)*. In contrast to humans, gender or neutering status have not been proven to impact the frequency of DED in dogs *(O'Neill et al. 2021)*.

Metabolic and immune-mediated diseases are risk factors with regard to KCS. Diabetes mellitus increases the risk of KCS by altering several parameters, such as reduction of corneal sensitivity, reduction of the quantity and quality of tear production, reduction of the density of goblet cells in the conjunctiva (Cullen et al. 2005) and alteration of the tear film proteome (Winiarczyk et al. 2020). Hypothyroidism is also linked with increased risk of developing DED, although the exact mechanism remains unknown. Systemic immune-mediated conditions can also affect the lacrimal unit and be associated with dry eye.

TAKE HOME MESSAGE:

DED has lots of aetiologies, yet is **most frequently auto-immune in dogs**. Environmental conditions can trigger clinical signs. **Risk factors (breed, age, systemic diseases) need to be identified by vets as red flags** and lead to further investigation and closer follow-up.

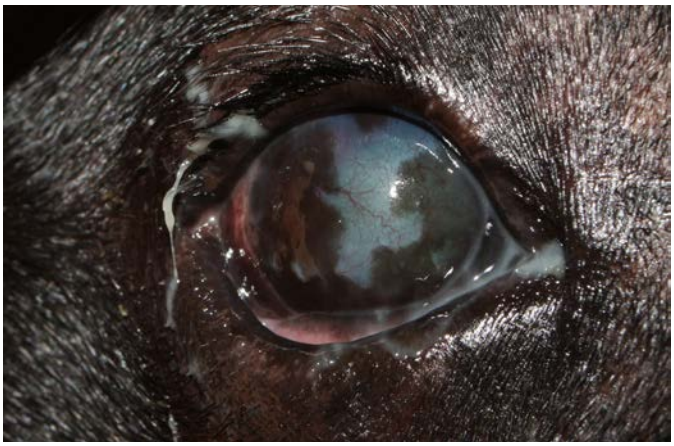
4 THE **MOST COMMON SIGNS** OF DED

Non-specific clinical signs will be the initial alert that a tear film disorder is present. The presence of even just one of these signs should be a trigger dry eye investigation.

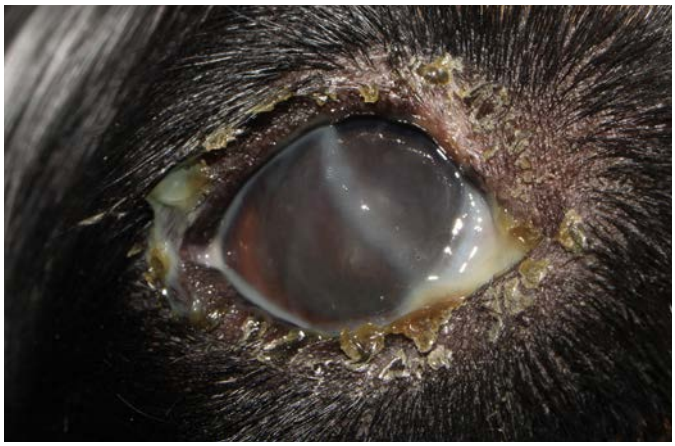
MUCOID OR MUCOPURULENT DISCHARGE

With aqueous tear film deficiency, you will typically see thick tenacious discharge adhering to corneal ocular surface. The underlying causes are likely over-production of mucins to compensate for aqueous deficiency. Be aware that analogous mechanisms result from mucin or lipid deficiency; for example, in case of a mucin deficiency there will be an increase in aqueous production and likely a less visible increase in lipid production resulting in epiphora. One question you should ask the owner is whether their dog has mucoid or mucopurulent ocular discharge in the morning.

Mucopurulent discharge might be misleading and raise suspicion for bacterial infection. Because white blood cells may be present as a result of the inflammation associated with drying of the ocular surface, the presence of mucopurulent discharge does not necessarily indicate secondary bacterial infection (Pictures 1 and 2). Conjunctival cytology can be useful to differentiate whether the discharge is sterile or septic.



Picture 1: *Mucopurulent eye discharge in a dog with immune-mediated dry eye disease. (© A. Guyonnet)*



Picture 2: *Mucopurulent eye discharge associated with secondary bacterial infection in a dog with immune-mediated dry eye disease. (© A. Guyonnet)*

CONJUNCTIVITIS

In the early stages, dry eyes appear red and inflamed and present with repeated bouts of conjunctivitis that recur when topical medication is discontinued. Conjunctival thickening due to squamous cell metaplasia is common.

OCULAR DISCOMFORT

People with dry eye report a foreign body sensation and stinging. Dogs present with variably severe blepharospasm and third eyelid protrusion, most likely related to frictional irritation as the lids move over the dry ocular surface. Because dogs rarely rub their eyes when irritated, ocular discomfort can be difficult to detect in this species, and will be more obvious in the more acute cases.

KERATITIS

These secondary changes are relatively non-specific and reflect the chronic nature of the disease. Corneal vascularisation and pigmentation are common and can lead to loss of vision. The cornea appears lacklustre and sometimes cloudy (Picture 3). Corneal ulceration can occur in severe or acute cases, and **recurring ulcers should raise suspicion**. Due to the lack of tear production, the healing of corneal ulceration is severely impaired.

Picture 3: *Chronic keratitis in a dog showing lacklustre and cloudy cornea, with advanced neovascularisation. (© G. Payen)*

BLEPHARITIS

Inspissated meibomian glands and multiple chalazia occur with meibomianitis which is associated with qualitative tear film deficiency. Disruption of the superficial lipid layer production leads to increased evaporation of the aqueous tear film. Swollen eyelid margins and periocular dermatitis can also occur secondary to accumulation of periocular discharge, as shown in picture 4.

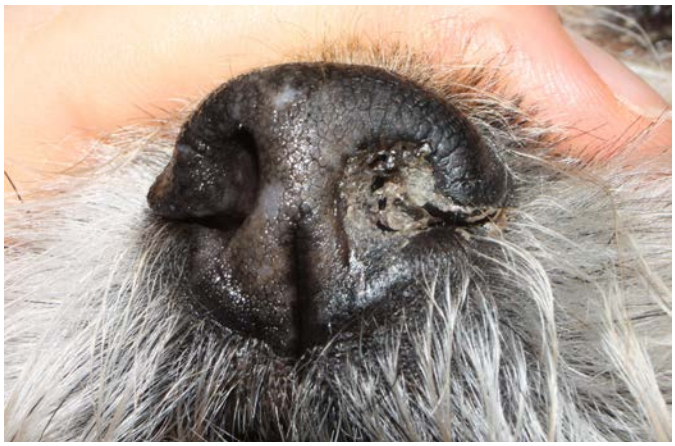
Picture 4: *Blepharitis and periocular dermatitis in a dog. (© G. Payen)*

VISUAL DEFICITS

Blurry vision is a typical clinical sign is reported by human patients especially when the central cornea becomes irregular. This should be kept in mind when finding a lustreless cornea in veterinary patients. Chronic keratitis as described above can however lead to loss of vision.

IPSILATERAL DRY NOSTRIL

Dry nares are a common sign with neurogenic KCS. It is associated with impaired innervations of the lateral nasal gland in addition to the lacrimal glands (Picture 5).



Picture 5: *Dry left nostril in neurogenic KCS (left eye) in a dog. (© A. Guyonnet)*

TAKE HOME MESSAGE:

Classical clinical signs of DED include: **mucopurulent discharge and conjunctivitis that recur** when topical medication is discontinued; **blepharospasm**, **third eyelid protrusion**; and, in a more chronic phase, **keratitis** and **blepharitis**.

Aqueous discharge and **mild signs of ocular irritation** can also be an indication of qualitative DED.

Recurring corneal ulcers should also raise suspicion.

5 DIAGNOSTIC TESTS FOR DED

The diagnosis is based on the history (see causes) and clinical signs. Diagnostic tests should be performed in the following order for accurate assessment, as some tests can impact the results of others:

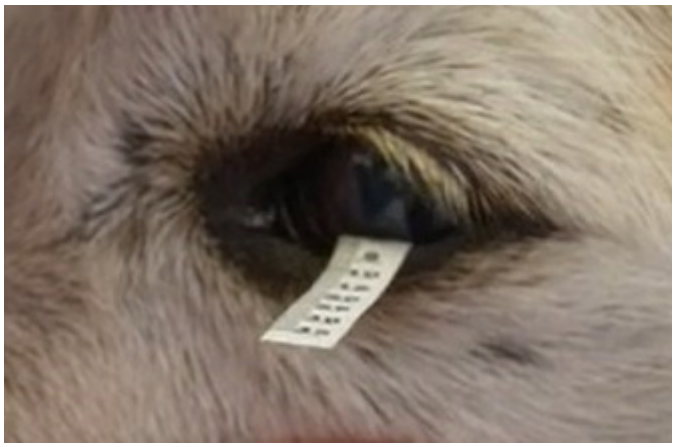
ASSESSMENT OF THE BLINK RATE AND EFFECTIVENESS

Assessment of the blink rate and effectiveness is especially helpful in dogs with a brachycephalic eyelid configuration. In case of incomplete and infrequent blinking one must assumes greater evaporative loss. Taking slow-motion videos can help identify incomplete eyelid closure.

THE SCHIRMER TEAR TEST (STT)

The Schirmer tear test (STT) remains the standard means for quantifying the aqueous tear production and diagnosing quantitative tear film deficiency *(Featherstone and Heinrich 2021)*.

The STT should be performed on every patient with an eye complaint*. It should be performed before the neuro-ophthalmic tests to avoid falsely high values from reflex tearing associated with manipulation of the eye, and prior to application of any topical agents *(Featherstone and Heinrich 2021)*. Although it is preferable to keep the patient's eye open while performing it, maintaining the eye closed is an option. In any case, it should always be performed in the same manner to create personal reference range. The Schirmer tear test strips are bent at the notch prior to removal from the sterile pack. Without touching the bent end, the strip is then inserted into the lateral half of the lower conjunctival fornix (see Picture 6). The strip remains in place for one minute and the readings are taken immediately after removal.



Picture 6: *Schirmer Tear Test strip in place for tear production measurement. (© Digital Academy by Dômes Pharma)*

Schirmer tear test values in a normal adult dog vary from 18.64 ± 4.47mm/min to 23.9 ± 5.12mm/min *(Gelatt et al. 1975; Hamor et al. 2000; Harker 1970; Hirsh and Kaswan 1995; Saito and Kotani 2001; Visser et al. 2017; Wyman et al. 1995)*.

Values between 10-15 mm/min can be consistent with aqueous tear deficiency if compatible with clinical signs, values between 5-10 mm/min are highly suspicious and values of less than 5mm/min are characteristic of severe disease. *(Featherstone and Heinrich 2021)*. Dynamics of progressive wetting of the STT strip can be indicative of DED even with normal values. If the initial flow is slow and then increases, it may be indicative of reflex tearing and therefore low basal tear production.

It is important to note that the tear production fluctuates throughout the day and week *(Berger and King 1998; Giannetto et al. 2009; Håkanson and Arnesson 1997; Piccione et al. 2009)*. Serial STT measurements in conjunction with further clinical tests as well as interpretation of the results in the context of the patient's history and current topical treatment regime are essential and the diagnosis or exclusion should not be based on a single reading *(Hamor et al. 2000)*. In case of doubt a re-examination should be scheduled for repeat measurement.

OPHTHALMIC EXAMINATION

Complete an ophthalmic examination to assess vision, clinical signs of dry eye disease and neurological abnormalities. In addition, assessment of the nares for dryness is essential in diagnosing neurogenic dry eye.

* There are instances however in which the practitioner should refrain from performing a STT: in case of a fragile eye (e.g., with deep corneal ulceration and descemetocele), or of a perforated cornea.

STAINS

Stains such as fluorescein can be used to assess the integrity of the epithelium and function of the precorneal tear film.

• Epithelial integrity

Fluorescein staining is readily available and an important test to assess the corneal epithelial integrity (corneal erosion and ulceration) as well as to assess corneal epitheliopathy associated with dry eye disease *(Iwashita et al. 2023; Saito and Kotani 1999)*. It can be seen as fluorescein positive stippling also referred to as punctate fluorescein staining *(Saito and Kotani 1999)*. It is a sign of epithelial suffering and dry eye disease. *(Bron et al. 2015; Mokhtarzadeh et al. 2011)*. To perform the test one drop of fluorescein is applied to the ocular surface, flushed out with saline and the ocular surface is observed with a cobalt blue light. Picture 7 below shows the right eye of a dog with punctate keratitis.

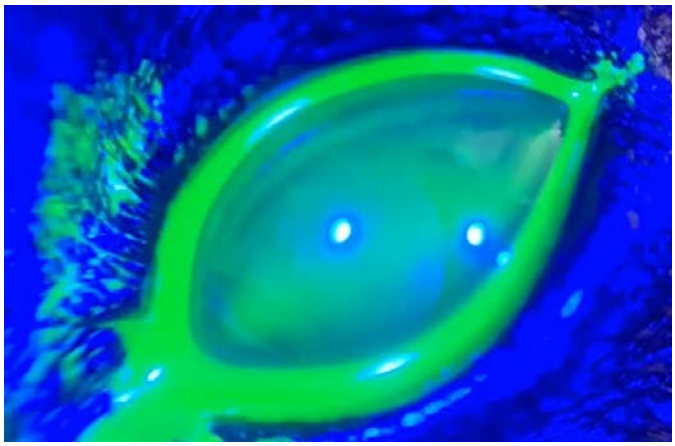
• Tear film breakup time (TFBUT)

Fluorescein can also be used to evaluate the tear film break up time (Pictures 8 and 9), a method to assess the quality of the tear film and capability of the cornea to maintain a homogenous tear film layer *(Giuliano 2021)*. Slit lamp biomicroscopy using a cobalt blue filter is required for detailed observation *(Featherstone and Heinrich 2021)*. Although inter- and intra-observer test reliability are reported to be poor to moderate, the differences in results are not likely to change the clinical interpretation *(Seyer et al. 2021)*. Interpretation can be challenging due to the wide reference range 6.1 ± 2.3 seconds to 21.53 ± 7.42 seconds *(Beagle; Moore 1990; Palmer et al. 2021; Saito and Kotani 2001)* but is interpreted alongside the patient's clinical signs.

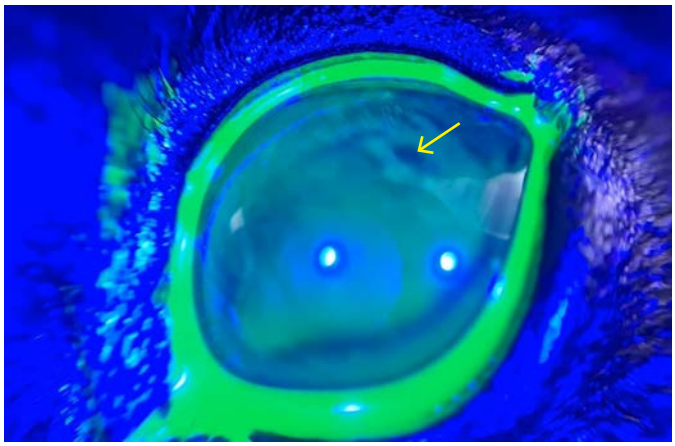
• Lissamine green and Rose Bengal

This test can further aid the diagnosis but are more commonly used in referral practices.

Picture 7: *Punctate fluorescein staining on the right eye of a dog with dry eye. (© A. Guyonnet)*



Picture 8: *Fluorescein evenly spread over the corneal surface at the start of the Tear Film Break Up Time.*
(© B. Michaud - Digital Academy by Dômes Pharma)



Picture 9: *A black dot appears (yellow arrowhead) showing tear film evaporation or poor tear film adhesion to the cornea during a Tear Film Break Up Time test.*
(© B. Michaud - Digital Academy by Dômes Pharma)

FURTHER INVESTIGATION

a. Assessment of the goblet cell density by **conjunctival impression cytology or conjunctival biopsies** for histopathologic evaluation from the palpebral/forniceal sites can support the diagnosis of mucin deficiency.

b. Corneal sensitivity testing to diagnose deficits in the trigeminal nerve innervation, which is responsible for sensing ocular dryness, reflex and basal tearing, and blinking as well as providing trophic factors to the ocular surface. Low cornea sensitivity results in reduced aqueous tear production, development of neurotrophic corneal ulcers and progression of pigmentation *(Bolzanni et al. 2020; Labelle et al. 2013; Sebbag et al. 2019)*. The corneal sensitivity is significantly lower in brachycephalic dogs compared to non-brachycephalic dogs *(Bolzanni et al. 2020)*. Corneal sensitivity is also affected by diabetes mellitus and various ocular surgical procedures *(Good et al. 2003; Sebbag et al. 2019; Sebbag et al. 2020a; Weigt et al. 2002; Khanal et al. 2008)*.

c. Lipid deficiency can be diagnosed by close **examination of the eyelid margin** and everting the eyelid to assess the meibomian glands. Swollen rounded eyelid margins, a reduced number of meibomian glands or abnormal secretion (gentle expression does not yield a normal clear, viscous oil, but instead thick, cream-cheese like coiled strands) and chalazia can be found.

d. Cytology, bacterial culture and antimicrobial sensitivity testing of the expressed meibum can be considered in these cases to adjust treatment.

A full physical examination and further investigation should be taken into consideration to rule out systemic underlying causes such as metabolic and immune-mediated diseases (see Aetiology and epidemiology of DED)

TAKE HOME MESSAGE:

When suspecting dry eye, diagnostic tests should be performed in this order:

1. **Evaluation of blink rate**
2. **Schirmer tear test:** values between 5-10 mm/min are highly suspicious and values of less than 5mm/min are characteristic of severe disease.
3. **Complete ophthalmic examination**
4. **Fluorescein staining**
5. **Full physical examination and further testing as appropriate**

6 TREATMENT AND FOLLOW UP

When confronted with dry eye patients, the practitioner should remember to treat the patient as a whole, and not just a STT value. Ocular pain, comfort and complications are as critical as tear production, if not more. Additionally, the owner will be more mindful of clinical signs than of diagnostic test results.

Having the owner on board and aware of the challenges of dry eye management is essential for treatment compliance and long-term results.

Reminding them that improvement may take several weeks to be visible will avoid unrealistic expectations and ensuing frustration. In addition to administering treatment, the owner can be involved in the detection of early signs of failing disease control.

OWNER EDUCATION: GOOD PRACTICES OF TREATMENT ADMINISTRATION

Prior to treatment administration, the owner should be instructed to **remove all the secretions** in and around the eye, to reduce the crusting and blepharitis, with a soft gauze wet with warm water. The use of an eye comb (Picture 10) or an appropriate ocular cleaner can clean the hair of the eyelids and avoid cutting the animal's hair (which may result in trichiasis and cause corneal ulceration).

Treatment administration is also an opportunity for the owner to examine their pet's eyes and spot warning signs of failure of disease control. The sooner these are identified, the earlier treatment can be adjusted. The owners can therefore ask for a follow-up visit in case of reappearance of gunk in the morning, ocular redness, or if ocular cleansing is required more frequently.

Picture 10: *Eye combs with round-ended teeth to prevent injuries to the eyes and skin while cleaning the hairs on the eyelids.*

MANAGEMENT OF DED

Appropriate ocular hygiene (i.e., frequent cleaning of discharge) is essential to minimize the accumulation of debris with microbes and degradative enzymes that contribute to ocular surface inflammation and ulceration.

• Tear supplements (lacrimomimetics)

Tear substitutes contain ingredients, or combinations of ingredients, to replace deficiencies in one or more of the three primary tear components (i.e., aqueous, mucin, lipid). Unfortunately, there is no ideal product that adequately replaces all functions served by the tears, and the response to tear supplements is individual-dependent. Despite their limitations, lacrimomimetics are warranted in the treatment of tear film abnormalities and as an adjunct to lacrimostimulant therapy. The ideal tear supplement exhibits high viscosity, physiological, tear film-like pH, and, because they are prescribed on a long-term basis, no preservatives (which could destabilize the tear film).

Sodium hyaluronate or hyaluronic acid is a naturally occurring, high molecular weight glycosaminoglycan with excellent viscoelastic and lubricating properties. Evaluation of the biologic and physical properties of these substances typically show excellent rheologic properties (i.e., elasticity, viscosity, and pseudoplasticity), thereby indicating lacrimomimetic formulations containing sodium hyaluronate should serve as effective protectants for the ocular surface *(Giuliano 2021)*, in particular in aqueous-deficient dry eye patients. The nature of hyaluronic acid (concentration and linear or cross-linked) impacts the frequency at which these tear supplements should be administered *(Montiani-Ferreira et al. 2022)*.

Topical **mucomimetics** are the mainstay of mucin-deficient dry eye treatment. The more viscous lubricants mimic mucin by enhancing the ocular surface wettability and providing extended contact time with the epithelial surfaces *(Giuliano 2021)*. Viscoelastic substances with mucomimetic properties include sodium hyaluronate/hyaluronic acid, chondroitin sulphate, and 1-2% methylcellulose preparations.

• Stimulate the natural tear production (lacrimostimulants)

Immunomodulating agents. **Ciclosporin A (CsA)**, a calcineurin inhibitor, remains the cornerstone of immune mediated dry eye treatment. It should **always be used as a 1st-line treatment**. The recommended regimen is topical application every 12 hours. Ciclosporin typically increases tear production within 2-3 weeks of therapy but some dogs may require 2-3 months of therapy before improvement of STT values are observed *(Kaswan et al. 1989; Morgan and Abrams 1991; Miller 2008)*. Lifelong treatment is usually needed in most dry eye patients, in particular when an immune-mediated process is involved.

Both immune-modulating and tear stimulating properties account for the response observed in many affected dogs. CsA will, however, only be effective if some functional lacrimal gland remains *(Kaswan and Salisbury 1990)*. Clinical improvement of keratitis, evident as decreased mucopurulent discharge, corneal vascularization, and pigmentation, occurs in most patients, even in dogs whose tear production does not increase *(Giuliano 2021)*.

Cholinergic agents. The use of **pilocarpine** for dry eye is indicated in cases of parasympathetic denervation of the lacrimal glands (e.g., neurogenic KCS) and will only be effective if some functional lacrimal gland remains. Ophthalmic pilocarpine solution can be administered either topically or orally as a tear stimulant:

- **The optimum systemic dose** is reported as 2% eye drops given orally in food at one drop per 10 kg body weight every 12 hours. The dose is increased every 2-3 days until systemic side effects are observed including vomiting, diarrhoea, drooling, bradycardia, and weakness; the dose is then lowered back to the highest tolerated dose.
- **Diluted pilocarpine can be applied directly to the eyes, or given orally**. Concentrations of either 0.125% or 0.25% can be formulated by adding 1 mL of 2% pilocarpine to 15 mL of artificial tears (0.125% solution) or 2 mL of 2% pilocarpine to 14 mL of artificial tears or saline (0.25% solution). Oral administration of diluted pilocarpine can prove beneficial in dogs prone to ocular irritation.

• Reduce ocular surface inflammation

Anti inflammatory therapy may be a valuable adjunct to other medical therapy in improving clinical signs of dry eye. Caution must be exercised when administering topical corticosteroids and they are not recommended, because their use may significantly complicate healing of an ulcerated cornea and predispose the eye to secondary infections and ulceration. Chronic administration of topical corticosteroids can also cause local immunosuppression *(Giuliano 2021)*.

CsA has anti-inflammatory properties in addition to its marked lacrimostimulant effects, and is therefore adapted to aqueous, mucin *(Moore et al. 2001)*, and lipid *(Hisey et al. 2023)* deficiencies. CsA appears to be well tolerated when used in the presence of corneal ulceration as it does not alter the ocular surface flora *(Salisbury et al. 1995)*. Topical NSAIDs are also good anti-inflammatory treatments.

Note: Some medications discussed in this guideline are not veterinary licensed and their prescription should be made only after careful evaluation of the prescribing cascade and all available options.

• Control secondary infections

Mucopurulent discharge is commonly observed in cases in KCS. Secondary bacterial infections are frequent in dry eye due to inadequate cleansing of the ocular surface. Various types of ocular cleansers specifically formulated for animals and containing surface active agents (polysorbate), chelators (Tris, EDTA) as well as antiseptic compounds (salicylic acid, sodium borate) are available on the market.

Antibiotic treatment is usually not indicated as the discharge will most likely disappear with control of the underlying disease. Topical antiseptics (povidone iodine 1.5%) should be preferred over antibiotics to avoid bacterial resistance. N-acetylcysteine has also been shown in vitro to exert antimicrobial activity *(Walter et al. 2023)*. Topical broad-spectrum antibiotics are essential if corneal ulceration is present.

• Mucolytic Agents

To facilitate removal of abundant exudates and mucoid debris that may accompany dry eye, **N-acetylcysteine** may be applied topically two to four times daily *(Giuliano 2021)*.

• Other options

Omega-3 diet supplementation has been studied both in veterinary and human medicine *(Hisey et al. 2023)* but no strong evidence supports its efficacy.

Heat therapy is commonly recommended in patients with meibomian gland disease, as they often have inspissated meibomian glands. The aim is to melt the concretions of meibum, facilitating its release onto the ocular surface *(Hisey et al. 2023)*. The use of warm compresses and palpebral massage have been reported in dogs but the use of a specific device to apply heat and pressure has not been reported.

In case of ciliary spasm, Tropicamide and Cyclopentolate can be used.

Atropine should not be used as it decreases lacrimation!

• Referring to veterinary ophthalmology specialists

In the absence of response to 1st-line treatment, or in the case of concomitant eye disease (such as deep ulceration), referring your patient to a **veterinary ophthalmologist** is advised. Here are examples of treatments available in referral centres:

- When response to 0.2% CsA ointment is unsatisfactory, the concentration of topical CsA can be increased to 1-2%
- Off-label tacrolimus prescription can be considered for the most CsA-refractory dry eye patients, as per the cascade in your country.
- Uncooperative patients can benefit from an episcleral CsA implant. The effect may last over one year. CsA is ineffective in neurogenic dry eye, drug-induced and congenital acinar hypoplasia.

In dry eye cases refractory to medical treatment, surgical intervention should be considered. Autologous serum eye drops can be used in severe cases, although their possible benefits are inconsistent *(Pan et al. 2017)*. Parotid duct transposition (PDT) is often the surgical option of choice for patients in whom medical management has proven unsuccessful.

FOLLOW-UP

Improvement of dry eye disease and treatment efficacy are best assessed by the owner than by the vet. Tear production measurement, epithelial integrity and tear film stability evaluation are means of tracking response to treatment, but those indicators are less sensitive than ocular redness and discharge *(Miller 2008)*.

• Treatment adjustment

Artificial tear adjustment

There is a wide variety of artificial tears in the market: different concentrations and architectures (linear vs cross-linked) of hyaluronic acid or other natural polysaccharides, lipids, liposomes, artificial polymers, etc. Some patients are improved by the combination of different tear replacements, so the search of the perfect combination can be useful. Adapting the tear supplements to the time of day can be a useful way of optimising disease control. e.g. drops during the day, and thicker gels or ointments at night.

Topical immunosuppressive drug reduction

Many of the causes of dry eye in the dog need lifelong treatment. This treatment is sometimes expensive, and laborious, so finding the minimum effective treatment regimen is ideal. In some cases, dogs with controlled immune-mediated dry eye disease can be managed with one administration of topical CsA (or other immunomodulating drug) every 48 hours. However, the benefit of twice daily ocular examination and regular hygiene by the owner needs to be taken into account.

• Follow-up visits

Here is a suggested schedule for the follow-up of dry eye patients:

Figure 3: *Proposed schedule for follow-up visits of a patient diagnosed with dry eye disease.*

TAKE HOME MESSAGE:

Ciclosporin and tear supplements should always be used as a 1st line treatment and ongoing management of Dry Eye Disease.

Topical application of Ciclosporin A every 12 hours is recommended, after cleaning the eye. Cholinergic agents can be used in addition to Ciclosporin and tear supplements in cases of neurogenic dry eye.

Follow-up should be scheduled 1 month after initiation of treatment.

In the absence of response to 1st line treatment, referring your patient to a veterinary ophthalmologist is advised.

Involvement of the owner is essential in the management of DED: teaching them good practices of eye cleaning and treatment administration is essential. Make sure they understand improvement can take several weeks, and treatment is often life-long.

7 ABOUT **CATS**

AETIOLOGY

DED is the most important lacrimal disease in the cat, but much less frequent than in dogs. Possible causes include *(Gelatt and Plummer 2022; Sebbag et al. 2018)*:

- **Most commonly, chronic blepharoconjunctivitis**, at least some of which appears in turn to be secondary to recurrent or chronic feline herpesvirus (FHV-1) infection. The virus can cause denervation of cornea, and attack of the lacrimal unit due to inflammation and immune destruction.
- **Neurogenic KCS** may occur secondary to diseases disrupting parasympathetic innervation of the lacrimal glands, such as dysautonomia
- Use of atropine or general anaesthesia/sedation may transiently decrease tear production

DIAGNOSIS

It is debated whether stress impacts tear production in cats, one study showed that sympathetic tone did not influence aqueous production *(Sebbag et al. 2020b)*. Stress was even associated with increased tear production in another study *(Donat Almagro et al. 2024)*.

STT 1 values in the normal adult cat vary from 14.3 ± 4.7 mm/min to 17.5 ± 6.9 mm/min. As in the dog, less than 5 mm in 1 minute is considered to be diagnostic, though many cats will have no clinical signs associated with such low values. Topical rose Bengal staining of the cornea and conjunctival surfaces may assist in the confirmation of KCS in cats. Feline KCS is characterized by conjunctival hyperaemia, mild and diffuse corneal opacification resulting from epithelial hyperplasia, and rarely, corneal vascularization and pigmentation as well as conjunctival discharge. In some cases, corneal ulceration may also be present *(Gelatt and Plummer 2022; Donat Almagro et al. 2024)*.

MANAGEMENT

Management of feline KCS differs little from that of canine KCS.

Palliative relief is achieved by application of artificial tear products as needed and topical antibiotics to prevent bacterial infection. Pilocarpine may be used (one or two drops of 0.25–0.50% solution mixed in the food), but the patient should be monitored for any adverse systemic reaction.

Topical Ciclosporin and tacrolimus are the current therapies of choice for the treatment of canine KCS, but the **efficacy in feline KCS has not been established**. Cats tolerate the ointment formulation of Ciclosporin better than the oil formulation *(Chaudieu and Bouhanna 2018)*.

Anti-virals should be considered where there is suspicion of active FHV-1 infection. Treatment for corneal ulceration should be instigated if present.

8 SUMMARY

Dry eye disease, or keratoconjunctivitis sicca, results from the dysfunction of one or multiple structures of the integrated tear system, leading to clinical signs (mucopurulent discharge, recurrent conjunctivitis…) along with interaction with environmental conditions.

DED has lots of aetiologies, most frequently auto-immune in dogs and post-herpetic in cats. Some risk factors as breed, age or systemic diseases are red flags the GP should take into consideration. The diagnostic process involves several steps, including quantification of tear production with a Schirmer tear test. In dogs, Ciclosporin A is the first-choice treatment. Owner compliance is critical in the success of DED management, and they must be fully aware that KCS is a chronic disease and that treatment must be continued for life.

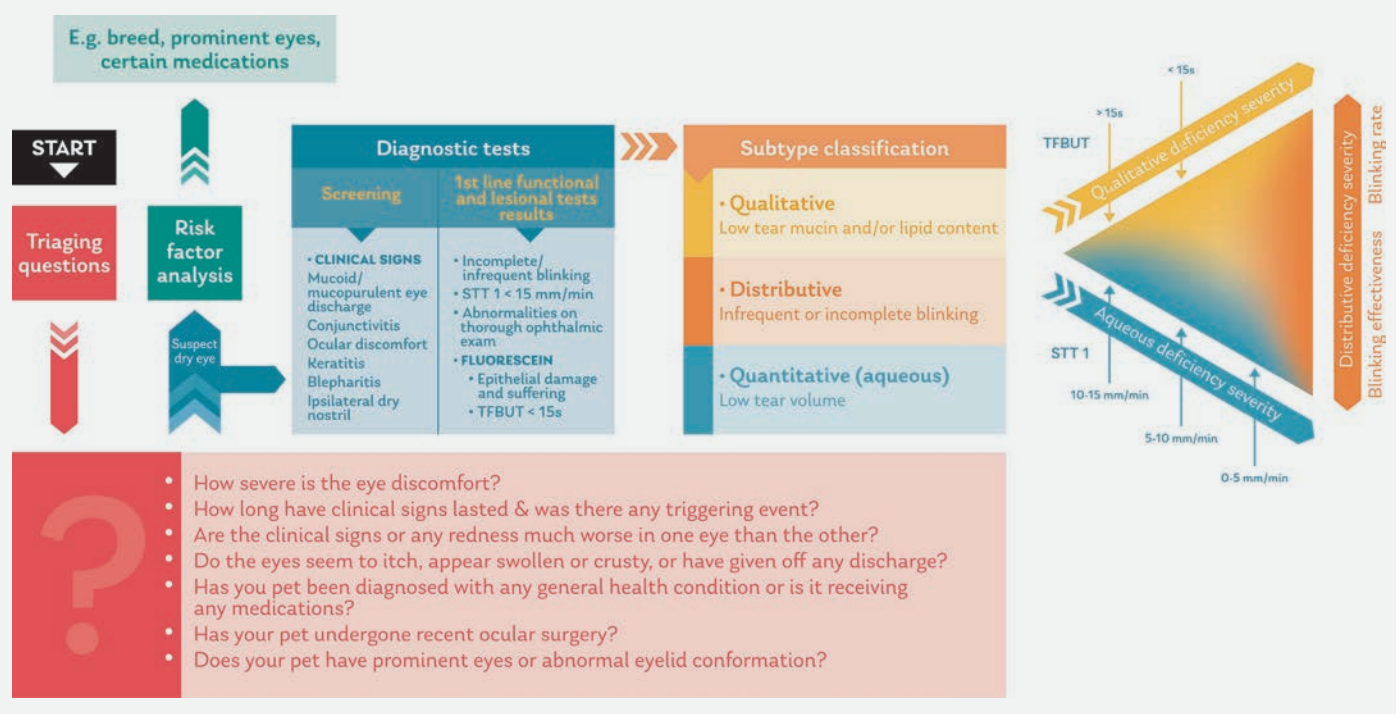


Figure 4: *Summary of the diagnostic of dry eye disease in cats and dogs. Adapted from (Wolffsohn et al. 2017).*

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