

Management of Complicated Corneal Ulcers: What to do when antibiotics aren't working

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Corneal ulcerations are one of the most common ophthalmic conditions seen in veterinary patients and have a broad range of causes. Normal epithelialization should occur within 72 hours, no matter how large the ulcer. Therefore, if an ulceration does not completely epithelialize within this time period, then it is appropriate to assume that something is preventing it from healing. These ulcers are classified as complicated and warrant a detailed search for the underlying cause of delay.

Corneal Wound Healing

Superficial corneal ulcers are breaks in the epithelium that do not extend into the epithelial basement membrane. With simple, superficial corneal ulcers, healing should occur very rapidly. Following corneal ulcerations, epithelial cells will begin to slide over the damaged cornea. In addition, basal cells will replicate to re-establish epithelial thickness. In the event of simple corneal ulcers, treatment with a topical antibiotic two to three times per day should allow for appropriate healing within 72 hours.

Causes of Complicated Ulcerations: Etiologies and Treatment

Entropion

Entropion is an abnormal inversion of the eyelids that most commonly presents in dogs younger than 2 years of age. Severity can vary from minor incidental nasal entropion (most commonly seen in brachycephalic breeds) to more severe cases such as dorsal eyelid entropion associated with abundant forehead skin folds (occasionally seen in Shar-peis and bloodhounds). Persistent corneal irritation from the entropic hairs can lead to non-healing ulceration. Treatment options for entropion include topical lubrication with topical ointments for mild cases, temporary correction (with everting sutures, staple blepharoplasty or dermal filler injections), or definitive surgical correction.

Ectopic Cilia and Distichiasis

Ectopic cilia and distichiae are eyelashes that grow from an anomalous follicle located in the base of the meibomian gland. These hairs will either grow out of the meibomian gland opening (i.e.: distichia) or grow through the palpebral conjunctiva (i.e.: ectopic cilia). These aberrant hairs will often rub against the cornea to cause chronic irritation and subsequent ulceration. Ectopic cilia are most commonly located in the central aspect of the dorsal eyelid and are considered an ophthalmic emergency because they can create rapidly progressive ulcers that are prone to rupture. Ectopic cilia can be difficult to localize without magnification, particularly when these hairs lack pigment. Treatment options include surgical excision of the follicle, cryoablation and diathermy.

Keratoconjunctivitis Sicca (KCS)

KCS is one of the most common ocular diseases of dogs. The most common cause in canines is immune mediated; however, other causes include metabolic, neurogenic, congenital (i.e.: lacrimal gland aplasia/hypoplasia), infectious, pharmacologic and iatrogenic. Low tear production is diagnosed based on a Schirmer tear test reading less than 15mm/min along with symptoms such as mucopurulent

discharge, conjunctival hyperemia, corneal vascularization and corneal fibrosis. However, early cases will often present with a STT of 16-19mm/min. The tear film contains many nutrients such as glucose, vitamin A, growth factors, immunoglobulins, lysozyme and protease inhibitors that the cornea needs for normal health and healing. Therefore, low tear production is often associated with chronic corneal ulcerations. When making a diagnosis, it is important to consider that ulcers cause reflex tearing, which can cause Schirmer tear test values to appear normal despite the presence of KCS.

Indolent Ulcers (SCCEDs)

Indolent corneal ulcers are seen most commonly in dogs 7 years of age and older. These ulcers are over-represented in Boxers but can occur in any breed. The etiology has to do with the loss of basement membrane and the development of an acellular hyalinized zone within the superficial stroma, which can be seen on histology. These changes prevent the epithelium from attaching to the underlying stroma. Therefore, these ulcerations tend to be spontaneous but may also occur following a traumatic event. They are typically non-healing, often have a waxing/waning course and commonly change in both shape, number and location. Treatment options include debridement with a cotton tip applicator, linear grid keratotomy, superficial punctate keratotomy, diamond burr keratotomy, or superficial keratectomy.

Melting Ulcers

Certain bacteria, fungi and inflammatory cells produce proteases and collagenases that will jeopardize the cornea's architectural support. Once compromised, the corneal stroma will become more gelatinous with an appearance that resembles melting. Treatment requires aggressive topical therapy including up to hourly doses of broad-spectrum topical antibiotics and anticollagenases (serum, EDTA, n-acetylcysteine, tetracyclines). Occasionally, surgical intervention is necessary to prevent the cornea from rupturing.

Stromal Ulcers + Descemetocoeles

Corneal infections can invade and erode the deeper layers of the corneal stroma, leaving a deep ulceration that may extend to Descemet's membrane. Surgical management should be considered for ulcers that extend beyond 75% stromal depth. Measurement of depth requires use of a slit beam, but any indentation should raise concern for an active or previous infection.

Mycotic Ulcerations

Rarely, ulcerations can develop mycotic infections that will, therefore, be unresponsive to antibiotics. *Aspergillus* spp. are the most common isolates in cases of mycotic ulcerations and frequently result in corneal malacia. Ulcerations infected with *Candida* sp. are often associated with raised corneal plaques that range from grey to yellow in color. Mycotic ulcerations are best diagnosed via cytology and subsequent fungal culture. Natamycin is the only commercially available ophthalmic anti-fungal available in the US. However, there are a wide variety of topical antifungals, such as itraconazole and voriconazole that can be compounded for off-label use.

Corneal Mineral Degeneration

Corneal mineral degeneration occurs as a result of calcium accumulation within the stroma. Causes include genetic, age-related, chronic irritation (such as entropion, distichiasis etc.), chronic topical steroid use and hypercalcemia. These deposits may partially slough off the cornea or crack to result in chronic ulcerations. Topical EDTA can be used in attempt to chelate the calcium underlying ulcerations to promote appropriate epithelialization, although this medication does not penetrate the intact epithelium. Diamond burr mineral debridement or, in severe cases, surgical keratectomy, may become indicated when the patient is blepharospastic or when ulcerations do not heal.

Corneal Endothelial Dystrophy

Corneal endothelial cells have several properties that promote corneal dehydration, which allows the cornea to remain transparent. Endothelial cell dystrophy causes premature death of endothelial cells, which results in progressive corneal edema. Advanced cases can develop corneal bullae that may ultimately result in superficial ulcerations that are slow to heal and may recur. Treatment should include topical 5% NaCl ointments to help reduce the severity of edema. However, thermokeratoplasty may be indicated in the event that topical NaCl is unrewarding. A few ophthalmologists are performing corneal endothelial transplant procedures as a means to permanently reverse the majority edema.

Neurogenic Ulcers

Neurogenic corneal ulcerations occur due to damage of the trigeminal nerve, which is responsible for corneal sensation. Lack of sensory innervation to the cornea results in decreased cell metabolism and epithelial cell proliferation, which can lead to chronic superficial ulcerations that occur without trauma and take several weeks or even months to heal. These ulcerations are typically located within the central aspect of the cornea and are not associated with discomfort.

Chemical Burns

Corneal ulcerations due to chemical burns often exhibit delayed healing. The two main types of chemical burns are alkali and acidic, of which the former tends to be much more severe. Alkali substances are lipophilic and cause cell death via saponification of cell membrane fatty acids. Acid burns cause protein coagulation in the corneal epithelium but are less likely to affect the stroma. Household sources for alkali corneal chemical burns include lye, lime, ammonia and sparklers/flares (which contain magnesium hydroxide and phosphorus). Hydrofluoric acid can be found in rust removers and several cleaning agents. Copious flushing for up to 30 minutes is important to dilute the chemical and neutralize corneal pH.

Herpesvirus

FHV-1 is the most common cause for recurrent and non-healing corneal ulcerations in cats. Several reports suggest that over 95% of cats are infected, particularly in multi-cat households, although most will never become clinical. FHV-1 achieves a latent state within the trigeminal nerve but can be activated with stress or corticosteroid treatments. Therefore, topical corticosteroids should be used with caution in all cats, even those without history of a previous FHV-1 infection. Although ocular infections are commonly self-limiting, treatment with topical or oral antivirals is often necessary. Most topical antivirals require frequent application of at least 6-8 times per day to be effective. However, cidofovir 0.5% has been shown to exhibit similar efficacy at just a BID dose. Oral famcyclovir is the only oral anti-viral.

Eosinophilic Keratitis

Eosinophilic keratitis is an immune mediated condition that results in raised white plaques on the cornea and/or conjunctiva that are usually fluorescein positive and associated with prominent keratitis. The etiology of this condition is not completely understood. However, it is frequently observed as an immune-mediated sequela to FHV-1. Confirmation of the diagnosis is made via detection of eosinophils on cytology samples taken from the plaques. Treatment includes local immunosuppression with topical tacrolimus, cyclosporine, or corticosteroids. However, it is important to understand that these medications may exacerbate a concurrent herpetic infection. Systemic megestrol acetate is extremely effective, but should be used with extreme caution considering due its potential side effects.

References

Bentley, E. Spontaneous Chronic Corneal Epithelial Defects in Dogs: A Review. *Journal of the American Animal Hospital Association* (2005) 41, 158-165.

Gelatt, K.N. (2013) *Veterinary Ophthalmology*, 5th edition. John Wiley & Sons.

Maggs, D., Miller, P., Ofri, R. (2012) *Slatter's Fundamentals of Veterinary Ophthalmology*, 5th ed. Saunders.

Tasman, W. (1998) *Duane's Foundation of Clinical Ophthalmology*. Lippincott.

Williams, D. (2008) *Veterinary Clinics of North America Small Animal Practice* 38, 251-268.