Relevant Anatomy and Physiology

The cornea is a clear, avascular structure, which serves as the major refractive structure of the eye (along with the tear film). In dogs and cats there are 4 main layers, the epithelium, stroma, Descemet’s membrane, and the endothelium. However, when discussing corneal anatomy and disease, the tear film should be considered an integral component as it provides nutrition, oxygen, and plays a role in corneal immunity.

The epithelium is the most superficial layer and is made of 5-7 cellular layers that are constantly replaced. Cellular regeneration occurs simultaneously from the limbus, to replace the basal layer, and as the basal layer divides to replace the more superficial cellular layers. The next layer, the stroma contributes to ~90% of the corneal thickness, and is a relatively acellular structure, other than occasional keratocytes. Collagen fibrils form lamellae that are organized parallel to the surface of the cornea, contributing to the corneal clarity. Glycosaminoglycans and nerves are present amongst the lamellae contributing to hydration and sensory functions respectively.

The next 2 layers, Descemet’s membrane (DM) and the endothelium, are closely related as DM is the basement membrane of the endothelial cells. Descemet’s membrane is only about 10µm thick, but does get thicker with age. This layer does not uptake fluorescein, which becomes clinically relevant, as discussed below. DM has elastic properties so has some capacity to stretch, get thinner, or break. The endothelium is only a single layer thick, with limited capacity to replicate. Ion transport pumps in this layer maintain the relative dehydration of the cornea, so loss of these cells results in significant edema.

The properties of the tear film and the above layers contribute to the corneal clarity, and disruption of any of these components can result in loss of clarity. Assessing the loss of this clarity can contribute to diagnosing ulcers, as well as potential causes, which can alter treatment choices.

Corneal Wound Healing

So what happens when corneal anatomy is disturbed and the cornea is wounded? And what do we do about it? To understand how to treat corneal ulcers, an appreciation of the corneal wound
healing process is beneficial. This not only allows you to choose appropriate treatments, but also allows you to better assess when things are not healing appropriately and to take appropriate action to correct the delayed healing or complications.

Within minutes of injury, the epithelial cells surrounding a defect begin to slide and cover the affected area. Once they have covered the area they will replicate to restore the normal epithelial thickness. Once you have stromal involvement, the process becomes more complicated. With small and/or uncomplicated stromal ulcers, activation of keratocytes to fibroblasts results in synthesis of collagen and extracellular material to replace the lost tissue by reformation of the lamellae. Neutrophil and macrophage recruitment results in removal of debris. This initial healing results in irregular lamellae which can be seen as a corneal opacity. Continued remodeling of the following weeks will decrease scar density to restore clarity. For more complicated ulcers, and ones in which a larger portion of the stroma is disrupted, a vascular component of healing can be seen. Cellular infiltrate around the defect can be more extensive, and the combination of vasculature and greater cellular response can result in more significant scar tissue formation. Damage to the endothelium and DM in full thickness ulcers can have more significant scarring or long-term effects due to the limited regenerative capacity.

**Corneal Pathologic Responses**

Once we understand how the cornea heals, we can better understand the pathological processes of how the cornea responds to injury. Having an appreciation for these processes will aid in our determination of potential causes of the corneal ulcer as well as guide our treatment protocol decision. Common pathologic responses include edema, vascularization, fibrosis, stromal white blood cell infiltrate, and stromal malacia (melting).

Corneal edema occurs when there is an anatomical or functional defect in the epithelium or endothelium resulting in excess fluid accumulation. Endothelium disruption results in more significant edema, and can result in corneal bullae (blister) formation that can eventually lead to an ulceration. Lack of epithelium can result in a ‘fluffy’ edema, but this edema is often limited by a functional endothelium.

Corneal vascularization can be seen with a variety of corneal ulcers. The general rule on growth rate is a “3 day delay then growth of 1 mm a day”. Vascularization can be either deep or superficial, and taking note of which layer the vascularization occurs can give you an idea of what the primary problem in the eye is. Superficial vascularization is generally a response to superficial disease involving the anterior 1/3 of the stroma. Multiple branches can be seen and the vessels can also be seen crossing the limbus. Deep vascularization is suggestive of intraocular involvement. These vessels are often more straight with less branching, and they cannot be seen crossing the limbus.

Corneal fibrosis occurs after the healing response and is due to irregular patterns of corneal lamella and collagen types. The normal cornea has primarily Type I collagen, while a healing
cornea has increased levels of type III collagen. This change in collagen type alters the lamellae attachments and arrangement, resulting in opacity clinically. Fibrosis occurs to a lesser degree in younger animals, and cats tend to have a lower fibrotic response than dogs.

Stromal white blood cell infiltrate can also appear as a cloudy corneal infiltrate and should not be confused with corneal fibrosis. The opacity appears as a white/yellow/grey discoloration with indistinct borders. Thickening and edema of the cornea in this region can also be appreciated in most cases. This infiltrate can be seen alongside or quickly turn into, keratomalacia.

Stromal malacia (melting) can occur due to an excessive response of normal proteolytic enzymes. These enzymes (matrix metalloproteinases, plasmin, etc.) have a normal physiological role in turnover and excessive activity is prevented by proteinase inhibitors that are also present in the normal cornea. A pathological degradation occurs when the balance favors the proteinase activity. Proteinases can come from both endogenous (keratocytes, epithelial cells) and exogenous (microorganisms) sources. This disrupted balance results in keratomalacia, or excessive breakdown of corneal tissue.

**Diagnosing Corneal Ulcers**

When attempting to diagnose a corneal ulcer, setting yourself up for success is essential for the best determination of the presence, and a possible cause, or the corneal ulcer. A dark room will help with assessing the cornea as well as other ocular structures (aqueous humor, lens, etc.) which may be a cause of ocular disease.

As mentioned previously, assessing the tear film is an important aspect of evaluating any patient with a corneal ulcer. Measuring the Schirmer tear test in dogs when the cornea is stable, can aid in assessing if tear production is a contributing factor to corneal ulcer formation. Fluorescein is the mainstay in highlighting corneal ulcers, and should be used concurrently with a cobalt blue filter. Discussion of how to interpret these findings can be found below.

The use of proparacaine can be useful to decrease discomfort associated with corneal ulcers, and this may allow better visualization and assessment of the cornea. However, this medication should not be utilized as a pain medication and should never be sent home as a part of a treatment protocol.

Other diagnostics that may be utilized for corneal ulcers include cytology and culture and sensitivity, especially if an infectious component is suspected. If these tests are warranted, effort should be done to collect samples prior to fluorescein and proparacaine administration, as these two topicals can interfere with microbial assessment.

Once you have determined that there is an ulcer present, you should attempt to further classify it, as this aids in the best treatment selection. First, assess the depth of the ulcer. Then determine the rate of progression, based on history and your clinical findings. If prior treatment has been
attempted, evaluate its response to therapy. And finally, determine if there are complicating factors present, such as melting or inflammatory cell infiltrate.

**Interpreting Fluorescein Staining Patterns**

Fluorescein is a hydrophilic substance and thus will stain exposed stroma. The corneal epithelium and DM are both hydrophobic and thus to not retain fluorescein. Appreciating this basic concept aids in classifying corneal ulcers.

*Uncomplicated, superficial ulcers* occur when only corneal epithelium is lost, with no stromal involvement. There is stain uptake with well-defined edges and a cavitation/crater should not be present. There is typically no or minimal neovascularization present.

*Spontaneous Chronic Corneal Epithelial Defects (SCCEDs, or Indolent ulcers)* is when loss of epithelium occurs with loose epithelium lip at the edges due to abnormal healing responses between the stroma and epithelium. There is NEVER stromal involvement with these types of ulcers. The stain uptake appears bright in the center with a ‘halo’ surrounding due to fluorescein diffusing under the loose epithelial lip. These ulcers are considered chronic and thus have been going on for >2 weeks.

*Stromal ulcers* occur when there is loss of epithelium and varying amounts of underlying stromal tissue. There is uniform uptake throughout the ulcer bed, and pooling can occur, so flushing the eye with eyewash can aid in better assessment on depth. Descemetocle’s occur when there is loss of epithelium and all the stromal tissue to the level of the endothelium and basement membrane. The center of the ulcer does not uptake stain, and a ring of fluorescein may be noted in the surrounding wall of stromal tissue. In these cases, flushing out the eye with eyewash is imperative to differentiate between a stromal ulcer with fluorescein pooling and a descemetocle. Without staining, the center of a descemetocle may appear clearer compared to the rest of the cornea due to the disease of the surrounding stroma (edema, infiltrate, etc.).

Stromal ulcers and descemetocles can also be sub-classified as melting ulcers. This is when the ulcer bed or edges have a soft, gelatinous appearance with a white/yellow discoloration. The melting tissue may also be edematous and appear to protrude from the surface of the cornea.

**Treatment - Antibiotics**

Now that we know what the normal cornea looks like, and understand how it responds to injury, we can start to determine the best approach to treat the patient. Ulcers may have varying treatments, both due to classification of ulcer and clinician preference, however, there are general principles that guide our selection of medical and adjunctive treatments including surgery.
During your exam, you should attempt to determine if there is an underlying cause, such as entropion, distichiasis, or trichiasis. Removal of the cause is instrumental in allowing the ulcer to heal, preventing it from progressing, and decreasing the likelihood that it will return after it has healed. Another contributing factor to non-healing can be self-trauma; thus, every pet with an ulcer should receive an e-collar. Donut and soft e-collars are not recommended for the ophthalmology patients as this still allows them to rub their face of furniture, carpet, legs, etc.

All patients with corneal ulcers should be placed on some form, of topical antibiotics. Not all ulcers are infected, and actually many of them aren’t, however the cornea has a unique immune system, limiting its ability to fight off infection. Corneal infection is most often secondary to a normal commensal organism that is better able to inhabit and invade the cornea when there is compromise in the tear film and epithelium. The antibiotics we will discuss are the most common topical antibiotics utilized for corneal ulcers, but this is by no means an exhaustive list, which is continually growing.

The first, and probably most commonly used antibiotic, is triple antibiotic. This comes in an ointment form which include neomycin, polymyxin-B and bacitracin. The solution form replaces the bacitracin for gramicidin, as bacitracin is not stable in a solution form. This is a broad-spectrum antibiotic, and is effective against many *Pseudomonas* spp., the bacteria most often associated with globe threatening keratomalacia. These medications should be used cautiously in cats, as there have been reports of anaphylactic reactions to ophthalmic medications containing polymyxin B in this species. It does not preclude the use of this antibiotic, but the patient should be assessed for any potential adverse reactions.

The next common category is the aminoglycosides such as gentamicin and tobramycin. This are bactericidal antibiotics, but do have decreased efficacy against gram positive organisms. Gentamicin has been shown to be more epitheliotoxic than tobramycin, so should be used cautiously for longer periods of therapy.

Our next category of medications are the tetracyclines, of which we use both topically (Terramycin) and systemically (doxycycline, minocycline) for corneal disease. There are reports of increasing bacterial resistance to this medication, however we are most often utilizing these antibiotics for other, non-antibacterial properties. First, it is known to inhibit matrix metalloproteinases and other inflammatory mediators that could contribute to melting. It also acts as a reactive oxygen species scavenger with anti-apoptotic and anti-inflammatory effects, all of which aids in clinical corneal healing. Our second utilization of this antibiotic are in refractory canine ulcers, or indolent ulcers. It has been shown that Terramycin decreased healing times of indolent ulcers.

The fluoroquinolones are also seeing greater use in veterinary ophthalmology. The most frequently used group are the second-generation fluoroquinolones, ofloxacin and ciprofloxacin. These antibiotics have a strong efficacy against gram negative isolates, particularly
*Pseudomonas spp.* They do have some gram-positive efficacy, but are not consistently effective, and resistance is growing. These are considered a stronger antibiotic and are generally reserved for ulcerations with evidence of infection. Third generation fluoroquinolones, such as levofloxacin, and fourth generation, such as moxifloxacin, are also increasing in use in the literature and human ophthalmology. However, at this point, use is cautioned in veterinary patients and good reasoning (i.e. culture) for utilization of higher generation antibiotics should be provided prior to use.

The last group of antibiotics we often use are the cephalosporins, mainly cefazolin. This antibiotic is used systemically prior to and during surgery. When given systemically it is shown to cross the blood ocular barrier with effective concentrations in the anterior chamber and tear film. It can also be compounded with artificial tears into a topical medication and is often used in combination with fluoroquinolones to provide more broad-spectrum coverage in infected and/or melting ulcers.

**Treatment – Other Medications**

Protease inhibitors are indicated when there is evidence of keratomalacia. As discussed earlier, the proteinases are elevated in the precorneal tear film of companion animals with ulcerations, and thus we need to help the cornea return the balance to normal by supplementing with protease inhibitors. Protease inhibitors include acetylcysteine, EDTA, serum and tetracyclines. The first two were used more commonly historically but have fallen out of favor with the availability of serum and tetracyclines. Serum is probably the most common protease inhibitor used for ophthalmology, and can be stored in the clinic freezer or drawn from the patient and spun down at the appointment. Tetracyclines, as discussed before, are also utilized systemically for the protease inhibiting activities. With melting ulcers, we typically utilize systemic tetracyclines, which are shown to be present in the precorneal tear film at normal doses.

Reflex uveitis can result from stimulation of corneal nerves when an ulcer is present. This is seen clinically seen as flare, hypopyon, and miosis with ciliary body muscle spasm. This can result in discomfort for the patient and the desire to rub the eye which can contribute to delayed healing and/or globe rupture. The combination of miosis and inflammatory cells within the anterior chamber can also result in posterior synechiae. Thus, utilization of a cycloplegic agent, such as atropine, causes pupillary dilation (preventing synechiae formation) and paralyzes the ciliary muscle improving comfort level for the patient. Of note, the medication tropicamide, does result in pupillary dilation but does not paralyze the ciliary muscle, and thus does not relieve discomfort associated with spasms of this muscle. These medications have been shown to increased intraocular pressure and decrease tear production, and thus should be avoided in patients with glaucoma and/or KCS.

Systemic anti-inflammatories and analgesics should also be used to improve patient comfort. Systemic NSAIDs can decrease corneal WBC infiltration and inflammation associated with
reflex uveitis. Topical NSAIDs, such as flurbiprofen and diclofenac, should be avoided when ulcers are present, as these have been shown to potentiate keratomalacia and delay corneal wound healing.

The above noted medications are a summary of general guidelines, and do not cover all possible medical treatments for corneal ulcers. In many ulcers we may choose to use a combination of medical and surgical management as discussed below.

**Treatment – Surgical Management**

Most ulcers do not need surgical intervention, however, in some cases this becomes necessary for vision sparing and/or salvage of the globe. Surgeries that are performed by ophthalmologists that we won’t discuss extensively include conjunctival grafts, corneal grafts, biomaterial grafts, cyanoacrylate glue, and corneal collagen cross-linking. I am happy to discuss any of these procedures with you further if you desire more information.

One set of procedures that we will further elaborate on are the grid keratotomy and the diamond burr debridement. These procedures should only ever be used on SCEEDs/indolent ulcers and should never be used if stromal involvement is suspected. In corneas with a SCEED, there is a hyaline zone present on the surface of the stroma, and it is thought that this zone prevents appropriate attachment of the epithelium. First, removal of the loose epithelial tissue with dry cotton-tipped applicators, will allow regeneration of new, healthier epithelium. This procedure alone has an ~50% success rate of healing indolent ulcers. The grid keratotomy or diamond burr debridement can be used in conjunction with the cotton-tipped applicator debridement and is used to breakdown/remove the hyaline zone, creating tracks for the epithelium to adhere to. A grid keratotomy can be done with a 25ga needle used to ‘scratch’ a grid pattern over the exposed stroma, using caution to not create deep tracks in the cornea. A diamond burr is a newer instrument that utilizes the same concepts, but is potentially safer due to the non-sharp burr contacting the cornea.

Other procedures that are used by some veterinarians and veterinary ophthalmologists concurrently with the medications discussed above, include temporary tarsorrhaphies and third eyelid flaps. These are used to provide some protection to the globe and decrease irritation that the eyelids may create when blinking occurs. However, these procedures can trap bacteria and proteases on the corneal surface, potentiating worsening of the disease process. It also prevents monitoring of the ulcer by the owner and the veterinary staff, so evaluation of both the benefits and disadvantages should be done prior to performing these.

**References available upon request**

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