Keratoconjunctivitis sicca (KCS) is a relatively common condition in dogs. Although KCS can be diagnosed readily with a thorough ophthalmic examination, the diagnosis is often overlooked.

KCS is an inflammatory condition of the cornea and conjunctiva, secondary to a deficiency of the precorneal tear film (PTF). KCS is categorized by tear film deficiency:

- **Quantitative KCS** is a decrease in the *aqueous component* of the tear film as measured with the Schirmer tear test (STT); it is recognized more commonly in veterinary medicine.
- **Qualitative KCS** is a decrease in the *lipid or mucin components* of the tear film and diagnosed by documenting decreased tear film breakup time (TBUT).

**PATHOPHYSIOLOGY**

Tear film deficiencies lead to:
- Chronic inflammation of the ocular surface secondary to increased surface friction
- Secondary infection
- Dehydration and malnutrition of the corneal and conjunctival epithelium.

This latter combination makes ulcerations more prone to infection, possibly resulting in keratomalacia and perforation.

### THE LACRIMAL SYSTEM & TEAR FILM

Normal PTF is estimated to be anywhere from 3 to 45 microns thick in humans and, in most species, is composed of aqueous, lipid, and mucin layers, which were once thought to be present in a laminar arrangement (Table 1). More recent evidence suggests that PTF may resemble a muco-aqueous pool covered in a very thin lipid layer rather than a trilaminar structure.

<table>
<thead>
<tr>
<th>AREA OF PRODUCTION</th>
<th>FUNCTION</th>
<th>TYPE OF DEFICIENCY</th>
<th>DIAGNOSTIC TEST</th>
</tr>
</thead>
</table>
| LIPID               | Meibomian glands | • Limits evaporation  
• Binds tear film to cornea  
• Provides surface tension to prevent tear film overflow | Qualitative | Decrease in TBUT |
| AQUEOUS             | Orbital and nictitans lacrimal glands | • Provides corneal nutrition, surface lubrication, and smooth surface for optical clarity  
• Removes waste material and bacteria | Quantitative | Decrease in TBT |
| MUCIN               | Conjunctival goblet cells | • Enhances spread of tear film | Qualitative | Decrease in TBUT |

Lacrimal secretion is stimulated via sensory input from the cornea, periorbital structures, and globe. The ophthalmic and maxillary divisions of the trigeminal nerve serve as the afferent part of the reflex arc; then motor input travels to the lacrimal glands via the parasympathetic division of the facial nerve as the efferent arc. Tears are then secreted following contraction of lacrimal acinar myoepithelium.

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**TABLE 1. Structure of Precorneal Tear Film**

<table>
<thead>
<tr>
<th>AREA OF PRODUCTION</th>
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Chronic surface irritation results in:
- Conjunctival hyperemia
- Squamous metaplasia of the surface epithelium
- Hyperkeratinization of the surface epithelium
- Thickening of the corneal epithelium.

Inflammatory cells and blood vessels enter the anterior corneal stroma, depositing pigment, lipids, and calcium. The vascularization and deposits stabilize the cornea and make it less susceptible to ulceration; however, their presence can result in vision loss.

### Diagnosis & Treatment of Keratoconjunctivitis Sicca in Dogs

#### Chronic Surface Irritation

- Conjunctival hyperemia
- Squamous metaplasia of the surface epithelium
- Hyperkeratinization of the surface epithelium
- Thickening of the corneal epithelium.

#### Inflammatory Cells and Blood Vessels

- Inflammatory cells and blood vessels enter the anterior corneal stroma, depositing pigment, lipids, and calcium. The vascularization and deposits stabilize the cornea and make it less susceptible to ulceration; however, their presence can result in vision loss.

### Table 2. Causes of Quantitative KCS

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PATHOGENESIS</th>
<th>PREDISPOSITION</th>
<th>DURATION</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease (Ophthalmic)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic severe conjunctivitis</td>
<td>Swelling of excretory ductules of lacrimal gland</td>
<td>None</td>
<td>Variable: Permanent if scarring present</td>
<td>Good</td>
</tr>
<tr>
<td>Immune-mediated lacrimal adenitis (primary KCS)</td>
<td>Immune-mediated destruction of lacrimal tissue with secondary atrophy&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Most common cause of canine KCS&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Lifelong</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Disease (Other)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canine distemper virus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lacrimal adenitis</td>
<td>Unvaccinated animals</td>
<td>Variable: Many spontaneously recover</td>
<td>Good to fair: If systemic disease survived, many recover</td>
</tr>
<tr>
<td>Idiopathic neurogenic&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Idiopathic: Present with ipsilateral dry nose</td>
<td>Middle-aged female dogs</td>
<td>Variable</td>
<td>Good to fair: Some spontaneously resolve</td>
</tr>
<tr>
<td>Leishmaniasis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Lacrimal adenitis, especially surrounding lacrimal gland ducts, where amastigotes accumulate</td>
<td>Animals in Mediterranean region or with travel history</td>
<td>Variable</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Hereditary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital alacrima</td>
<td>Developmental absence of lacrimal tissue</td>
<td>Yorkshire terrier overrepresented&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Permanent; present at birth</td>
<td>Poor: Often requires surgery</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etodolac&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Nitrogen-containing pyrimidine/pyridine rings have direct toxic effect on lacrimal acinar cells</td>
<td>None</td>
<td>Variable</td>
<td>Fair: If etodolac administration &lt; 6 months, more likely to recover</td>
</tr>
<tr>
<td>Sulfa-derivative medications&lt;sup&gt;g&lt;/sup&gt; &amp; related compounds&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Nitrogen-containing pyrimidine/pyridine rings have direct toxic effect on lacrimal acinar cells</td>
<td>Typical onset within 30 days of medication initiation&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Variable: May resolve in 45–60 days or sometimes lifelong</td>
<td>Fair: Discontinue medication immediately after decrease in STT</td>
</tr>
<tr>
<td><strong>Treatment/Trauma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic: Removal of third eyelid gland</td>
<td>May decrease tear production and TBU&lt;sup&gt;t&lt;/sup&gt;</td>
<td>None: History of removal of gland</td>
<td>Variable</td>
<td>Fair</td>
</tr>
<tr>
<td>Local radiation therapy&lt;sup&gt;l&lt;/sup&gt;</td>
<td>Acute adverse effect of radiation exposure</td>
<td>None</td>
<td>Variable: Dose dependent and patient sensitivity</td>
<td>Fair</td>
</tr>
<tr>
<td>Trauma to lacrimal gland or nerves&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Decreased production/distribution of PTF due to decreased blinking and/or increased evaporation secondary to lagophthalmia&lt;sup&gt;j&lt;/sup&gt;</td>
<td>None</td>
<td>Variable</td>
<td>Fair to poor</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Based on initiation of medical management
<sup>b</sup> Many breeds are predisposed to primary KCS, including, but not limited to, the American cocker spaniel, cavalier King Charles spaniel, West Highland white terrier, and brachycephalic breeds (eg, English bulldog)<sup>i</sup>

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**Quantitative KCS**

**Causes**

Causes of quantitative KCS—organized by type of cause—are listed in **Table 2**. The most common cause is immune-mediated lacrimal adenitis. Transient decreases in tear production can be iatrogenically caused by:
- General anesthesia: Significantly decreases tear production for up to 24 H<sup>f</sup>
- Xylazine, medetomidine, and butorphanol: Significantly decrease tear production temporarily<sup>j</sup>
- Topical or systemic atropine: Causes secondary decrease in tear production that is not clinically significant in most dogs.
Therefore, artificial tear ointments are important adjuncts to sedation and anesthesia regimens, and should be continued until dogs are fully responsive and consistently blinking appropriately.

Clinical Signs
Clinical signs associated with quantitative KCS are listed in Table 3.

Diagnosis
KCS is diagnosed after consideration of:
• History: Ask historical questions that explore previous drug administration, vaccinations, and surgical procedures.
• Ophthalmic Examination: Perform a complete ophthalmic examination in all dogs presenting with new clinical signs (Table 3) or disease progression.
• STT: This test is the cornerstone of quantitative KCS diagnosis; interpret results in light of clinical signs. A Schirmer tear test 1 (STT1)—performed without application of surface anesthetic agents—assesses reflex tear production. Normal production in dogs is > 15 mm/min.

QUALITATIVE KCS
Causes
The causes of qualitative tear film deficiency are not completely understood.
• Chronic blepharitis with meibomianitis can lead to decreased production of the lipid layer. Infectious causes of blepharitis include Staphylococcus, Candida, and Malassezia species.19
• Decreased goblet cell density and subsequent mucin layer deficiency are most likely caused by chronic conjunctival inflammation secondary to infectious disease or immune-mediated disease.20

Clinical Signs
Clinical signs of qualitative tear film deficiency are more subtle than those seen with quantitative disease, and include:
• Blepharospasm
• Mild corneal neovascularization
• Mucus discharge.

Diagnosis
If qualitative KCS is suspected based on history and clinical signs:
• STT: Perform a STT to rule out quantitative aqueous deficiency; STT results are normal in patients with qualitative KCS.
• TBUT: Perform a TBUT to assess for deficiency in the PTF’s mucin component.
  1. Apply 1 drop of fluorescein stain to the eye, holding the eyelids open.
  2. Under cobalt-blue illumination, examine the cornea. Note how many seconds it takes for dark spots to appear as the PTF “breaks up” the fluorescein layer.

![Figure 1. Two-year-old castrated male chihuahua. Note corneal neovascularization and pigmentation, thick and adherent mucopurulent discharge, and keratinization of corneal epithelium; STT was 0 mm/min.](image1)

![Figure 2. Four-year-old castrated male mixed breed dog. Note descemetocele, corneal edema, and mucopurulent ocular discharge; STT was 0 mm/min.](image2)

![Figure 3. Three-year-old spayed female Shih Tzu. Note corneal neovascularization and mild keratinization; STT was < 5 mm/min.](image3)

![Figure 4. Three-year-old spayed female Olde English Bulldogge. Note conjunctival hyperemia, corneal neovascularization, pigmentation, keratinization, and thick mucopurulent discharge.](image4)

**TABLE 3. Clinical Signs of Quantitative KCS**

- Thick, adherent mucopurulent discharge (Figure 1)
- Conjunctivitis
- Blepharospasm
- Dry, lusterless corneal appearance
- Ulcerative keratitis, ranging from superficial ulcers to perforations (Figure 2)
- Corneal pigmentation (Figures 3 and 4), neovascularization, and/or keratinization

Of the breeds predisposed to KCS, many have distichia, physiologic exophthalmia with lagophthalmos, and medial canthal entropion—all conditions that can cause conjunctivitis and keratitis.
3. A normal TBUT is $\geq 20$ seconds. Animals with quantitative deficiencies often have a TBUT of $< 5$ seconds, which indicates an unstable PTF.\textsuperscript{20}

- **Conjunctival Biopsy**: In cases of suspected mucin deficiency, obtain a conjunctival biopsy specimen to quantify conjunctival goblet cell density.

- **Eyelid Margin Examination**: With a focus light and magnifying source, carefully examine the eyelid margin to identify deficiencies of the lipid component, which often occur secondary to blepharitis (Figure 6) or meibomianitis.

**MEDICAL MANAGEMENT OF KCS**

Primary medical therapy of both quantitative and qualitative KCS consists of tear stimulants and tear replacements. Topical antibiotics and anti-inflammatory drugs are also commonly used.

Dogs with KCS may have increased sensitivity to pain associated with topical medications, because abnormal PTF cannot provide a reflex dilution effect. This may be especially problematic with frequent application of tear replacement medications that contain preservatives; some artificial tear products are available without preservatives, but the lack of preservatives requires single-use ampules, which most owners find inconvenient.

In most patients with KCS, topical therapy is required indefinitely. Clients should be educated about the chronicity of KCS and the necessity of lifelong therapy.

**Tear Stimulation**

1. **Cyclosporine A (CsA)**

   **Mechanism of action.** Cyclosporine is an immunomodulator that blocks normal production of interleukin-2, which inhibits proliferation of T-helper and cytotoxic T cells in the lacrimal gland and allows normal lacrimation.\textsuperscript{21}

   Cyclosporine also acts as an anti-inflammatory, decreases pigmentation, normalizes goblet cell mucin secretion,\textsuperscript{22} and directly stimulates lacrimation, but the latter mechanism is still poorly understood.\textsuperscript{23}

   **Efficacy.** Topical preparations are very effective for tear stimulation and reducing inflammation, with 81.8% of dogs showing improvement (Figure 7, page 20).\textsuperscript{24,25} Dogs with a STT $< 2$ mm/min respond with increased tear secretion in approximately 50% of cases, while dogs with a STT $\geq 2$ mm/min have an approximately 80% chance of responding.\textsuperscript{18}

   **Formulation.** CsA is available as Optimmune 0.2% ophthalmic ointment (merck-animal-health-usa.com). Compounded formulations are available in 1% and 2% corn or
olive oil solutions; they may be more effective, but may also be more irritating to the eye.

**Therapeutic recommendations.** Apply ¼-inch strand of topical CsA Q 12 H, with a recheck STT in 1 month. For optimal results, perform the STT approximately 3 to 4 H after application of CsA. Treatment failure can be diagnosed only after 12 weeks of consistent topical application. If treatment fails, attempt treatment Q 8 H or initiate treatment with tacrolimus.

With long-term use, CsA decreases corneal pigmentation and vascularization, even in patients that do not experience increased tear production; therefore, its use is often continued in these patients.\(^{18,24}\)

2. Tacrolimus

**Mechanism of action.** Tacrolimus has a similar, but more potent, mechanism of action compared with that of CsA.

**Efficacy.** Patients that are unresponsive to CsA may respond to tacrolimus.\(^{26,27}\)

**Formulation.** Tacrolimus is generally compounded to a 0.03% ophthalmic aqueous suspension; however, formulations may vary.

**Therapeutic recommendations.** Apply 1 drop of topical tacrolimus Q 12 H, with a recheck STT in 1 month. Continue treatment for several months before considering treatment failure. In addition to increasing tear production, tacrolimus may decrease clinical signs, such as pigmentation associated with chronic KCS, even if tear production does not increase, but no long-term studies exist.

Tacrolimus use for treating KCS in dogs is off-label; therefore, the U.S. Food and Drug Administration approved therapy—CsA 0.2% ophthalmic ointment (Optimmune)—should be used as first-line treatment, with tacrolimus reserved for cases unresponsive to CsA.

3. Pilocarpine

**Mechanism of action.** Parasympathomimetic drug (stimulates or mimics the parasympathetic nervous system). Upregulation of parasympathetic receptors secondary to denervation results in increased sensitivity of the lacrimal system to pilocarpine when compared with the rest of the body.\(^2\)

**Efficacy.** May be used to stimulate tear production in cases of neurogenic (quantitative) KCS. These cases are diagnosed when ipsilateral dry nose is present in conjunction with a low result on STT.

**Formulation.** 1% or 2% solutions

**Therapeutic recommendations.** Sprinkle 1 to 2 drops of 2% pilocarpine per 10 kg on top of food Q 12 H. Systemic administration of pilocarpine is preferred because it can be irritating when applied topically.\(^{28}\)

Note that pilocarpine has a narrow therapeutic window, and while some clinicians advocate increasing the number of drops applied to food by 1 drop each day until systemic adverse effects are observed—such as vomiting, diarrhea, ptyalism, anorexia, and bradycardia—we prefer to avoid these effects by only increasing the total dose by 1 or 2 drops before considering pilocarpine ineffective. Client education about adverse effects is important.

**Tear Replacement**

Tear replacement therapy provides lubrication until tear stimulants are effective. Lifelong tear replacement therapy may be needed in dogs that never respond to CsA or tacrolimus. These medications are available as solutions, gels, and ointments, and have a wide variety of constituents.

1. **Artificial tear solutions** commonly contain 0.1% to 1.4% polyvinyl alcohol. Artificial tear solutions are useful for removing debris and mucus from the ocular surface; however, they are not feasible as monotherapy in most dogs with KCS due to the need for frequent application in order to achieve adequate lubrication.

2. **Cellulose-based solutions/gels and viscoelastic products** are more viscous and have slower evaporation times than artificial tear solutions. They require application Q 4 to 6 H. Examples of cellulose-based solution and viscoelastic products are hydroxypropyl and hyaluronate, respectively.

3. **Artificial tear formulations containing petrolatum, mineral oil, or lanolin** are the most viscous products and provide long-term lubrication, but can result in debris accumulation. They are best suited for patients with:
   - Lipid layer deficiencies
   - Lagophthalmos (administered prior to sleep)
   - Owners who will be absent for long periods.

**Antibiotics**

A severe, mucopurulent discharge suggests a secondary bacterial infection. Generally, use a broad-spectrum ophthalmic antibiotic, such as triple antibiotic ointment (neomycin/bacitracin/polymyxin B) Q 6 to 8 H for approximately 2 weeks. If empirical treatment fails to resolve the discharge, perform culture and sensitivity.

![Figure 7. Seven-year-old spayed female miniature pinscher. Note corneal vascularization and pigmentation; STT was 7 mm/min (A). Same patient 3 months after topical CsA therapy; note resolution of corneal vascularization and thinning of pigment (B).](image-url)
ULCER THERAPY

While superficial, uncomplicated ulcers can be treated with triple antibiotic ointment, CsA, and lubricants, ulcers secondary to KCS are usually complicated and require more intensive therapy.

1. Perform culture and cytology on stromal ulcers and ulcers with a cellular infiltrate.
2. Apply topical antibiotics Q 2 H to infected ulcers until the cornea stabilizes. Appropriate antibiotics include:
   - Ciprofloxacin 0.03% ophthalmic solution, or other ophthalmic fluoroquinolones, used alone or
   - Tobramycin 0.03% ophthalmic solution and ceftazolin (33 mg/mL in artificial tear solution).
3. Use topical atropine to dilate the pupil and decrease ciliary spasm, even though it is associated with decreased tear production. If the patient remains uncomfortable while on atropine therapy, the addition of oral NSAIDs may be considered.
4. Consider conjunctival graft placement in addition to KCS therapy and frequent antibiotic therapy for deep ulcers.

Anti-Inflammatory Agents

Anti-inflammatory therapy may be useful if conjunctival inflammation is severe, possibly occluding lacrimal excretory ducts. Corticosteroids can be used on a short-term basis (1–4 weeks); discontinue if patient is nonresponsive. Only consider using them, though, in animals with no uptake of fluorescein dye.

Apply topical prednisolone acetate 1% or dexamethasone 0.1% topically Q 6 to 8 H. Use caution when using topical corticosteroids because dogs with KCS can develop ulcerative keratitis, infection, and keratomalacia.

Mucolytics

If a patient with KCS has copious mucopurulent discharge, acetylcysteine 5% is often administered; however, its use is not common due to its expense and toxicity to the epithelium. In addition, the mucous layer provides some protection to the cornea. Frequent flushing with sterile eyewash, instead, simply removes mucus without side effects.

SURGICAL MANAGEMENT OF KCS

After 3 to 6 months of medical therapy with no response, surgical treatment for KCS can be considered. Surgery is not always successful and, even when it is, patients often need ongoing topical therapy.

Treatment of Choice

Parotid duct transposition—in which the parotid duct and papilla are dissected free of the oral mucosa, mobilized, and transposed to the inferior cul-de-sac—is the surgical treatment of choice. Open and closed methods have been described.

Challenges

This surgery is often performed by a board-certified ophthalmologist due to the difficulty of the procedure in some dogs and often complicated aftercare. Potential complications include severance of the duct, occlusion of the duct secondary to scar formation, development of white mineral crystalline corneal deposits, facial dermatitis, periorcular pyoderma, and excessive saliva production.

PROGNOSIS & MONITORING

Prognosis depends on the underlying etiology of KCS and the patient’s response to treatment (Table 2). If KCS does not respond to medical therapy, the prognosis is worse for vision retention. In addition, most patients will require lifelong therapy with topical immunosuppressive medications.

Recently, chronic keratitis treated long-term with tacrolimus or CsA has been tentatively associated with increased risk for corneal squamous cell carcinoma. However, because the study was retrospective, clinical data are lacking, and KCS alone may have resulted in a predisposition to this condition. While this study is interesting, KCS should be treated as described in this article.

Dogs with a diagnosis of KCS should be evaluated every 6 to 12 months to assess effect of treatment and progression of disease.

References

14. Bryan GM, Slater DH. Keratoconjunctivitis sicca induced by...
As with all drugs, side effects may occur. In field studies, the most common side effects reported were ocular itching, burning, or inflammation in animals sensitive to the product. Prolonged use may result in the overgrowth of non-susceptible organisms including fungi. VETROPOLYCIN ONLY—Do not use as a pre-surgical ocular lubricant. VETROPOLYCIN HC ONLY—This product is not for use in animals with corneal ulcers, fungal infections, or viral infections. Patients should be monitored for signs of corticosteroid overdose. The safe use of this product has not been evaluated in pregnant animals. Refer to the prescribing information for VETROPOLYCIN and VETROPOLYCIN HC for complete details or visit www.dechra-us.com.