

All About Corneal Ulcers: Mastering the Fluorescein Positive Patient

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CORNEAL ULCERS AND EROSIONS

General goals of treating corneal disease include quickly arriving at an accurate diagnosis as to the depth and severity of the lesion, determining the underlying cause of the lesions, ensuring mechanical integrity of the cornea, collecting the appropriate samples prior to therapy, preventing sepsis, and controlling intraocular pain and inflammation. In layman's terms, one should decide if the fluorescein positive lesions is superficial or deep, infected or non-infected and if there is an underlying condition contributing to the ulceration.

EROSIONS:

Corneal erosions and ulcerations are quite common, and differentiating between the two is crucial for developing a treatment plan. Corneal erosions imply loss of the corneal epithelium only, with the stroma remaining intact. Corneal ulcers imply loss of corneal epithelium, basement membrane and variable amounts of corneal stroma including down to Descemet's membrane. Perforation is possible, particularly with deep and/or infected ulcers.

It is important to always try to determine the depth of the ulcer and identify an etiology. Oblique illumination is best to determine the depth. Epithelial defects tend to look like the skin has been peeled off a grape, and the epithelium may be loosely adherent. In ulcers there is a depression or frank crater, or a "bubble/blister" (often a descemetocele). If perforation has occurred the defect may be filled with blood, fibrin, or uveal tissue. The most common causes of erosions/ulcers seen on an emergency basis are secondary to foreign bodies and trauma. Other causes of corneal problems are adnexal disease or poor conformation leading to exposure or mechanical injury to the cornea, both quantitative and qualitative tear film abnormalities, abnormalities in globe position leading to lagophthalmia (incomplete closure of the eyelids) and facial nerve paralysis causing lagophthalmia. Appropriate management of corneal disease includes a thorough ophthalmic exam to ensure that lid function is normal, tear function is normal, and that no other ocular abnormalities are present which could contribute to the formation or persistence of a corneal erosion.

The most important aspect of treatment is to determine and correct the underlying cause, if present. If an ulcer is melting, treatment will be aggressive and rechecks frequent (see section below) but in superficial erosion cases topical treatment is aimed at preventing problems rather than promoting healing. Many superficial erosions caused by trauma will heal rapidly and uneventfully, however, if there is an underlying cause (such as KCS, entropion, etc) then the erosion will not heal without addressing the underlying cause.

Simple corneal ulcers:

Uninfected ulcers with no underlying contributors should heal in 3-5 days so all simple ulcers should be healed at a one week recheck. Treatment of superficial erosions (urgent non-emergencies) includes topical antibiotics prophylactically. A broad spectrum antibiotic such as neomycin/polymyxin/gramicidin is suitable with a BID to TID frequency for a non-infected erosion. It is important not to over-treat the erosion and impair wound healing. Consider atropine only if secondary uveitis present, however, it is often not necessary. Remember, atropine is contraindicated with concurrent KCS as it will further lower tear production and delay wound healing. E-collars

are always recommended. If the ulcer is not healed at the one week recheck, re-evaluate for underlying conditions or the presence of infection before proceeding to the treatment for SCCED. Please make sure there is no dry eye, incomplete or absent blink or foreign material. Remember that primary indolent ulcers should be a disease of the older dog. In a younger dog, a superficial ulcer that does not heal in 7 days is almost certainly related to an underlying condition such as ectopic cilia or entropion.

Spontaneous chronic corneal epithelial defects:

Spontaneous chronic corneal epithelial defects (SCCEDs) in dogs are chronic erosions with no apparently underlying cause that fail to resolve through normal epithelial wound healing. Various names have been applied to this condition, including boxer erosions, indolent erosions or ulcers, canine recurrent erosions, recurrent epithelial erosions, persistent corneal erosions, refractory corneal ulcers, nonhealing erosions, and idiopathic persistent corneal erosions. The typical clinical appearance of a SCCED is that of a superficial, noninfected erosion surrounded by a sheet of nonadherent or loose epithelium. The epithelium sometimes appears thickened, and fluorescein stain often leaks beneath the abnormal, nonattached epithelium. Left untreated or if improperly treated, these erosions can persist for weeks to months and sometimes for even over a year. These erosions usually occur in middle-aged dogs (i.e., 7 to 9 years) and in all breeds of dogs, Boxers are often overrepresented.

Diagnosis: A spontaneous, chronic, corneal epithelial defect should be suspected in any middle-aged dog with a nonhealing corneal erosion (i.e., an uncomplicated erosion that has not healed within 1 to 2 weeks). Careful examination must be performed to eliminate any possible underlying causes for delayed wound healing, such as mechanical trauma from lid abnormalities (e.g., lid mass, entropion, lagophthalmos) or foreign bodies, infection, tear film abnormalities, exposure (e.g., conformational, neurogenic, secondary to globe abnormalities such as exophthalmos or buphthalmos), or corneal edema causing secondary bullous keratopathy. If any underlying causes are found, addressing those issues generally results in resolution of the corneal erosion.

Diagnosis is also aided by the typical clinical appearance. A rim of loose epithelium around the erosion is characteristic in SCCEDs. The erosion is highlighted by diffuse staining with fluorescein, and a less intense ring of fluorescein staining surrounds the defect. The lesion is superficial, with no loss of stromal substance Figure 1. Any corneal edema is confined to the area of the erosion. Diffuse stromal edema implies that endothelial disease, with secondary corneal edema and bullous keratopathy, is the more likely underlying cause of the erosion. The amount of blepharospasm, epiphora, and corneal vascularization varies tremendously. A central corneal lesion may commonly exist weeks to months without any vascular response at all. Peripheral lesions are more likely to vascularize.

Treatment: Multiple treatment modalities have been recommended for the management of SCCEDs. It is important to remember that because SCCEDs are by definition nonseptic, frequent application of antibiotics is not necessary and may delay corneal wound healing. Topical antibiotics are administered prophylactically only, and application is needed only *q* 12 to 8 hours. Changing antibiotics seldom results in healing, unless the animal is suffering a toxic response to the antibiotic. After all the procedures described below, animals should be maintained on antibiotics until epithelial closure occurs. It is also important to communicate to the owners that these erosions often require multiple treatments and often recur in one or both eyes. For dogs with multiple

recurrences, sometimes limiting access to bushes and tall dry grass decreases the frequency of recurrences, as superficial trauma likely initiates SCCEDs.

Epithelial debridement has long been a mainstay of therapy for SCCEDs. After application of a topical anesthetic (i.e., proparacaine), dry, sterile, cotton-tipped applicators are used to gently remove the loose epithelium, starting in the center of the erosion and working outward in a radial motion. Normal corneal epithelium is very firmly attached to the underlying stroma and is not easily removed with a cotton-tipped applicator, so debridement is continued until all loose epithelium is removed (without fear of unnecessary removal of normal epithelium) Figure 1 predebridement and Figure 2 postdebridement. Often, a much larger area of epithelium is removed than originally indicated by fluorescein staining. Combining the outcomes of the various studies in the literature results in an overall success rate of approximately 50%. One study also noted that adding a contact lens or a third eyelid flap to protect the cornea increased healing rates after epithelial debridement to 58% and 64%, respectively.

Another therapy for SCCEDs involves either burring the surface of the cornea or making small punctures or linear scratches in the superficial stroma, which likely creates channels for epithelial cells to penetrate the abnormal superficial stromal hyalinized zone noted on histopathology of these samples. Various names have been given to these procedures, including corneal burr debridement, punctate keratotomy, anterior stromal puncture, multiple punctate keratotomy, multifocal superficial punctate keratotomy, and grid keratotomy. To perform an anterior stromal puncture, a 25-gauge needle is clamped in a hemostat so that the tip of the needle is barely exposed. This allows the hemostat to be used as a handle and controls the depth of the puncture. Alternatively, a commercially available anterior stromal puncture needle can be used. After application of topical anesthesia and debridement of loose epithelium, multiple small punctures are made 0.5 to 1 mm apart across the surface of the exposed stroma and extending 1 mm into the normal, surrounding attached epithelium. To perform a grid keratotomy, small lines are made in a crosshatched pattern extending from normal cornea across the epithelial defect. A cornea can be burred with an Algerbrush II with a medium grit 2.5mm burr tip applied to the surface of the eye for approximately 1 minute.

Combining the outcomes in the various studies in the literature results in a success rate of approximately 80%. A contact lens or third eyelid flap may also be used after these procedures; one study found that 100% (12/12) of eyes healed after treatment with grid keratotomy followed by a third eyelid flap.

A more invasive procedure for the treatment of SCCEDs is superficial keratectomy. This procedure, unlike the two described above, requires general anesthesia and is best performed under an operating microscope. As a result, veterinary ophthalmologists generally perform this procedure. To perform a superficial keratectomy, the loose epithelium may or may not be debrided. If it is not debrided, careful examination of the cornea must be done to ensure that the entire area of nonadherent epithelium is removed with the keratectomy. The area is either outlined with a corneal trephine of appropriate size or with a 64 Beaver blade, and then it is undermined with a corneal dissector. The flap of cornea, usually 150 to 200 μ m thick, is then removed, and any attachments are trimmed as necessary. Following the keratectomy, either a contact lens or third eyelid flap may be placed. Superficial keratectomy probably works by completely removing the abnormal superficial zone of stroma, allowing epithelial adhesion. The success rate with this surgery has been reported to be 100% (24/24 eyes, 9 days average healing time; 4/4 eyes, 14 days healing time). Although this procedure results in rapid healing, it is often

not recommended as an initial therapy because of the need for referral, its higher cost, the risks inherent with general anesthesia, and the increased likelihood of corneal scarring.

Non-healing erosions in cats: Non-healing erosions in cats are often associated with herpes virus infections and are much harder to treat than in dogs. Epithelial debridement can be performed, with or without a contact lens or third eyelid flap. Consider using trifluridine in difficult cases. Some evidence exists suggesting that anterior stromal puncture or grid keratotomy can lead to corneal sequestrum formation. Even without those procedures, a long standing epithelial defect can become a sequestrum, particularly in brachycephalic cats. Oral Famciclovir at 90mg/kg BID for 3 weeks is recommended as well.

Melting Ulcers: The cornea's protection mechanism is to grow blood vessels and to liquify areas of suspected infection in the cornea. Malacic or "melting" corneal ulcerations are commonly encountered in dogs, and less commonly encountered in cats. The "melting" appearance of these ulcerations results from an enzymatic breakdown of corneal proteins or "collagenolysis". Clinically, malacia leads to corneal opacification that may vary from bluish to green-yellow, and a very "goosey" texture to the surface of an ulceration. On first glance, malacia can sometimes be confused with mucoid discharge. Malacia, however, cannot be rinsed from the ocular surface.

Collagenolytic enzymes, namely serine proteases and matrix metalloproteinases (MMP-2, MMP-9) are produced by microorganisms. The most commonly implicated organisms include the bacteria *Pseudomonas aeruginosa* and the fungal agents *Fusarium spp.* and *Aspergillus spp.* Matrix metalloproteinases, however, are also produced excessively by corneal epithelial cells and stromal cells (keratocytes) during times of inflammation and injury. Therefore, even if the above-mentioned organisms are not clinically suspected or cultured from an ulceration, collagenolysis and melting may still occur.

In any eye with a malacic ulceration, an infection should be suspected. Diagnostically, corneal cytology should be performed to look for evidence of a fungal infection (typically indicated by the presence of fungal hyphae) and to characterize any bacterial populations present (i.e. cocci, rods, or both). Fungal infections, however, are rare in dogs and cats. Cytology of melting ulcers also commonly demonstrates a large population of neutrophils, many of which may be degenerate. Immediately following cytology, a swab should be gently rolled across the area of the malacia and submitted for aerobic culture and sensitivity.

Most malacic ulcerations are better candidates for medical therapy than for immediate surgery (i.e. a conjunctival or corneal grafting procedure), since soft, malacic corneal tissue does not adequately hold the sutures needed to successfully place grafts. See more on surgical treatment below. Furthermore, an advantage of medical therapy is that it may be less expensive and, if successful, often results in less scarring and opacification of the cornea. Ulcerations that are also associated with an active neovascular response in the adjacent cornea are also considered better candidates for medical management as the blood supply provided by corneal vessels will enhance the response to treatment and expedite healing. Note though that the deeper the ulcer at diagnosis, the more fragile the affected cornea is, and the more likely it is to rupture during medical therapy.

Antibiotics: For any melting ulceration, broad-spectrum coverage with a combination of two antibiotics is typically recommended due to the concern for a severe infection. Therapy may also be guided initially by what is observed on cytology. For cocci, topical antibiotics that provide gram positive coverage are preferred including neomycin-polymyxin-

gramicidin/bacitracin, chloramphenicol, or cefazolin (created in a 33-50 mg/ml concentration by combining artificial tears or saline with the lyophilized powder used for intravenous injection). For rods, gentamicin, tobramycin, or a fluoroquinolone (i.e. ciprofloxacin, ofloxacin, moxifloxacin) are indicated. Keep in mind that resistance of *Pseudomonas aeruginosa* to topical antibiotics is increasing, but fluoroquinolones are still particularly effective against this bacteria. Remember that malacic ulcerations are rare in cats and that bacterial agents that infect the cornea are slightly different than in dogs. In cats, intracellular bacteria like *Mycoplasma* spp. are commonly cultured from or suspected in rapidly-progressive stromal or malacic ulcerations. Therefore, a more appropriate antibiotic combination in cats would include two agents that effectively treat these tenacious intracellular bacteria. This author prefers a combination of oxytetracycline (Terramycin®) and a fluoroquinolone.

Equally as important as the *type* of antibiotics prescribed, is the *frequency* at which they're administered. The prescribed frequency may vary depending on severity; but since malacic ulcerations can progress and deteriorate very rapidly (i.e. within 24-48 hours), administration at least q 2 hours (no less than q 4 hours) of all prescribed antibiotics is recommended. In some cases, this may require hospitalization.

Anti-collagenase therapy: Anti-collagenase therapy should be considered in any case of progressive stromal corneal ulceration and particularly in corneas with evidence of malacia. Anti-collagenase agents will inhibit the activity of collagenolytic enzymes, reducing breakdown of corneal collagens that leads to malacia. The most commonly employed anticollagenase agent is serum (serum prepared from a same species patient). Serum is rich in the protein alpha-2 macroglobulin. An antiproteinase molecule, this protein binds and inactivates serine proteases and MMPs. Autologous serum can be prepared by collecting a whole blood sample in a red-top blood collection tube. The tube is then centrifuged and the undiluted supernatant collected. On average, 3 ml of whole blood will produce approximately 1 ml of serum. **It is important to note that serum MUST be kept refrigerated while in use and any unfrozen serum should not be used for greater than 1 week. Serum can be stored for future use in a standard clinic freezer for up to 6 months.**

Platelet-rich plasma is a blood product that may be available at some clinics. This product does contain alpha-2-macroglobulin and may be used as an anticollagenase agent, but this may be a much more expensive approach and its effects have not been formally studied in veterinary medicine.

Tetracycline antibiotics are effective at binding the zinc and calcium that MMPs require as a cofactor. Topical oxytetracycline is available in ophthalmic ointment (Terramycin®). Tetracyclines are also the only antibiotics reported to gain access to the tear film and ocular surface after oral administration in dogs and may be effective at inhibiting collagenolysis in this manner as well. Distribution of oral tetracyclines to the tear film has not been proven in cats.

0.2% EDTA also binds zinc and calcium and may be compounded for topical use. Signs of topical irritation from this medication have been reported. N-acetylcysteine can be used as well. Like tetracyclines and EDTA, NAC binds or chelates Zn and Ca.

Analgesia: Atropine can be used to alleviate the iridocyclospasm associated with severe corneal ulcerations and the often concurrent secondary or "reflex" uveitis. However, it should be used with caution if KCS is suspected to be the underlying reason for a corneal ulceration as the parasympatholytic activity can transiently reduce aqueous tear production. Atropine is typically prescribed used at a frequency that will achieve and maintain pupil dilation (typically BID-TID initially). Systemic non-steroidal anti-inflammatory drugs (NSAIDs) may also be used to reduce ocular pain and

inflammation. Topical NSAIDs (i.e. ketorolac, diclofenac, flurbiprofen) can exacerbate corneal melting and so are avoided with deep and/or malacic ulcers. Excessive physical activity and tension on the animal's neck should also be avoided.

An Elizabethan collar is always recommended in any case of malacic ulceration. Under no circumstances should a topical corticosteroid (i.e. dexamethasone or prednisolone) be administered to an eye with a corneal ulceration, especially a malacic ulceration. Steroids **promote** collagenolysis and will assuredly cause deterioration, often rapidly.

Monitoring: Malacic ulcerations should be monitored very closely while being treated medically. Initial recheck after initiation of therapy should occur within 24-48 hours to ensure lack of deterioration. Thereafter, a recheck examination every 3-5 days is recommended until an ulceration is showing steady improvement. Signs of improvement in malacia ulcers are lack of progression, corneal neovascularization, improvement of any secondary uveitis, decreased corneal infiltrate, decreased pain, and decreased corneal edema. Ultimately, most malacic ulcers that heal with medical management must completely vascularize for successful repair of the stromal defect. Some ulcers may require treatment for weeks at decreasing frequencies. If the ulcer is not healing, the clinician should consider repeating cytology and culture/sensitivity.

When indicated, surgical therapy for malacic ulcerations results in faster ulcer resolution and a higher success rate at maintaining the globe, but is usually more expensive and causes more scarring. For any stromal ulcer (with or without malacia), if the ulcer is deeper than 50% of the stromal depth, consider referral to a veterinary ophthalmologist for assessment and possible repair. Surgical options most commonly include conjunctival graft or flap, corneoscleral transposition, lamellar keratoplasty, or penetrating keratoplasty (corneal transplant). The decision of which procedure to perform is based on the area and depth of the ulcer, integrity of the surrounding corneal tissue, the prognosis for vision (i.e., unlikely to perform a corneal transplant on a dog that has a pre-existing complete cataract), and the owner's preference. Any ulcerated area of the cornea covered by a conjunctival flap will ultimately be too opaque to allow for useful vision. Perforated corneas should either be referred to a veterinary ophthalmologist or enucleated. Large corneal ruptures with extensive uveal prolapse and/or lens damage have a poor prognosis and are often enucleated.