Canine non-ulcerative corneal diseases
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Corneal Pathologic Responses
The normal cornea is clear, and any alteration in clarity signifies pathology. Pathologic changes include corneal vessels, edema, pigment, crystalline deposits, inflammatory cell infiltrates, destruction from degradative enzymes, and scarring. Such changes are usually non-specific and incited by numerous causes. Pathologic responses can occur singularly, but more often several occur simultaneously. Because corneal pathologic responses are usually secondary rather than primary, resolution is best achieved by identification and treatment of the primary cause.

Diagnostic Considerations
A complete physical examination, neuro-ophthalmic examination, ophthalmic examination and basic ophthalmic diagnostic tests (Schirmer tear test, Fluorescein stain, Tonometry) should be performed in almost all cases of corneal disease as pathologic changes can arise from a multitude of causes and multiple disease processes may be present. When deep ulceration is present, avoid a STT and tonometry.

A STT will rule out keratoconjunctivitis sicca as a cause and aggravator of corneal pathology. Corneal fluorescein staining should be performed in ALL cases of corneal disease. This test will identify concurrent ulceration and determine medications to be used. Remember that deep corneal ulcers will epithelialize first, then the stroma will remodel and fill in. The cornea may never fully regain its original thickness. This means fluorescein stain can pool in these divots, giving the appearance of a corneal ulcer. In these cases, eyewash should be dripped on the cornea while examining it with the cobalt blue filter, to distinguish pooling from a true corneal ulcer. Tonometry should be performed to identify concurrent primary or secondary uveitis and glaucoma.

Palpebral reflex (CN VII) will identify lagophthalmos (common in brachycephalic breeds) or eyelid paralysis (CN VII), which can cause exposure keratitis and ulceration. Lack or decreased corneal and periocular sensation can be associated with a neurotrophic ulcer (lack of substance P and other nutrients associated with loss of CN V innervation result in ulceration). Menace response, direct and consensual pupillary light reflexes and dazzle reflexes will help distinguish a visual and blind eye and can help determine treatment options (e.g. Lack of all response/reflexes indicates a blind eye. If a deep ulcer is present, a conjunctival pedicle graft would be performed only if the owner wishes to salvage the eye as vision will not be saved).

Examine the eyelids for distichiasis, trichiasis, ectopic cilia, and eyelid conformation, which can cause irritation and ulceration to the cornea. Likewise foreign material can become trapped behind the third eyelid, causing irritation and ulceration.

Finally, additional diagnostics such as corneal cytology or biopsy may identify the etiology. Corneal culture should be performed for stromal or melting ulcers for antibiotic selection. A tear film break up time using slit-lamp biomicroscopy is often performed with corneal and conjunctival disease to identify poor tear film quality.

Chronic Superficial Keratitis
Chronic superficial keratitis (or pannus) is an immune-mediated keratitis with genetic and environmental influencing factors. High altitude and ultraviolet radiation are the greatest environmental risk factors, and the most severe cases in this country occur in states such as Utah and Colorado. There is an obvious breed predisposition for German Shepherds and Shepherd crosses, and Greyhounds, but it can occur in any breed. It usually begins as a bilateral pink or red inflammatory lesion of the inferotemporal cornea and is often symmetrical. However, it can begin in other corneal quadrants and be asymmetrical. With progression, the entire cornea can be
affected and result in markedly diminished vision or blindness. Corneal pigment, fibrosis and crystalline deposits are prominent features in chronic cases. The nictitans can be involved simultaneously or exclusively (e.g., atypical pannus or plasmoma) and presents as multiple small pink nodules or depigmentation of the leading margin of the third eyelid. Age of onset is usually 3-5 years but may occur at anytime. Pannus can be more difficult to control in dogs affected at a young age. Diagnosis is based on clinical appearance, breed predilection, and corneal or conjunctival cytology. Cytology usually reveals a preponderance of lymphocytes and plasma cells. Histologically, the corneal infiltrate is characterized by plasma cells, lymphocytes, and blood vessels.

Like most immune-mediated diseases, pannus is a disease to be controlled rather than cured. Topical corticosteroid, cyclosporine, or tacrolimus are the primary treatments. The preferred steroid preparations are those with 1% prednisolone acetate or 0.1% dexamethasone. A steroid/antibiotic combination may be used initially if a mucopurulent discharge is present, suggesting secondary bacterial conjunctivitis. Subconjunctival steroids can be administered as an adjunct to topical treatment, for refractory or severe cases, or for dogs difficult to treat. Triamcinalone, methylprednisolone, and betamethasone are similarly effective, but conjunctival granuloma formation may be less likely to occur after betamethasone injection. Topically applied cyclosporine in concentrations of 0.2%, 1% or 2%, or tacrolimus in concentrations of 0.02% or 0.03%, are also effective treatments. Some pannus cases are effectively controlled with cyclosporine or tacrolimus alone. In other cases, their use allows the steroid treatment to be reduced, thereby minimizing undesirable side effects (e.g. exacerbation of crystalline deposits).

The required frequency of administration of topical medications varies with the time of year and severity of pannus but is usually 2-4 times daily. Often once the disease appears to be controlled, the frequency can be tapered to a once or twice daily treatment. Treatments can often be reduced during the winter months but must be increased again during the summer months.

Beta-irradiation and lamellar keratectomy are additional treatment options, but they are no longer commonly employed since immunosuppressive topical medications have become widely used. Plasma cells and lymphocytes are particularly sensitive to beta-irradiation, and radiation is an effective treatment for difficult cases. However, stringent licensing requirements for the Strontium-90 probe have made irradiation an impractical treatment. UV-blocking contact lenses have been studied recently with no obvious benefit in reducing the clinical signs of pannus.

Scleritis/Episcleritis
This is an immune-mediated condition that occurs as a nodular to diffuse inflammation of the sclera or episclera. It can be unilateral or bilateral. Often only one quadrant is affected, and when it has a nodular appearance, scleritis can be mistaken for a neoplasm. However, scleral neoplasms other than limbal melanoma are rare. There is a breed predilection for the Cocker Spaniel and Airedale. The condition can be severe in the Airedale where concurrent uveitis is common (i.e., sclerouveitis). The adjacent cornea is usually affected with a variable degree of vessels, inflammatory cell infiltrates, and secondary lipid degeneration evident. Lymphocytes, plasma cells, and histiocytes are typical histologic features. Deep necrotizing scleritis is rare but often causes serious and intractable extraocular and intraocular disease (e.g., retinal detachment). It has the same histopathologic features as non-necrotizing scleritis/episcleritis, except there is a degeneration of collagen in affected structures and is bilateral.

Diagnosis of episcleritis is by clinical appearance and positive response to topical and subconjunctival immunosuppressive medications. Biopsy can be performed but is rarely necessary. Immune function tests (e.g., ANA, Coomb's, etc.) are often negative and of little benefit. Treatment usually involves a combination of topical and subconjunctival steroids, cyclosporine or tacrolimus, or systemic treatment. Effective systemic treatments include prednisone, azathioprine, and combination treatment with tetracycline and niacinamide. Long-term treatment is likely to be required.
Pigmentary Keratitis
Pigmentation of the corneal epithelium or stroma is called pigmentary keratitis (also called corneal melanosis or corneal pigmentation). Several conditions can contribute to corneal pigment including irritation from adnexal hairs (e.g., nasal trichiasis), redundant facial folds, dry eye, or lagophthalmos. Dry eye is probably the most common cause of corneal pigment in most breeds (except in the Pug). Pigment can occur subsequent to healing of an ulcer or in association with inflammatory conditions such as pannus. As a distinct or primary clinical entity, it occurs most often in the Pug. In this breed, contributing factors may include breed-related exophthalmos and corneal exposure, nasal lower lid entropion, and nasal canthal trichiasis. However, the greatest single factor is probably genetics because other breeds with similar conformation have far less pigment (e.g., the Bulldog, Pekingese, Shih Tzu, etc.). This has been recently supported by a recent study where the disease was identified in 82% of pug eyes, usually in a mild form.

All treatments are designed to control the progression of corneal pigment. Once pigment has developed, it is impossible to cure and is rarely reduced. Nasal canthoplasty surgery (or permanent medial tarsorrhaphy) is most often advocated to slow or reduce progression of corneal pigment in the Pug. The advantages of this procedure include greater protection to the eye by reducing the palpebral fissure, elimination of nasal trichiasis hairs, and correction of nasal canthal entropion.

In Pugs, a combination of surgery and topical treatment is usually appropriate. Topical treatments that may slow or reduce corneal pigment include cyclosporine, tacrolimus, and corticosteroids. There is no evidence that cyclosporine is more effective than tacrolimus, or vice versa, so select the one best tolerated by the patient.Judiciously applied steroids can be of benefit, but they should always be used in a brachycephalic breed because of their propensity for corneal ulcers. Beta-irradiation, lamellar keratectomy, and CO$_2$ laser ablation to remove corneal pigment are rarely effective treatments and are usually reserved for patients where pigment has progressed to the point of substantial visual impairment. The pigment usually re-establishes itself quickly.

Corneal Endothelial Dystrophy
This condition is caused by a defective corneal endothelium and results in excessive corneal edema, thereby imparting a bluish-grey haze to the cornea. The primary differential diagnoses for edema are corneal ulceration, uveitis, and glaucoma, each of which is usually easily distinguished from this condition. Endothelial dystrophy is slowly progressive, typically beginning in the lateral cornea and progressing to involve the entire cornea of middle-aged or older dogs. There is breed predilection for the Boston terrier, Dachshund and Chihuahua, but it can be seen sporadically in just about any dog breed. It is non-painful in the early stages. Advanced endothelial dystrophy will cause fluid pockets/bullae to form on the corneal surface, which can rupture leading to ulcerative keratitis, and pain.

Medical therapy is palliative with a hyperosmotic 5% sodium chloride ointment or suspension (Muro-128) used BID-QID to reduce edema and bullae. However, do not expect dramatic clearing of the cornea. Topical antibiotics or atropine are indicated if the cornea is ulcerated. Conjunctival hyperemia can be pronounced in some affected dogs, and the cause is not clear. If the eyes are especially irritated and there is no ulcer, topical steroids can be used cautiously. Topical NSAIDs (e.g., flurbiprofen) are sometimes of benefit. Thermal cautery (or thermokeratoplasty) may be beneficial in advanced cases where recurrent ulceration is a problem. This procedure will not clear the cornea substantially but results in enough scarring to prevent progressive edema and bullae, thereby preventing pain associated with recurrent ulcers. The technique involves making multiple superficial corneal stromal burns using a disposable low temperature ophthalmic cautery unit or carbon dioxide laser. Surgical discretion is advised because the cornea can "melt like butter" under the heat of the cautery unit or laser. Penetrating keratoplasty (or corneal transplant) can be performed in selected instances, but fresh corneas for transplantation are difficult to come by.
Lipid or Calcium Keratopathy

Lipid or calcium corneal deposits may appear similar but have different causes, and absolute clinical distinction is not always possible. Nevertheless, three conditions are generally recognized: corneal dystrophy, corneal degeneration, and lipid keratopathy. The term corneal dystrophy refers to an inherited, bilateral, and often symmetric corneal lipidosis, although involvement of one eye may precede the other. Lipid corneal dystrophy occurs in a variety of dog breeds including the Siberian Husky, Samoyed, Cocker Spaniel, Airdale Terrier, Cavalier King Charles Spaniel, Shelties, and Beagle. Clinically, the lipid deposits may impart a nearly imperceptible crystalline haze to the central or paracentral cornea, or the affected cornea may be opaque. The lipid is typically subepithelial or stromal and includes cholesterol, neutral fats, and phospholipids. There is no associated systemic disease. The cornea is usually non-ulcerated and there is an absence of inflammation or vascularization. Seldom does corneal dystrophy cause any significant visual impairment, nor does it cause any discomfort to the dog. For these reasons, specific treatment is not usually required. When treatment is desired, lamellar keratectomy is usually effective in removing the lipid deposits, however, the condition may recur.

Corneal degeneration refers to lipid or calcium deposits, or both, in the corneal epithelium or stroma secondary to pre-existing ocular disease. Prior disease may include corneal ulceration, keratitis, uveitis, intraocular implantation or phthisis bulbi. In contrast to corneal dystrophy, corneal degeneration is often unilateral and is usually associated with corneal vascularization. The degenerative area of cornea is often quite opaque, may be roughened, and there is frequently disruption of the epithelium. The crystalline deposits "flake out", resulting in epithelial or stromal ulceration. Rarely, a descemetocoele or corneal rupture may occur. Concurrent inflammation, vascularization, and pigmentation are common. A lipid corneal degeneration is thought to occur following long-term topical corticosteroid treatments, such as that used after cataract surgery. Furthermore, any pre-existing corneal deposits are thought to be exacerbated by topical steroid use. The degeneration may regress somewhat following discontinuation of therapy.

Lamellar keratectomy is the preferred treatment if the animal is in pain or visually impaired (and the eye worth saving), but the condition may recur. In some instances, a topically applied chelating agent (e.g., 0.4 to 1.38% EDTA solution) may be beneficial in dissolving or stabilizing calcium deposits when used either alone or in combination with keratectomy. Trichloroacetic acid debridement may also be utilized to dissolve crystalline deposits (and normal corneal tissue) and smooth out the corneal surface to encourage healing of refractory ulcers associated with corneal degeneration. This method of treatment often results in an increased keratitis during the healing phase and initially, the patient is more painful.

Lipid keratopathy is characterized by peripheral or central corneal crystalline opacities and has been associated with systemic lipid abnormalities. Screening bloodwork for diabetes mellitus, hypothyroidism, pancreatitis, hyperlipoproteinemia and post-prandial elevations in plasma lipids should be performed. Identification of fasted levels of serum triglycerides, cholesterol, and total lipids should be evaluated. Lipid deposition into the cornea is thought to be via corneal blood vessels or in situ deposition as tear lipid levels are usually normal. These underlying etiologies should be addressed to help prevent the progression, and in some cases reduce lipid crystalline deposition.

Lipid deposits that occur in a ring in the peripheral cornea in association with systemic hyperlipidemia are called arcus lipoides corneae. Although the condition can occur in any breed, a predisposition for German Shepherds with hypothyroidism is suggested. Arcus lipoides corneae is typically bilateral, and there may be mild inflammation and vascularization.

Treatment, as previously stated, is directed toward resolution of the primary disease condition. Keratectomy can be performed in severe cases, resulting in reduced vision. However, opacities often recur, even if the underlying etiology is addressed. For all types of corneal crystalline deposits, topical
tacrolimus or cyclosporine BID may be tried as a treatment option. Although there is no scientific basis for this treatment, anecdotally, progression of the disease can be slowed and I have occasionally seen improvement in the crystalline deposits. The mechanism of action is also unknown.

**Superficial Punctate Keratitis**
This is a relatively uncommon condition for which the Dachshund appears predisposed. Punctate keratitis appears to be immune-mediated, and this is the one instance of corneal ulceration where topical steroids are indicated. Affected eyes usually have multifocal punctate corneal opacities that sometimes retain fluorescein stain, and one or both eyes can be affected. Topical cyclosporine drops or ointment may be effective treatments, but more consistent results are usually obtained with topical steroid. Topical antibiotics should be employed when lesions retain fluorescein stain.

**Sheltie Corneal Dystrophy**
This condition has an obvious breed-predisposition for the Sheltie, and the cause is unclear. Affected dogs have multifocal circular opacities of the cornea, many of which retain fluorescein stain. Secondary lipid degeneration may occur. It can appear very similar to immune-mediated punctate keratitis, and may respond similarly to treatment. However, topical steroid should be used cautiously in these dogs, as their response to steroid is less predictable than in superficial punctate keratitis. Affected eyes may have marginal tear production and reduced tear film breakup times, but overt dry eye is not a feature of this disease.

**Corneal Neoplasms**
Tumors of the cornea (or sclera) occur infrequently. Corneal dermoid and limbal (epibulbar) melanoma are most common. Dermoids are benign choristomas (normal tissue found in an abnormal location) that occur most often in the temporal cornea. The lesions usually consist of normal skin tissue with a haired surface. They can usually be removed in their entirety by lamellar keratectomy. This surgery is indicated primarily to reduce irritation by hair rubbing on the normal corneal surface.

Limbal melanomas are darkly pigmented, smooth masses at the corneoscleral junction. They can have malignant histologic features (23% of cases in one study), but they behave almost invariably in a benign manner. They tend to be slow growing but if ignored can become large enough to destroy the globe. German Shepherds, Golden Retrievers and Labrador Retrievers appear to be predisposed. There may even be a genetic factor in Retrievers. Interestingly, this type of tumor occurs most commonly in 2 separate age groups: 2-4 years and 7-11 years of age. Differentiation between a limbal melanoma and external extension of an intraocular melanoma should be made by intraocular examination, gonioscopy and ultrasonography, as the treatment is different.

Surgery will markedly slow progression of the tumor and may even be curative. However, complete excision is usually not possible without penetration of the globe, so there is no consensus as to the most effective treatment. Surgical options include full-thickness excision followed by a grafting procedure (i.e., with nictitans cartilage, etc), or partial excision followed by laser treatment or cryoablation. Partial excision with cryoablation with conjunctival grafting appears to be a successful procedure. In one study, there were no recurrences of the tumors and although post-operative complications were relatively, common, most were transient and/or mild.

Other corneal tumors that have been reported, but are less common, include: squamous cell carcinoma, papilloma, lymphoma, hemangioma/sarcoma and adenoma/carcinoma.

**Spontaneous Chronic Corneal Epithelial Defect (Indolent Ulcer, Recurrent Erosion, or Boxer Ulcer)**
This is unique type of corneal ulcer that is frustrating for veterinarians and clients alike. They are typically chronic, superficial, non-infected (except in cats with feline herpesvirus), and minimally to moderately painful. Most are characterized by redundant corneal epithelial edges and variable
corneal vascularization. Indolent ulcers are believed to result from an abnormality of the corneal epithelial basement membrane. An indolent ulcer is suspected when a superficial ulcer persists for more than 7-10 days with no obvious cause or predisposing factor (recall that any simple superficial traumatic ulcer will heal in 48-72h). It is a diagnosis of exclusion (rule out ectopic cilia, distichia, foreign bodies, KCS, corneal crystalline deposits, corneal endothelial dystrophy, etc….) and high suspicion based on signalment and typical appearance of the ulcer (redundant epithelial tissue). Any breed can be affected, but most affected dogs are middle-aged or older (generally over 6 years of age, but I have seen a handful of these ulcers in 5 and 6 year olds).

Appropriate topical treatment should include an antibiotic (e.g., neo-poly-bac or tobramycin) b.i.d. and 1% atropine once every other day for comfort can be considered. Topical hyperosmotic treatment with 5% sodium chloride ointment or drops may facilitate healing by reducing corneal edema and reduce the risk of recurrence. Remend has only shown improved healing in experimentally-induced ulcers in rabbits. Topical cyclosporine is helpful to reduce corneal vascular infiltrates and scarring, and can help in the final healing stages if the persistent ulcer is overlying this tissue only. An E-collar is essential during the healing process.

Mechanical debridement via cotton-tipped swab, grid-keratotomy, or diamond burr keratotomy is most often recommended to facilitate healing. A superficial lamellar keratectomy comes with the highest success rate, but I have never had to resort to this invasive treatment modality. The intent of these procedures is to disrupt the abnormal basement membrane to allow for more effective attachment of epithelium to the underlying stroma. Epithelial debridement is performed after application of topical anesthetic and using a sterile dry cotton-tipped swab. One study estimated that approximately 40% of indolent ulcers heal after debridement alone, and this is probably an accurate percentage if the ulcer debrided aggressively, the ulcer is small after debridement and there is minimal corneal vascularization. In all other cases, grid keratotomy will likely be required. I usually allow for at least 10 days of healing after either procedure since most indolent ulcers require at least 1 week and up to 3 weeks to heal completely.

Linear Grid Keratotomy (LGK)
This procedure is only intended for the treatment of superficial and non-infected ulcers and should NEVER be performed on a stromal or deep corneal ulcer. Realize that all ophthalmologists treat these ulcers a little differently. This is how I do it….

General anesthesia is recommended for fractious dogs or the first few times this technique is performed. In compliant animals, topical anesthesia and good restraint or sedation is all that is required. A more thorough procedure can be performed with sedation or general anesthesia, which I suspect leads to a higher success rate.

Start with debridement of the entire cornea, if possible, as this tends to be a disease affecting the entire cornea. I have never had a recurrence of an ulcer after this procedure and have never had to repeat the entire procedure for an ulcer to heal (knock on wood!). I believe a factor for this success is that I treat the entire cornea. I often start with a cotton-tipped applicator, but need to use a #64 Beaver blade to complete the debridement. A 25 gauge needle is used to make superficial cuts or striations of the anterior stroma in a grid pattern. This is done by dragging the needle across the cornea at an approximately a 30-45 degree angle. Deep corneal penetration should be avoided. Although some advocate that the keratotomy should extend into normal cornea for 1-2 mm past the ulcer edges, I recommend performing the grid over the entire cornea, making the grid lines more concentrated over the area of the original ulcer. As this is a more invasive procedure compared to a simple cotton-tipped applicator debridement, I recommend increasing the frequency of a topical antibiotic and sodium chloride ointment to t.i.d. Oral anti-inflammatory and analgesics should be provided (e.g., a non-steroidal and tramadol), and the dog fitted with an Elizabethan collar. Most ulcers are healed within two weeks after a LGK. Occasionally "touch ups" need to be performed (e.g., a local debridement or grid with topical anesthetic only) or immunosuppressive drops such as cyclosporine or tacrolimus need to be used to reduce excessive granulation tissue for the final stages of healing.
A variation on the LGK is the multifocal superficial punctate keratotomy (MSPK) where punctures are made throughout the cornea instead of a grid. This procedure is thought to result in less corneal fibrosis post-operatively, but the technique is much more difficult and should only be performed by an ophthalmologist.

**Diamond Burr Keratotomy**

Similarly to the grid keratotomy, this procedure is only intended for the treatment of superficial and non-infected ulcers and should NEVER be performed on a stromal or deep corneal ulcer. Again, realize that all ophthalmologists treat these ulcers a little differently. This is how I do it….

Begin with a debridement of the entire cornea, as for the grid keratotomy. A medium grit, 3.5 mm, Algerbrush® diamond burr is used for the keratotomy. This is a relatively inexpensive instrument with a motor and a quickly rotating burr that brushes or polishes the superficial tissues from the cornea. The epithelium can be removed with this instrument, but I worry that epithelial inclusion cysts are more likely. The entire cornea should be treated until it develops a lack-lustre appearance. One recent study showed that the basement membrane is more extensively affected when the burr is used for 45 seconds on the cornea compared to 30 seconds. Post-operative care is the same as for the LGK. The success rate of this procedure, when used with a contact lens bandage in a recent study, was 92.5% after 2 weeks. All corneas were healed after 19 days, although 12.5% of cases needed a repeat procedure. There was a 2.5% rate of post-operative bacterial corneal infection.

The advantages of the diamond burr keratotomy include: the technique carries a lower degree of difficulty, it is easier to perform in awake patients (I still prefer sedation for a more thorough procedure), and depth of cornea affected is relatively uniform (grid lines can easily be made too deep).

Disadvantages of the diamond burr keratotomy include: instrumentation is more expensive and corneal abscessation and infection are more likely post-operatively than with a LGK as the burr can be difficult to be kept clean. We examine our burrs with a slit lamp before each use, ensure lint-free materials are used to handle the burr and we only use each burr a maximum of 8 times, before disposal.