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Corneal ulcerative disease – I:
Confusing terms explained: deep ulcer, melting ulcer and much more

Corneal ulcers should heal when the cause has been established and eliminated, at least in principle. Corneal ulcer progression and melting occur when a large number of proteases from keratocytes, neutrophils and possibly bacteria are present in the wound and overwhelm the repair mechanism (normally a balance between breakdown and repair that occurs early on in the repair process). Corneal ulcers may be complicated by undiagnosed dry eye, entropion, secondary infection and/or any process that causes significant ocular surface inflammation. Problems like these will not allow the cornea to heal and pose a significant risk for the development of corneal melting (i.e. malacia). Corneal abscesses form when inflammatory cells accumulate in the stroma and may or may not be accompanied by a bacterial component. Abscess development may be localized or widespread and often takes an off-white to yellowish hue that must not be confused with corneal edema, which has a bluish hue. Corneal abscesses are not true pockets of cells and fluid that can be drained. Abscesses soften the corneal stroma, making it friable and more prone to damage, and are often associated with a rapid process of collagenolysis that can affect a large part of the corneal surface. Melting may develop in a very small section of the cornea (localized melting) and lead to a discrete, round, deep ulcer, and even perforation, in a matter of a handful of few days and in a cornea that otherwise has a healthy appearance. It is worth keeping in mind that ulcer bed deepening and widening are signs that corneal collagen is melting at the corneal wound edge and base independent of the original ulcer wound diameter and depth.

Corneal melting can progress very rapidly and in most cases prompt referral is urgently required as often, surgical debridement and repair is needed. Changes in the color of the cornea (to whitish-yellow), ulcers that deepen and/or widen, and the development of a central clear lesion (descemetocele) are all causes of serious concern.

Corneal ulcerative disease – II:
General rules for treatment; what can I do?

It is important to be able to interpret corneal changes in affected eyes. It is also important to develop an expectation of healing and how long we think the healing we expect will take.

The general use of a topical antibiotic is recommended with corneal ulceration. However, it should be noted that the cause of the ulceration should be investigated and determined, or the use of an antibiotic will not prevent it from worsening (i.e., if there is dry eye, or if there is entropion or an ectopic cilium), as these irritating problems will continue. In other cases, there is an imbalance (i.e., a lot of inflammation) and antibiotics will not be enough to slow or stop the ulcerative process. Lastly, changing antibiotics to see if 'something might help' is also not a good approach, as there is no obvious goal in mind.

Generally speaking. If an ulcer continues to deepen and or enlarge in diameter, referral should be strongly recommended or there is a risk of perforation. Corneal surgery works best (i.e., is able to restore vision best) in cases that have not perforated. Therefore, early referral is extremely important.

Chloramphenicol antibiotic is a common choice. This may be combined with a gentamicin (or tobramycin) antibiotic, depending on local regulations for antibiotic use. Double or triple antibiotic drops may be available too. They may be applied 3x day, 30 minutes apart. Topical antibiotics may be applied every 1h in cases where the veterinarian is attempting to stop corneal melting.

It is sometimes useful to take a sample of the area of the cornea affected for cytology and/or culture and sensitivity in case help is required to elect or change the antibiotics initially chosen. However, it is worth remembering corneal melting can develop much sooner than laboratories are able to offer us results of culture and sensitivity, which limit the use of this practice. It is much more important to attempt to arrest of the melting process as soon as possible- this may be possible through aggressive medical intervention and hospitalization though it sometimes, if not often, requires surgery.

If melting has not shown signs of improvement in 24-48 hours or stopped in 48-72 hours, referral is strongly advised. Melting can lead to perforation in as little as 3 to 5 days.

Serum eye drops may be used in combination with a topical antibiotic to control melting. Serum should be kept in separate dose-vials and frozen until use, at which point it may be refrigerated. Separate dose refrigeration allows for discarding of unused parts on a daily basis. If the melting process appears to be under control, the frequency of application of drops may be gradually reduced or even stopped.

Fluoroquinolone antibiotic eye drops also exist, but they should be reserved, always, for cases with culture and sensitivity that show they are responsive only to it.

In addition, the use of a dilator (mydriatic) and a cyclopegic (cyclopegia: relaxation of the ciliary body musculature) such as atropine is indicated (once daily for two to three days, depending on the case). Atropine leads to temporary dry eye and should be used with great caution in those cases with ulcers related to KCS. Lastly, oral antibiotics are used in cases with perforated corneas and oral antiinflammatories such as carprofen or meloxicam are deemed beneficial to help control pain and inflammation.

Corneal ulcerative disease – III:
The importance of eyelid diseases and dry eye in CUD

The tear film is a tri-layered structure composed of a mucus layer (with a glycocalyx and a mucinous layer), which is in contact with the cornea and is followed by an aqueous layer (some people refer to these two layers as a single layer called the mucino-aqueous layer). The aqueous layer contains many different solutes, including immunoglobulins, and is covered by a thin layer of lipid, which stops it from evaporating easily. This complex set up keeps the corneal surface moist, offers protection against small surface ocular irritants and infectious organisms and helps in keeping the ocular surface clean. With each blink, the tear film is moved from lateral to medial towards the puncta, where tears are drained via the cannaliculi to the nasolacrimal sac, then the nasolacrimal duct and, lastly, the nose. The mucinous part of the tear film is made by the corneal epithelial cells and the conjunctival goblet cells, which are situated for the most part in the conjunctival fornices. The aqueous portion of the tear film is made by the gland of the third eyelid, which contributes approximately 30% of it, and the lacrimal gland, which contributes approximately 70% (there are additional lacrimal glands that produce under 10% of the watery part of the tear film and are not accounted for in this count). Finally, the lipid layer is made by the meibomian glands, of which there are approximately thirty per eyelid.

Dry eye disease (or keratoconjunctivitis sicca KCS) can occur with a deficiency in any of the three layers. A deficient mucin layer leads to an unstable tear film and a deficient lipid layer leads to a tear film that evaporates very rapidly. Eyes that have an incomplete blink, a decreased blink rate or a prominent globe that is overexposed although it might have a complete blink with a normal blink rate may suffer from excessive evaporative loss.

KCS can be primary or secondary. Secondary causes of KCS include trauma, distemper, radiation therapy, neurological deficit, chronic, uncorrected prolapse of the nictitans gland, third eyelid gland removal and destructive FHV-1 infection. It is recommended that prolapsed glands are repositioned early and not removed in dogs and cats. Several systemic diseases have been associated with the development of KCS, including diabetes mellitus, Cushing's disease and hypothyroidism. In addition, systemic administration of certain pharmaceutical agents has been reported to cause dry eye. These agents include many of the sulphonamides and etodolac, although KCS is usually reversible if detected early. Other drugs have been reported to cause transient dry eye in dogs including general anaesthetics, tropicamide, topical and systemic atropine, whether given alone or in

conjunction with a general anesthetic. Also known to cause transient dryness are intramuscular sedative and opioid combinations as well as medetomidine and the combination of medetomidine-butorphanol, in which the transient dryness effects of medetomidine are reversed with the use of atipamezole.

Primary, immune mediated KCS is a relatively common disease in dogs. Several breeds are affected. Originally, dry eye was seen a chronic problem of middle-aged dogs that affected more females than males, and that also had a less common, acute presentation. However, a study of 229 cases revealed some very interesting findings. The study comprised 44 breeds of which, 4 breeds made up almost 60% of the cases (English Cocker Spaniels, Cavalier King Charles Spaniels, West Highland White Terriers and Shih-Tzus). The study found two breed dependent disease patterns of KCS, one chronic and one acute. English Cocker Spaniels and West Highland White Terriers were affected at approximately 5 years of age and more females than males were affected. They presented with conjunctival hyperemia, mucopurulent discharge and had a relatively low incidence of ulcerative keratitis (4% to 20%). In contrast, Cavalier King Charles Spaniels and Shih-Tzus presented with a much more acute disease pattern. They had significantly less conjunctival hyperemia and mucus discharge and presented with a biphasic age distribution. This meant Cavaliers and Shih-Tzus were affected either at a few weeks to less than 2 years of age, or from 4 to 6 and 8 years of age, respectively. In addition, there were more males than females affected, and they had a significantly higher incidence of ulcerative keratitis (50% to 70% of the cases), which in almost 40% of the cases developed into corneal perforation.

The findings of these study are not surprising considering a later, large population study (104,000 dogs including brachycephalics and non-brachycephalics) was able to prove, that breeds such as the Pug and Boxer, and generally speaking, brachycephalic dogs and spaniels, demonstrated a clear predisposition to corneal ulcerative disease compared to mixed breed dogs.

The Schirmer tear test reference range is a guideline. An ulcerated dry eye may present with tear readings of 17mm/minute or 18mm/minute. This is clearly too low for an eye with an ulcer, which should be painful and tearing excessively. The other eye of that dog might have typical, mild signs of dry eye: tear readings of 14mm/minute to 16mm/minute and a history of mild, recurring conjunctival hyperemia and mucus that respond to antibiotics. The clinician must remember that dry eye is not symmetrical, although it affects both eyes, and that it is progressive. Tear readings must be measured in all cases with conjunctival hyperemia and/or mucus discharge and/or ulcerative disease. It is very important that tear readings are interpreted in accordance to the patient's history. A diagnosis of dry eye is independent of patient age, breed, and sex. However, it is important to remember that a study showed that dogs up to three months of age still need to develop their ability to produce tears and might therefore have a low tear reading on the STT-1 test, which is normal for them. The authors of that study suggested that these patients should not be diagnosed with a pathologic KCS and that a lacrimostimulant such as cyclosporin should not be started.

Treatment of dry eye is mainly medical and consists on the application of cyclosporin, usually for life, as well as tear supplementation. Viscous preparations have longer retention times and preservative-free preparations are also preferred for long-term use. Topical cyclosporin may take from 4 to 6 weeks to have an effect and should be trialed for at least that long. Ocular solutions containing mucolytics (ie. acetylcysteine) may be used to help break down thick and adherent mucus. Recently, acetylcysteine has been shown to have some antibacterial properties.

Eye flushes should be used to flush the mucus out, sterile saline is great for this and is pH balanced. Topical antibiotics should only be used short term to treat established ocular infections or prophylactically, in cases of ulcerative disease.

The sooner dry eye therapy is started the more successful the outcome will be. Treatment success should be measured by one or more of the following: an improvement of one or more of the previously mentioned clinical signs and/or an increase in tear production.

It is important to inform the client that some eyes do not respond to cyclosporin by increasing tear production. Some eyes will have a significant increase, while others might only show a mild increase. Even in cases with no increase in tears, treatment can help stabilize mucus production, by improving its quality and regulation of release from goblet cells. It can also help stabilize ocular surface flora, ocular pH, and decrease/prevent corneal pigmentation.

Parotid duct transposition is the only surgical method available to help increase ocular surface moisture in severe cases of KCS where eyes continue to suffer from significant discomfort despite medical treatment. There are several complications that owners must be made aware of such as the deposition of crystalline material on the cornea, excessive salivation that leads to facial staining and facial skin dermatitis and inherent surgical problems. PDT should not be a first option treatment without attempting medical therapy first.

KCS related deep central or paracentral corneal ulcers in dogs require conjunctival pedicle grafts or corneolimboconjunctival transpositions, with the latter offering the clearest cornea possible. Corneal repair at this level requires high magnification, specialized equipment, and training in microsurgical techniques for the ocular surface. The use of topical cyclosporine is not contraindicated in the presence of ulcerative disease and therefore it is used immediately after surgery in cases of dry eye.

Sanchez RF *et al.* Canine Keratoconjunctivitis Sicca (KCS): Disease trends in a review of 229 cases. *Journal of Small Animal Practice* 2007; 48(4):211-7.

O'Neill DG, Brodbelt DC, Keddy A, Church DB, Sanchez RF. Keratoconjunctivitis sicca in dogs under primary veterinary care in the UK: an epidemiological study. J Small Anim Pract. 2021; 62(8):636-645.

Corneal ulcerative disease – IV:
What are SCCEDs, how do I diagnose them and treat them?

A SCCED is a condition recognized in dogs that was formerly known by names such as indolent ulcers (indolent means nonpainful as some of the dogs might present without obvious signs of pain, but this is a poor term), Boxer ulcers (as it was commonly noted in Boxers, but the fact is that it can affect any breed) and chronic recurring epithelial erosion, a much more accurate name. More recently, the term *Spontaneous Chronic Corneal Epithelial Defects* or SCCEDs (pronounced "skeds") is used.

As the term SCCED indicates, these ulcers occur spontaneously as there seems to be a predisposition of some eyes to develop this lesion. Very minor trauma near the eye that would normally not cause an ulcer, and even rough play between dogs, can lead to the spontaneous development of a SCCED in predisposed eyes, and for this reason pet owners often think of SCCEDs as traumatic. It is important that owners understand SCCEDs are spontaneous and that they can recur in the same eye or the other eye. The ability of the epithelium to grow over the defect is not impaired. What is impaired is the ability of the epithelium to adhere to the underlying stroma. This results in redundant epithelium around an area of exposed stroma. Researchers have discovered that the affected cornea contains a PAS-positive hyaline acellular membrane (and abnormalities in certain epithelium to stroma attachment factors such as with fibronectin, laminin, collagen IV and VII), which probably does not allow the epithelium to adhere to the cornea. Treatment is primarily aimed at gently removing this hyaline zone and redundant epithelium, while avoiding opportunistic infections and other problems. SCCEDs tend to remain superficial, although if the ulcer bed becomes infected or is traumatized it may become deep.

There are different treatment options.
Superficial debridement (75% healing rate after one treatment) may be used with a bandage lens to increase patient comfort. Though bandage lenses that are not protected by a lateral temporary tarsorrhaphy (this is a suture and needs a general anesthesia) may fall out. A protective collar is always recommended.

More recently, the use of diamond burr debridement with bandage lens placement has been shown to offer good results (around 80% healing rate after one treatment), though the highest success rate is with keratectomy followed by bandage lens placement and lateral temporary tarsorrhaphy (99% healing after 1 treatment).

Medical therapy is also important. Postoperatively, a topical antibiotic is used prophylactically until the ulcer heals, a mydriatic-cyclopegic, such as atropine, is used for two days to reduce the sensation of pain secondary to intraocular muscle spasm (remember it will decrease tear production) and serum eye drops are applied to help with healing.

The use of third eyelid flaps has rapidly faded out in favor of the techniques described here, as third eyelid flaps offer no obvious benefit in contrast to the use of a bandage lens

and can obstruct the clearing of mucus from the eye and can interfere with the administration of topical drugs.

It is worth noting that SCCED treatments are often described as being “well tolerated” in non-sedated patients. One must remember that well-tolerated does not necessarily mean the patients are comfortable or not afraid, and so one must consider sedation, or general anesthetic could be a more humane approach to veterinary patients with SCCEDS. In cases of poor health where general anesthesia or sedation is contraindicated, debridement through any of the following methods might be performed in the cooperative patient under topical anesthesia. Otherwise, sedation or general anesthesia is suggested for all patients and is required for any uncooperative patient.