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 continues to be present after this period, 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 to the epithelial basement membrane. With simple, superficial corneal ulcers, healing should occur very rapidly. Following corneal ulceration, epithelial cells will begin to slide over the damaged cornea, to prevent an open wound. In addition, basal cells will replicate to re-establish epithelial thickness. In the event of simple corneal ulcers, treatment with a topical antibiotic twice a day (three times daily in brachycephalic breeds) should allow for appropriate healing within 72 hours, regardless of how large the ulcer is.

**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 seen in brachycephalic breeds to more severe cases such as dorsal eyelid entropion associated with abundant forehead skin folds (as occasionally seen in breeds including the Shar Pei and Bloodhound). Persistent corneal irritation from the entropic hairs can lead to non-healing ulceration. Treatment options for entropion include topical lubrication, temporary correction (with everting sutures or staple blepharoplasty), 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 including metabolic, neurogenic, congenital (i.e. lacrimal gland aplasia/hypoplasia), infectious, pharmacologic and iatrogenic exist. Low tear production is diagnosed based on a Schirmer Tear test reading less than 18-19mm/min wetting along with symptoms such as mucopurulent discharge, conjunctival hyperemia, corneal vascularization and corneal fibrosis. Tears contain 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 corneal ulcerations and delayed healing. 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 ulcers are seen most commonly in dogs over the age of 7 and are over-represented in Boxers. These ulcers are typically spontaneous but may also occur after a traumatic event. Often, indolent ulcer will have a waxing and waning course. They can also change in shape and location. The etiology has to do with the loss of basement membrane. In addition, affected corneas develop an acellular hyalinized zone within the superficial stroma (which can be seen on histology) that acts as a preventative barrier for the formation of new basement membrane. 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 this support structure is compromised, the cornea stroma will become more gelatinous and look as if it were melting. Treatment for this requires aggressive topical therapy including up to hourly doses of broad spectrum antibiotics and anticollegenolytics (serum, EDTA, n-acetylcysteine, tetracyclines). Occasionally, surgical intervention is necessary to prevent the cornea from rupturing.
Stromal ulcers/Descemetoceles
A focal corneal infection that does not turn malacic can still erode the deeper layers of the corneal stroma leaving a deep ulcer that may extend to Descemet’s membrane. Surgical management should be considered for ulcers that extend beyond 50% stromal depth and is strongly recommended when the ulcer extends beyond 75% depth. Measurement of depth requires use of a slit beam, but any indentation should raise concern for infection.

Mycotic Ulcerations
Rarely, ulcerations can develop mycotic infections that will, therefore, be unresponsive to antibiotics. Aspergillus sp. are the most common isolate 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 voriconizole that can be compounded for off-label use.

Corneal Mineral Degeneration
Corneal degeneration occurs as a result of calcium accumulation within the stroma. Occasionally, these deposits will slough or crack and result in ulcers that are resistant to healing. Medications, including topical EDTA, can be used in attempt to chelate the calcium to allow for appropriate epithelialization. Other treatment modalities aimed towards removing these deposits include diamond burr keratotomy, trichloroacetic acid (TCA) debridement, or surgical keratectomy.

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. The edema may become severe to the point of resulting in bullae that ulcerate. Often, these ulcerations are slow to heal and can recur. Treatment should include topical hyperosmotic medications (5% NaCl). However, thermatokeratoplasty may be indicated in the event that topical NaCl is unrewarding.

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. Lack of sensory neurotransmitters decreases epithelial cell proliferation, which can lead to chronic superficial ulcerations that occur without trauma and take weeks or even months to heal.

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/flare (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.

Herpes Virus
FHV-1 is a common cause for recurrent and non-healing ulcerations in cats. Several reports suggest that over 95% of cats are infected (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. Topical antivirals (excluding cidofovir) require frequent application of at least 4-8 times a day to be effective.

Eosinophilic Keratitis
The underlying cause of Eosinophilic Keratitis remains unknown. However, it is frequently observed as an immune-mediated sequella to FHV-1. Eosinophilic keratitis is often distinguished by the presence of multiple raised opaque plaques on the cornea or conjunctiva and is typically associated with prominent neovascularization. Confirmation of the diagnosis is made via detection of eosinophils on cytology samples taken from the plaques. Fluorescein staining will adhere to the raised plaques, and may or may not be associated with true ulcerations. 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 Megesterol Acetate is extremely effective, but should be used with caution considering its potentially severe side effects.