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I. CORNEA

The cornea is the most powerful refractive surface of the eye; it supplies 70% of the eye's refractive or light bending power. The cornea is also an extremely strong tissue. It is transparent so that light rays can enter the eye. Transparency is maintained by several anatomic mechanisms: 1) lack of blood vessels; 2) lack of pigment; 3) non-keratinized anterior surface epithelium; 4) precise organization of the stromal fibrils; 5) small size of the stromal fibrils; 6) relatively dehydrated compared to sclera.

Most domestic animal species have 4 corneal layers. The outermost stratified squamous epithelium has 3 cell types (superficial squamous cells, wing cells, and basal cells). This layer is a barrier to the precorneal tear film. A basement membrane is secreted and attaches to stroma. The stroma constitutes approximately 90% of the corneal thickness, and it is relatively acellular (mostly collagen). Descemet's membrane is the basement membrane secreted by the corneal endothelium. It is produced throughout life, and therefore the thickness increases with age. It is about 14 µm thick! The innermost endothelium is only 1 cell layer thick, and contains a sodium ATPase pump. This feature is very important in maintaining corneal transparency, as the pump helps to keep the stroma relatively dehydrated.

Most of the corneal nerves are concentrated superficially. They are branches of the trigeminal nerve, and form a very dense anterior sensory neural network. The cornea is actually one of the most sensitive tissues in the body. There are no nerves in Descemet's membrane. The corneal thickness varies by species. It is often thinner centrally than peripherally, depending on the species. The average thickness of the central dog cornea is 0.6 mm; in the horse the central cornea is approximately 1 mm thick.

Limbus and Sclera

The limbus is located at the peripheral edges of the cornea. It is about 1 to 1.5 mm wide, and forms the transition zone between the cornea and sclera. The epithelium of the cornea merges with the bulbar conjunctival epithelium in this area. The sclera constitutes the major portion of the outer fibrous tunics (5/6). The equator is the thinnest region in most species.

ULCERATIVE KERATITIS: The most important disease of the cornea.
Ulcerative keratitis (corneal ulceration) means that the corneal epithelium and possibly varying amounts of underlying corneal stroma are missing. In simple traumatic corneal injuries in which a small amount of epithelium is absent, healing is rapid. Normal corneal epithelium is a very effective barrier against invading bacteria. If the ulcer becomes infected or the epithelium is unable to attach to the underlying stroma, healing is delayed.

In chronic or infected ulcers, proteases and collagenases digest protein and collagen of the stroma and may greatly speed the progression of an ulcer to a descemetocele, rupture of the cornea, and then to iris prolapse (within 12-48 hours in some cases).

Corneal dissolution and liquefaction under the influence of proteases is often referred to as "melting". Ulcers in which proteases are active have a grayish-gelatinous liquefied appearance around the ulcer margin which must be distinguished from corneal edema.

Ulcerative keratitis is the most serious ocular disease for veterinarians. Regardless of the initial cause, all ulcers have the potential to progress to endophthalmitis if not treated.

I. CLASSIFICATION/CHARACTERIZATION OF CORNEAL ULCERS

A. DEPTH

Superficial ulcerations or abrasions should heal rapidly if they do not get infected. They can be traumatic in origin. It has been shown that normal horse corneal epithelium migrates at 0.6 mm per day. We guess that the dog and cat are similar or faster.

The following types of ulcers will be covered in detail: recurrent superficial corneal erosions; deep stromal ulcers; fungal keratitis; descemetoceles; perforating ulcers (iris prolapse); and corneal lacerations (superficial and full-thickness).

B. ETIOLOGY

There are multiple causes of corneal ulcers. Corneal ulcers can result from mechanical causes such as traumatic abrasion; corneal or eyelid foreign bodies; and eyelid anomalies (entropion, distichia/distichiasis, ectopic cilia, and trichiasis).

Infectious etiologies also cause corneal ulcers. Infectious organisms can be bacterial, fungal, or viral. Culture and sensitivity are important diagnostic tools to use with infectious ulcers.

Keratoconjunctivitis sicca (KCS or “dry eye”) can result in corneal ulceration. This is especially true with cases of acute onset KCS, in which corneal ulceration can occur rapidly and progress quickly. Ulcers are less common with chronic KCS.

Bullous keratopathy results in rupture of epithelial bullae that form with chronic corneal edema. Ulcers result from the rupturing of the bullae. These ulcers can range in size from small to very large and are variably painful. This is a devastating disease in the cat.

Exposure keratitis can result from either neuroparalytic disease (facial nerve paralysis, resulting in an inability to blink) or from neurotrophic disease (paralysis of ophthalmic branch of trigeminal nerve; corneal sensation is important to healing of corneal ulcers).
III. DIAGNOSIS OF CORNEAL ULCERS

A. CLINICAL SIGNS

The majority of animals with corneal ulcers present with pain as evidenced by blepharospasm. Corneal sensation is one of the major protective factors that the eye exhibits. Corneal sensory nerves are located mostly in the superficial cornea, and the nerves lose their myelination as they cross from the periphery into the center of the cornea. An “axon reflex” is thought to exist in the cornea such that when corneal touch and pain receptors are stimulated, miosis of the pupil, hyperemia, and increased protein levels in the aqueous humor occur. The axon reflex is responsible for the clinical signs of anterior uveitis observed with painful corneal conditions. These results appear to be mediated by prostaglandins, histamine, acetylcholine, and possibly substance P. Other clinical signs seen commonly with corneal ulceration include epiphora, photophobia, and corneal edema, causing a change in transparency. IT IS IMPORTANT TO REMEMBER THAT UVEITIS ALWAYS EXISTS WITH CORNEAL ULCERATION.

B. DIAGNOSTICS

Culture and sensitivity should be performed routinely when an ulcer is infected or “complicated.” Not all small animal ulcers need to be cultured the first time you see the patient. However, if the corneal ulcer appears to be “melting” or if the ulcer has not responded to proper treatment, these ulcers should be cultured. Schirmer tear test and/or phenol red thread test should be performed on all canine patients presenting with corneal ulceration. A large percentage of dogs with dry eye with initially present with corneal ulceration. An eye with an ulcerated cornea should have excessively high tear production resulting in epiphora. If the Schirmer tear test value is in the normal range or similar to the normal fellow eye, then KCS should be suspected.

Cytology can be performed using topical anesthetic. Remember to collect culture samples and perform Schirmer tear tests prior to applying topical anesthetic, as the anesthetics can interfere with interpretation of results.

ALL ulcers should be stained with fluorescein and sometimes with rose bengal. Fluorescein stain (which is hydrophilic) will adhere to exposed stroma, but will not stain epithelium or Descemet’s membrane. Rose bengal is used to evaluate mucin tear layer defects, and devitalized epithelium that is still attached but not healthy.

**PLEASE REMEMBER THE FOLLOWING**

1. CORNEAL ULCERS ARE FREQUENTLY NOT CLEARLY VISIBLE EVEN WITH PROPER EXAMINATION LIGHTING.

2. ALL RED OR PAINFUL EYES MUST BE STAINED WITH FLUORESCIN.

3. TOPICAL CORTICOSTEROIDS AND TOPICAL ANESTHETICS ARE CONTRAINDICATED WHEN THE CORNEA RETAINS FLUORESCIN STAIN.

IV. TREATMENT of Corneal Ulcers
There are multiple steps in the treatment of a corneal ulcer. **The deeper the ulcer, the more aggressive is the medical and likelihood of surgical therapy.** The first step is to determine the etiology, and remove or eliminate the specific cause. This means evaluating the eyelids and eyelashes, tear production, corneal culture, and corneal cytology.

Broad-spectrum **antibiotics** are usually administered; culture and sensitivity tests can guide selection in recurring, non-healing, or infected ulcers.

Prevention of collagen breakdown and ulcer progression are also important steps. Collagenases and proteases are derived from leukocytes in the tears and can be powerful in the destruction of corneal stroma. There are several drugs that can be used to help inhibit protease activity:

**AUTOLOGOUS SERUM and/or 0.05% EDTA.**

Serum contains an alpha-2 macroglobulin with anticollegenase activity. Blood is drawn from the patient or an animal of the same species, spun down, and serum drawn off and stored in the refrigerator in a dropper bottle or serum tube for up to 14 days. It should not be stored at room temperature, but the dose about to be given can be warmed to room temp immediately before administration. Serum is non-toxic, and should be used as many times a day as possible.

EDTA (0.17%) can be given several times a day as well.

**Acetylcysteine (5-10%)** is used topically for its collagenase and protease inhibiting properties. Acetylcysteine is unstable at room temperature, so the solution must be kept refrigerated. Frequency of treatment is decreased from every 1 to 2 hours for the first few days to 3 or 4 times daily for the next 7-10 days.

Treatment of accompanying anterior uveitis is also important with corneal ulceration. Topical 1% **atropine** is usually instituted to relieve ciliary spasm and pain (**CYCLOPLEGIA**) due to secondary anterior uveitis, and to decrease the formation of synechiae from the miotic pupil (as a result of uveitis). Be careful as it can cause a temporary KCS in small animal patients.

**Topical NSAIDs** can be used to treat ulcer induced uveitis in some cases.

In the treatment of deep corneal ulceration or descemetocles, provision of corneal support is important. Coverage with one of the various kinds of conjunctival flaps should be maintained for 10-21 days. Types of conjunctival flaps include: 360 degree, hood, island, pedicle, and bridge.

**V. REFRACTORY SUPERFICIAL CORNEAL EROSION**

A. Synonyms include Boxer ulcer, indolent ulcer, persistent ulcer, rodent ulcer, refractory epithelial erosion, recurrent corneal erosion syndrome. Middle to old age groups are most commonly affected, and there may be an increased incidence in females. Breed predilection has been demonstrated in the Boxer, Corgi, Pekingese, and Lhasa Apso, but refractory ulcers have been documented in more than 24 breeds of dog. History, signalment, and ophthalmic findings are all important in the diagnosis of refractory corneal ulceration.

**B. PATHOGENESIS**
Refractory corneal ulcers in the dog are usually primary. However, they can also be seen secondary to eyelash or eyelid abnormalities, corneal edema, infection, or tear film abnormalities. It is important to rule out conditions that can secondarily cause indolent ulceration in order to successfully treat the syndrome.

The specific pathogenesis of refractory ulcers is still not known. Normally the corneal epithelium attaches to the underlying stroma via hemidesmosomes in the basal epithelial cell membrane. Some animals with refractory corneal ulcers have been shown to have fewer hemidesmosomes as well as abnormalities in the epithelial basement membrane. Histologically, there are focal areas of epithelial separation with splitting of the basement membrane, and edema (in and between the basal cells) with accumulation of a basement membrane-like material.

C. CLINICAL SIGNS

Variable pain (manifested by tearing, blepharospasm, photophobia) is present, and there is no history of traumatic injury. On ophthalmic examination, a superficial corneal ulceration with an overlying lip of unattached epithelium around the edge of the erosion is evident. The use of fluorescein staining will illustrate the ulcer bed as well as reveal the degree of unattached epithelium as the underlying stroma will take up stain.

D. DIFFERENTIAL DIAGNOSES CAUSES for persistent ulcer: KCS, ectopic cilia, foreign bodies, entropion, infection

E. TREATMENT

1. DEBRIDEMENT of unattached and loosely attached epithelium is essential. Topical anesthetic and dry cotton-tipped applicator are used to remove abnormal epithelium.

Superficial grid keratotomy (GK) or multiple punctate keratotomy (MPK) have revolutionized the treatment of indolent ulcers. Animals require only topical anesthesia, or rarely light sedation. A 20 gauge needle is used to make cross hatches (“tic tac toe”) through the ulcer bed with the scratches approximately 1-2 mm apart into adjacent normal epithelium and stroma (GK) or multiple punctures into the anterior stroma (MPK) and adjacent 1-2 mm of epithelium. Both techniques have been shown to increase the healing rate of refractory ulcers. Superficial keratectomy has been shown to be very effective, especially in terms of decreasing recurrences. This requires more specialized equipment and magnification.

Chemical removal of the epithelium can also be accomplished with dilute topical povidone iodine or phenol.

2. Refractory ulcers are treated medically following debridement and possible keratotomy with the some or all of the following mechanisms. Topical broad spectrum antibiotic solutions (triple antibiotic or chloramphenicol; do not use gentamicin!!) 2-4 times per day; topical cycloplegic (1% atropine) as needed; topical hyperosmotic agent (2-5% NaCl solution) to decrease edema; bandage soft contact lens or collagen shields; Elizabethan collar to prevent self trauma; 0.2% sodium hyaluronate may also be beneficial topically [Adequan (100 mg/ml) for topical use: 50 mg/ml in polyvinyl alcohol artificial tears TID (Tears Naturale)]; and the growth factor in serum may be beneficial in persistent erosions.

VI. CORNEAL LACERATIONS

The management depends on the depth of laceration. All should be stained with fluorescein to help assess the depth and affected area of the laceration. Superficial lacerations are treated as “simple” ulcers (topical antibiotics and atropine). Deep, non-perforating lacerations are treated more aggressively. Topical broad spectrum antibiotics and 1% atropine are used. If the laceration is judged to be less than ½ thickness, treat as simple ulcer; if more than ½ thickness, suture cornea and place conjunctival flap.
**Perforating (full thickness) lacerations** are emergencies. Animals require systemic antibiotics, general anesthesia and surgical repair of cornea; topical antibiotic solution (not ointment), topical atropine solution, and surgical repair. This entails repositioning or amputating protruding iris, reforming the anterior chamber with Lactated Ringers, and suturing the corneal with #7-0 or #8-0 absorbable suture material. A conjunctival flap is also placed if needed.

If **iris prolapse** has occurred more than 2-6 hours earlier, and the iris appears nonviable, it should be amputated using cautery. The cornea should then be sutured as above.

**VII. MYCOTIC KERATITIS**

Mycotic keratitis with or without ulceration occurs most frequently in horses, especially after injury with objects of vegetable origin, but does also occur in dogs. The infection is frequently longstanding, is often associated with bacterial contamination, and is resistant to treatment with antibiotics. *Aspergillus* sp, *Fusarium* sp, *Mucor* sp and *Candida albicans* are frequently isolated.

**A. CLINICAL SIGNS**

Long-standing antibiotic resistant keratitis; focal cloudy opacities at the advancing edge of the lesion; corneal ulceration or abscessation with uveitis; striate opacities in the corneal stroma adjacent to the main lesion which may be edematous and opaque. The lesion is usually black in color in dogs. Nonspecific signs of corneal disorder are also apparent: blepharospasm, conjunctival and ciliary injection, photophobia, epiphora, and neovascularization.

**B. DIAGNOSIS**

Diagnosis is based on: clinical signs, history of topical antibiotic or steroid use, culture of corneal scrapings on Sabouraud's agar without inhibitors (as the majority of the fungi are saprophytes that do not grow in the presence of inhibitors), cytology (repeat scrapings may be necessary), and histopathologic examination of corneal tissues.

**C. TREATMENT**

Superficial keratectomy of the lesion and surrounding stromal opacities which may contain fungi; frequent topical treatment with the antifungal drug of choice (natamycin, amphotericin B, miconazole), topical antibiotics, atropine and systemic nonsteroidal anti-inflammatory drugs. These lesions can take several months to heal, and most will probably need conjunctival flap surgery.

**VIII. NEUROTROPHIC KERATITIS**

This is a chronic keratopathy resulting from damage to the sensory (trigeminal) innervation of the cornea. It occurs in all species of animals, but is more common in dogs and cats, especially following orbital trauma. Sensory denervation of the cornea leads to epithelial degeneration and stromal edema.

Treatment: Tarsorrhaphy to prevent trauma and desiccation. If there is no response in 2 to 3 weeks, tarsorrhaphy for up to 6 months may be utilized. Topical antibiotic therapy is used to prevent secondary bacterial infection. Response to treatment may be poor, and permanent tarsorrhaphy may be necessary.

**IX. NEUROPARALYTIC KERATITIS**

Neuroparalytic keratitis is seen clinically with facial nerve (CN VII) paralysis in which animals cannot
blink. This may lead to severe keratitis and ulceration due to inadequate tear film spreading, and may result in loss of vision or the eye. In the early stages, epithelial degeneration and stromal edema occur, but advanced lesions result in desiccation, corneal vascularization, and opacification. Ulceration may progress to perforation. Cats may tolerate some corneal exposure better than dogs. This condition may be idiopathic in American Cocker Spaniels, associated with ear trauma and otitis. Treatments - tarsorrhaphy; provide moisture to the cornea.

XI. BULLOUS KERATOPATHY

Chronic corneal edema leads to formation of small vesicles in the corneal epithelium that coalesce into larger bullae which may rupture, causing loss of epithelium and corneal ulceration.

Differential diagnosis - descemetocele, corneal foreign body, iris prolapse, corneal epithelial inclusion cyst, corneal endothelial dystrophy.

Treatment: Remove underlying cause; support cornea (nictitans flap and/or possibly a tarsorrhaphy prior to bullae rupturing); topical antibiotic and atropine 1%; topical hypertonic NaCl ointment or solution; corneal transplantation. In severe cases scar formation may be extensive.

SURGICAL PROCEDURES FOR TREATMENT OF CORNEAL INJURIES

Principles of corneal microsurgery

The corneal endothelium is very sensitive to mechanical trauma. It should never be touched with surgical instruments or flushed vigorously. When manipulating or holding corneal tissue, only the stroma and epithelium should be held with the corneal forceps.

Edges of corneal wounds are not debrided.

In iris prolapses, an attempt is made to replace protruding iris. If the tissue is damaged or necrotic, the protruding iris is excised with electrocautery. Hemorrhage is often severe if the major arterial circle of the iris near the root is transected.

Blood and fibrin clots in the anterior chamber are carefully removed by lavage, left alone, or TPA is used to remove it.

Partial thickness sutures (1/2 to 3/4 depth) are used in the cornea; full thickness penetrating sutures are never used.

The cornea is sutured with simple interrupted pattern (1 mm apart); 5-0 to 7-0 suture is best.

After wound closure is completed and the anterior chamber reformed with lactated ringer's solution (LRS) or a small air bubble. The air bubble helps maintain the anterior chamber and prevents the migration of fibrin.
Laceration issues

Whenever there is a penetrating corneal wound, great care must be taken to prevent pressure being placed on the globe to avoid the risk of further intraocular damage.

If specialist assistance is not available, a careful examination should be made to evaluate the extent of intraocular injuries. One of the most common causes for severe endophthalmitis and secondary glaucoma leading to enucleation in dogs is unsuspected damage to the lens and its capsule during a perforating corneal injury. If no other intraocular damage is evident, the corneal wound may be sutured.

Removal of corneal foreign bodies

Corneal foreign bodies are removed in order to limit pain, reduce the potential for infection, and prevent vascularization and scar formation. Small foreign bodies are removed with irrigation or a needle-shaped instrument. After removal of the foreign body, a broad-spectrum topical antibiotic and atropine are administered to limit infection and control pain due to secondary uveitis. Local anesthetics should not be used in the postoperative care, as they retard epithelial healing. Clumsy attempts to remove a corneal foreign body may result in penetration of the anterior chamber or in corneal damage resulting in severe vascularization and scar formation.

Intraocular Foreign Bodies

Gunshot fragments are usually left in globe. Attempt removal of plant material or porcupine quills.

Superficial Keratectomy - excision of a portion of the corneal epithelium and stroma.

Superficial keratectomy may be partial or total. Dissection is performed under magnification with a #64 Beaver, #15 Bard-Parker blade, or a Martinez corneal dissector. Postoperative topical antibiotics and atropine are used frequently, and the cornea is evaluated (daily) with fluorescein for reepithelialization.

Keratoplasty is the surgical transplantation of corneal tissue. There are two types of keratoplasties: lamellar (partial thickness) and penetrating (full thickness).

1. Corneoscleral transposition-lamellar type for feline corneal sequestration.

2. Penetrating keratoplasty: Because of the "privileged" immunological site of the cornea, corneal transplants have a better survival rate than do transplants in other parts of the body. Successful results can be achieved in dogs, cats, and horses. Meticulous surgical technique and postoperative care are needed for success.

Conjunctival Pedicle Flap

Conjunctiva (excluding Tenon's capsule) makes an ideal covering for deep or slow-healing corneal lesions (eg. deep ulcerative keratitis, mycotic keratitis). With the exception of cases of mycotic keratitis, flaps are infrequently used in the presence of active or uncontrolled infection.

Conjunctival flaps have the following advantages:

1. Structural support to corneal lesions;

2. Provide blood vessels for the vascular phase of corneal stromal healing;

3. Provide a source of fibroblasts and connective tissue;

4. Provide more support than does a nictitans flap;

5. May inhibit collagenase as plasma from the leaking vessels of the flap leaks directly onto the wound.
Treatment of Descemetoceles

Descemetocele is the exposure of Descemet's membrane through a near full thickness defect in the corneal epithelium and stroma. The membrane may or may not protrude through the defect. Due to the risk of rupture, a descemetocele is surgically repaired as soon as possible. The etiology of the corneal lesion is treated. Treatment may be summarized as follows:

1. **Careful** debridement of infected or severely damaged ulcer margins.

2. Direct suture closure of the defect if the defect is small (2-3 mm diameter). As the edges are often edematous, horizontal mattress sutures may be necessary. If direct closure is not possible, several alternatives are available. This is not recommended for large descemetoceles.

   a. Insertion of donor corneal button into the defect to add support. The lesion will eventually vascularize and the button will be rejected, but the cornea can often be saved.

   b. Use of a conjunctival flap to both support the lesion and aid in vascularization. Of the numerous kinds available, a 360° flap is the easiest to perform for the occasional operator. A conjunctival pedicle flap provides better vision capabilities for the animal. Further support can be given with a temporary tarsorrhaphy or on occasion with a nictitans flap. Therapy with topical antibiotics and atropine is used postoperatively.