Introduction to Corneal Ulceration

The cornea is composed of 4 main layers: the epithelium, stroma, Descemet’s membrane, and the endothelium. The cornea is a highly innervated structure containing branches from the trigeminal nerve (CN V), which provides large nerve plexi that extend throughout the stroma and epithelium. The cornea is normally avascular, obtaining its nutrients from the tear film externally, and the aqueous humor internally.

Corneal ulceration is a very common ophthalmic disorder in both dogs and cats and occurs when there is a breach of the epithelium and exposure of the stroma. Multiple descriptive schemes exist which classify the ulcer based upon its depth (superficial, deep, descemetocele, perforated) and etiology (traumatic, toxic, infectious, spontaneous).

Superficial Corneal Ulceration

Superficial corneal ulcers involve the epithelial cell layer and may extend to the anterior 1/3 – 1/2 of the corneal stroma. These ulcers are further classified by their ease of healing as uncomplicated, progressive, or refractory. Uncomplicated corneal ulcers are most often epithelial, and should heal within 2-7 days with appropriate treatment. Progressive corneal ulcers worsen over time despite concurrent medical therapy, generally with increasing depth and severe corneal and intraocular inflammation. Refractory corneal ulcers are superficial ulcerations that are non-progressive yet also fail to heal within 5-7 days even when treated appropriately.

Causes of Superficial Corneal Ulcers

Identification of the underlying cause of a corneal ulcer is an important first step in management. Close inspection of the eyelids can identify the presence of aberrant lashes (distichia, ectopic cilia), conformational disorders (entropion, ectropion), or masses that may have traumatized the cornea. Eyelid function should be evaluated to detect lagophthalmos (incomplete blinking), which may be associated with poor eyelid conformation, buphthalmos, exophthalmos, or cranial nerve deficits. The conjunctiva should be inspected for the presence of foreign bodies, or evidence of inflammation. KCS, especially in the acute phases, is a common cause of corneal ulceration. In addition, a variety of primary corneal diseases, such as edema or corneal deposits, may lead to ulceration. Chemically induced ulceration is uncommon in dogs, but can be seen following exposure to acidic (sulfuric, acetic, hydrochloric) or alkali (ammonium hydroxide, sodium hydroxide) chemicals.
Progressive corneal ulceration occurs when a superficial corneal ulcer advances to involve the stroma or beyond. Bacterial infection is the most common cause of this progression, and cytology and bacterial culture and sensitivity are indicated to determine the appropriate therapy.

**Clinical Signs of Superficial Corneal Ulceration**

A corneal ulcer is diagnosed using topical fluorescein stain instillation and examination under a cobalt blue light. The hydrophilic corneal stroma exposed due to damaged epithelium will retain the fluorescein stain while the normal hydrophobic epithelium will not. A superficial ulcer involves the epithelium or the anterior stroma, and should be described based upon its location, size, and shape. Ocular surface pain will result in blepharospasm, epiphora, enophthalmos and elevation of the 3rd eyelid. Exposure of the underlying nerves will often lead to a reflexive anterior uveitis, resulting in a miotic pupil and a lower intraocular pressure as compared to the contralateral eye. Mild corneal edema is often seen surrounding a superficial corneal ulcer.

**Treatment of Superficial Corneal Ulceration**

Broad-spectrum topical antibiotic therapy (neomycin-polymyxin B-bacitracin, erythromycin, tobramycin) should be used every 6-8 hours to prevent secondary bacterial infection. A topical cycloplegic (atropine) administered once or twice daily will reduce the pain associated with ciliary spasm, and oral non-steroidal anti-inflammatories or additional pain medications are also beneficial. A hard, plastic E-collar is necessary to prevent self-trauma. The underlying cause should be treated to allow for proper healing of the ulcer. Dogs with KCS should be treated with lacrimostimulants and topical lubricants. Corneal deposits of lipid and/or calcium can be challenging to treat, and some even require surgical removal (superficial keratectomy). Patients with refractory ulceration from corneal edema can benefit from topical hyperosmotic agents (e.g. 5% sodium chloride), which reduce the fluid accumulation and improve epithelial cells attachment.

**Refractory Corneal Ulceration**

Refractory corneal ulcers are superficial ulcerations that are not progressive yet also fail to heal within 5-7 days. The most common type of refractory corneal ulcers in dogs is a chronic corneal epithelial defect (CCED), otherwise known as an indolent ulcer. CCEDs are due to a failure of the epithelial cells to develop normal attachments to the underlying basement membrane. Any condition that interferes with normal epithelialization or epithelial cell adhesion can result in a CCED.

**Causes of Refractory Corneal Ulcers**

The first step in the management of a refractory corneal ulcer is to determine the underlying etiology. A thorough physical and ophthalmic examination is essential to identify factors that could be contributing to the refractive healing state. Refractory corneal ulcers can be caused by primary corneal disease or secondary to other processes. Eyelid abnormalities are quite common and may lead to a non-healing corneal ulcer. Specifically, persistent corneal trauma from distichia, ectopic cilia, entropion, or eyelid masses will interfere with normal cellular healing. Abnormalities that preclude normal blinking can predispose to refractory ulceration; lagophthalmos (incomplete blinking) may be associated with poor eyelid conformation, buphthalmos, exophthalmos, or cranial nerve deficits. Keratoconjunctivitis sicca (KCS, dry eye)
is exceedingly common in dogs, and both quantitative and qualitative tear film abnormalities will interfere with normal corneal healing and result in a refractory corneal ulcer. Determinations of a Schirmer Tear test (STT) value and tear film break up time (TFBUT) are important diagnostics to consider in cases of non-healing ulceration. A variety of primary corneal diseases will prevent or delay normal cell healing. Lipid, cholesterol, or calcium deposition in the cornea will inhibit the formation of strong cellular attachments. These conditions are often seen secondary to chronic corneal inflammation, or can be the result of systemic endocrinopathies such as hypothyroidism or hyperadrenocorticism. Corneal edema can lead to the formation of bullae, or fluid pockets, in the anterior corneal stroma. These areas are predisposed to ulceration that is often refractory in nature. The excessive stromal fluid inhibits normal epithelial cell attachment to the underlying stroma. Corneal edema may develop due to endothelial cell dysfunction from age-related degeneration, anterior uveitis, or glaucoma. Finally, superficial refractory ulceration that has no discernable underlying cause is known as spontaneous chronic corneal epithelial defects, or SCCEDs (“Boxer ulcers”, indolent ulcers).

Superficial Chronic Corneal Epithelial Defects
The boxer is the most common breed to develop SCCEDs, comprising approximately 25% of cases. Other breeds that have been reported to have an increased incidence of SCCEDs include poodle and poodle crosses, Welsh Corgis, Labrador retrievers, and German Shepherds and their crosses. The average age of dogs affected with SCCEDs is 7-9 years with no dramatic sex predilection. SCCEDs are often easily diagnosed by recognizing the typical clinical appearance of a superficial ulcer with a non-adherent epithelial border. Fluorescein stain can be classically seen diffusing under this loose lip of epithelial cells and appears as a less intense ring of stain uptake. SCCEDs are most often located in the axial or paraxial cornea, and are vascularized approximately 60% of the time. Without proper treatment, SCCEDs may persist for months to even years with an average time to referral of 7.5 weeks.

Normal corneal wound healing is accomplished via epithelial cell migration to cover the exposed stroma, followed by epithelial cell proliferation to restore the normal thickness of the epithelial layer. The epithelial cells develop firm attachments to the anterior corneal stroma via adhesion complexes composed of collagen fibrils and hemidesmosomes. SCCEDs develop when the formation of these epithelial-stromal adhesions is inhibited. Thus, SCCEDs ulcers are often noted to epithelialize normally, however this newly formed epithelium is easily denuded contributing to the refractory nature of healing. SCCEDs have been studied histologically and multiple hallmark alterations in the normal healing process have been described. In almost all SCCEDs samples, the epithelial cells adjacent to the ulcer are poorly attached to the underlying stroma. These epithelial cells display disorganization of the normal cellular architecture (epithelial dysmaturation), and vary significantly in thickness. Finally, there is formation of an acellular, hyalinized zone, which covers the exposed corneal stroma. This abnormal zone is now considered to contribute significantly to the pathophysiology of SCCEDs, as it interferes with the formation of strong epithelial-stromal adhesion complexes.

Treatment of Refractory Corneal Ulcers
Superficial corneal ulcerations are quite painful, as the corneal nerve density is greatest in this region. Despite the underlying cause, refractory corneal ulcers should be treated with topical prophylactic antibiotic therapy (every 8-12 hours), and a topical cycloplegic (e.g. atropine). Oral
non-steroidal anti-inflammatories or additional pain medications are beneficial in controlling the discomfort, and a hard, plastic E-collar is necessary to prevent self-trauma. As previously discussed, refractory corneal ulcers have a variety of causes, and all efforts should be made to identify and treat any predisposing conditions. The eyelids and eyelid margins should be thoroughly examined with and without magnification for conformational disorders or aberrant hairs located in the region of the eyelid abnormality. For example, a young dog with non-healing ulcer in the ventrotemporal aspect of the cornea should be evaluated for lower, lateral eyelid entropion. Ectopic cilia are most often located in the central, upper eyelids and will result in ulceration in the dorsal half of the cornea. If an eyelid abnormality is identified, this condition should be treated primarily and often the refractory ulcer will then be able to heal normally. A detailed neuro-ophthalmic examination should be performed on any dog with a refractory corneal ulcer; the menace response and palpebral reflex specifically will evaluate the ability of the eyelids to properly close. If lagophthalmos is present then treatment should then be directed at the underlying cause, and some dogs can benefit from temporary tarsorrhaphies or permanent canthoplasties. Determination of a STT and TFBUT is advised in dogs with refractory corneal ulceration. Dogs with KCS will have varying degrees of ocular discharge, hyperemia of the conjunctiva, and, depending on the chronicity, pigmentation, vascularization, and fibrosis of their corneas. A quantitative tear film disorder will yield a STT < 15 mm/min. In patients with clinical signs of dry eye, but normal STT values, a TFBUT should be performed. The TFBUT test measures the speed with which the tear film evaporates from the surface of the eye. Abnormalities in the quality of the tear film (oily or mucin layer) can lead to a faster evaporation of the corneal tear film and clinical signs of KCS. Dogs with quantitative or qualitative tear deficiencies should be treated for the underlying disorder, in addition to the therapy for refractory ulceration. Corneal deposits of lipid and/or calcium can be challenging to treat, and some even require keratectomies. Patients with refractory ulceration from corneal edema can benefit from topical hyperosmotic agents (e.g. 5% sodium chloride) which reduce the fluid accumulation and improve epithelial cells attachment.

Treatment of Superficial Chronic Corneal Epithelial Defects

Both medical and surgical methods for the treatment SCCEDs have been described. A variety of small, poorly controlled studies have investigated topical therapies such as substance P, polysulfated glycosaminoglycans (PSGAGs), fibronectin, and serum with reported success rates ranging from 30-82%. However, these studies also included epithelial debridement as part of the treatment, making it challenging to interpret the results. The foundation and crucial first step in all successful SCCEDs treatment modalities is epithelial debridement. Using a sterile cotton-tipped applicator to remove the loose epithelium can be safely performed after application of topical anesthetic. Normal epithelium is quite firmly adhered, and thus will not be removed with gentle debridement. It is not uncommon for a much larger area of ulceration to be present after epithelial debridement. Epithelial debridement on its own has a reported success rate of about 50%. Techniques that aim to remove or disrupt the acellular, hyalinized superficial stromal zone have improved published success rates over epithelial debridement alone. Punctate keratotomy and grid keratotomy are examples of techniques that create small punctures or linear channels through the acellular zone, allowing epithelial cell attachments to form to the underlying stroma. An average success rate of 80% is seen with these techniques across multiple studies. Disadvantages of these techniques include the risk of deeper stromal penetration, or full thickness corneal perforation, as well as the need for sedation or general anesthesia. Recently,
the use of tetracycline therapy in combination with debridement and grid keratotomy was described in dogs. Tetracyclines are known to modulate the expression of certain growth factors involved in corneal wound healing, and dogs that were treated with either topical oxytetracycline ophthalmic ointment or oral doxycycline healed faster than the control group. Thermal cautery has been described as a treatment for SCCEDs in a small study of 9 dog eyes. After epithelial debridement, a handheld thermal cautery unit is used to make small, superficial burns throughout the affected cornea. This technique is suspected to alter the acellular, hyalinized zone and allow epithelial adherence to the exposed stroma. This technique resulted in more significant scarring that punctate or grid keratotomy, however had a healing rate of 100%. Superficial keratectomy involves removal of the abnormal cornea with the aid of an operating microscope. This technique requires general anesthesia, is the most invasive, and should be performed by a veterinary ophthalmologist. The success rate with this surgery is 100%, however is generally not considered as a first line of therapy given the cost, invasiveness, and increased corneal scarring. The most recently reported therapy for SCCEDs is diamond burr debridement (DBD). DBD is performed using a handheld, battery powered polishing burr and has been described in human ophthalmology for the treatment of superficial, refractory ulcerations. The DBD technique was investigated histologically in dogs, and shown to safely remove the epithelial basement membrane (and presumably the stromal hyalinized zone) without penetrating deeper into the corneal stroma. Recently, the DBD technique in conjunction with bandage contact lens (BCL) placement was evaluated in a clinical setting in dogs with a success rate of 92.5% after a single treatment. Minimal complications were noted, and 95% of dogs retained the contact lens during the study. The BCL is thought to improve healing by protecting the migrating epithelial cells, as well as improve patient comfort by covering the exposed corneal nerves. Overall, DBD is considered advantageous due to the minimal cost, lack of specialized equipment needed, ease of the procedure, and little adverse effects. In clinical practice, the author of this manuscript treats SCCEDs in dogs with epithelial debridement, DBD, BCL placement, and oral doxycycline in addition to the standard topical antibiotic, cycloplegic, and often oral NSAIDs therapy as for any corneal ulcer. Anecdotally, a success rate of 90-95% is seen in the author’s practice, with an approximate 30% BCL retention rate. Very recently, the DBD/BCL technique is being investigated for use in other species with non-healing corneal ulcers such as cats, and horses.

DEEP CORNEAL ULCERS

Deep corneal ulcers involve a significant portion of the corneal stroma, clinically extending beyond 1/2 of the stromal thickness. A descemetocele results when the ulceration has obliterated the entire stromal thickness, leaving only the thin Descemet’s membrane and a single layer of endothelium. Once these final layers are penetrated, corneal perforation ensues with loss of aqueous humor and commonly iris prolapse.

Causes of Deep Corneal Ulcers

Deep corneal ulcers are most often the result of microbial infection. Less commonly, traumatic lesions (e.g. cat claw injury) may cause deep lacerations or perforating corneal injury. Bacterial infection is the most common cause of deep corneal ulceration. *Staphylococcus spp.* *Streptococcus spp.* and *Pseudomonas aeruginosa* are the most frequently encountered infections. After initial bacterial colonization, replication and spread occur along with release of bacterial endotoxins and proteases. This induces a massive inflammatory response with an influx of
leukocytes from the tears or pre-existing corneal vessels, leading to further degradation of the corneal stroma (corneal melting).

**Clinical Signs of Deep Corneal Ulcers**

Deep corneal ulcers are often intensely painful, however descemetoceles may be less painful than expected due to loss of stromal nerve endings. Mucoid to mucopurulent discharge is noted commonly, and the conjunctiva is often significantly hyperemic and chemotic (swollen). The cornea surrounding the ulcer will be intensely edematous, and a creamy or gelatinous appearance to the stroma is related to leukocyte infiltration and stromal degradation (melting). Within days, vascularization begins at the limbus and often appears as a 360 degree, dense “brush border” of vessels, known as ciliary flush. A moderate to severe anterior uveitis is often present, with miosis, aqueous flare, and even hypopyon. Any deep or progressive corneal ulcer should be suspicious for infection, thus cytology and bacterial culture and sensitivity should be performed. Care should be taken not to touch the fur, eyelids, or conjunctiva, and these tests should be avoided if there is concern for integrity of the globe (descemetocele). Descemetoceles have a characteristic appearance after fluorescein staining, with a ring of stain uptake around a dark center. Descemet’s membrane is hydrophobic and thus does not retain fluorescein stain, but will be surrounded by a fluorescein positive stromal defect. A perforated corneal ulcer will appear to be bulging or “filled” with material, often a combination of fibrin, blood, and iris.

**Treatment of Deep Corneal Ulcers**

Goals of therapy for deep (infected) corneal ulcers include treatment of the bacterial infection, controlling progressive stromal degradation, alleviation of associated uveitis, and stabilization of potential perforations. Aggressive medical therapy is necessary to prevent continued progression, and surgical stabilization is indicated when >50-75% depth is achieved, or if rapid progression continues in the face of appropriate medications.

Antibiotic choice should be based upon culture and sensitivity, however these results generally take several days to obtain. Initially, an infected ulcer should be treated with antibiotics every 2-4 hours. Empirical medical therapy should be effective against both gram-negative rods and gram-positive cocci. The author prefers to use combination therapy of a topical fluoroquinolone (ciprofloxacin, ofloxacin) and a cephalosporin (cefaclor) or neomycin-polymyxin B-gramicidin. Topical atropine administered twice daily will alleviate pain from ciliary spasm, and oral NSAIDs will reduce the uveal inflammation. Topical anti-inflammatories (steroids, NSAIDs, Cyclosporine, Tacrolimus) should be avoided when treating infected corneal ulcers. Oral antibiotics should be administered when the ulcer depth is concerning for perforation. A broad-spectrum antibiotic such as amoxicillin-clavulanic acid is an appropriate choice.

Corneal melting must also be controlled to prevent progressive deepening of the corneal ulcer, improve epithelial healing ability, and reduce corneal scar formation. The excessive protease activity causing stromal degradation is mediated by proteinases produced by bacteria, infiltrated leukocytes, and resident corneal cells. Proteinase inhibitors commonly used include serum, N-acetylcysteine (NAC), tetracyclines (doxycycline, oxytetracycline), and EDTA. Serum can be harvested from the patient, or from a donor if the size or temperament of the patient precludes obtaining sufficient blood. Approximately 10-15 mL of whole blood is drawn sterilely, placed into serum separator tubes, and allowed to clot. After centrifugation, the serum can be placed in
a sterile red top tube, individual syringes, or a sterile dropper bottle. The serum should be refrigerated and used for a maximum of 7 days. Serum is instilled every 1-2 hours for the first 24-48 hours, or until clinical improvement is noted (decreased pain and edema, static or improved depth of the ulcer, smoothing of the corneal surface), then every 4-6 hours. The author prefers the use of topical serum and/or oral doxycycline (10 mg/kg PO q24) for the treatment of corneal melt.

Surgical stabilization of deep or perforated corneal ulcers is most often performed by a veterinary ophthalmologist. Many options exist including conjunctival grafts, amniotic membrane grafts, corneal-scleral transpositions, and autogenous corneal transplantation. The goals of surgery are to provide tectonic support to the fragile tissue, and a blood supply to improve healing. The prognosis for vision is highly variable, depending upon the location, size, and severity of the corneal ulcer, but is usually favorable. The prognosis for salvage of the globe is generally good to excellent. Corneal perforations may allow for contamination of the anterior chamber and subsequent endophthalmitis, and carries a poor prognosis for vision and globe salvage.

REFERENCES

