Corneal Ulcers in Horses

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Abstract: Corneal ulceration is commonly diagnosed by equine veterinarians. A complete ophthalmic examination as well as fluorescein staining, corneal cytology, and corneal bacterial (aerobic) and fungal culture and sensitivity testing are necessary for all infected corneal ulcers. Appropriate topical antibiotics, topical atropine, and systemic NSAIDs are indicated for all corneal ulcers. If keratomalacia (melting) is observed, anticollagenase/antiprotease therapy, such as autologous serum, is indicated. If fungal infection is suspected, antifungal therapy is a necessity. Subpalpebral lavage systems allow convenient, frequent, and potentially long-term therapy. Referral corneal surgeries provide additional therapeutic options when the globe’s integrity is threatened or when improvement has not been detected after appropriate therapy.

Corneal ulcers are commonly seen in equine practice because of the prominence of the equine ocular globe and its risk for traumatic injury. Over the past 10 years in our veterinary teaching hospital, corneal diseases/conditions have accounted for 50% of equine ophthalmology cases, most of which (75%) involved corneal ulcers. Other referral hospitals have observed that 24% to 76% of all ophthalmic evaluations involve ulcerative keratitis.1–3 Because of the high prevalence of corneal ulcers in referral centers, equine practitioners are likely to regularly encounter corneal ulcerations and need to formulate a diagnostic and therapeutic strategy for their patients.

Anatomy
The equine cornea is a highly innervated, nonvascular, simple structure that is 0.8 to 1.0 mm thick (FIGURE 1). It protrudes beyond the bony orbit of the skull, where it is protected only by the eyelid. The normal equine tear film contains corneal nutritional elements, mostly gram-positive bacteria, and, occasionally, fungal organisms (TABLE 1). The corneal epithelium repels tears and keeps organisms from entering deeper layers. The stromal layer, which is approximately 90% of the corneal thickness, has few cells (keratocytes) and is mainly composed of water, with the remaining portion made of collagen fibrils, glycosaminoglycans, and glycoproteins.4 The Descemet membrane is a basement membrane that is resistant to penetration by bacteria, but not fungal organisms.2 The corneal endothelium, a single layer of hexagonal cells, forms a semi-occlusive barrier that allows careful regulation of water and nutrients from the aqueous into the cornea.6 Corneal innervation is through cranial nerve V, and nerve endings are located in the anterior stroma and basement membrane of the corneal epithelium.6 For this reason, a superficial corneal ulceration is more painful than a descemetocele.

Corneal Healing
The vast majority of equine corneal ulcers are secondary to trauma, which may begin as a micropuncture implanted with normal or...
Table 1. The Microbial Populations Most Commonly Isolated From Equine Corneas

<table>
<thead>
<tr>
<th>Microbial Population</th>
<th>Healthy Equine Eyes&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Equine Eyes With Corneal Ulceration&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Bacterial</td>
<td>Streptomyces spp, Staphylococcus spp, Bacillus spp, Streptococcus spp, Moraxella spp, Corynebacterium spp, Escherichia coli, Acinetobacter spp, Enterobacter spp</td>
<td>Streptococcus equi zooepidemicus, Staphylococcus spp, Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Fungal</td>
<td>Aspergillus spp, Cladosporium spp, Chrysosporium spp</td>
<td>Aspergillus spp, Fusarium spp</td>
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pathogenic bacteria or fungal organisms from the tear film. Corneal healing of epithelial defects has been shown to be most rapid during the first 5 to 7 days, followed by slower epithelialization.7 This difference has been attributed to exhaustion of surrounding epithelial cells or changes in the underlying corneal stroma.7 Corneal ulcerations may take several days to heal: one study reported that healing of a 7-mm, midstromal epithelial defect proceeded at 0.6 mm/d.7 The corneal epithelium may take 6 weeks to adhere to the underlying stroma after injury; therefore, an equine cornea remains fragile and may re-ulcerate during this period. After stromal injury, keratocytes become fibroblasts, proliferate, and synthesize collagen; however, after severe loss of stroma, it may take several weeks to rebuild, or a corneal facet (divot) may develop as successful reepithelialization arrests proliferation. Delayed healing is seen with infected corneal ulcers due to the infiltration of polymorphonuclear (PMN) leukocytes, cell death, and delayed reepithelialization. Keratomalacia (corneal “melting”) occurs when the proteolytic activity of enzymes arising from the tear film, dying corneal cells, PMN leukocytes, and infectious organisms becomes upgraded beyond the normal balance.7 Extensive corneal scarring may ensue due to severe stromal damage secondary to infection. Therefore, it is imperative to rapidly diagnose the condition and institute appropriate therapy to maximize corneal transparency and minimize tissue loss.

Clinical Signs

Due to the rich innervation of the cornea, many clinical signs that alert horse owners to an ulcer are nonspecific signs of ocular pain. Enophthalmos, blepharospasm, epiphora, photophobia, and miosis are the most common clinical signs in horses with corneal ulcers. Corneal edema, which appears as a bluish hue in the cornea, may also be noted in association with ulceration. Corneal neovascularization can be used as a marker of time, as blood vessels take approximately 4 days to bud at the limbus and grow ≤1 mm/d toward the ulcer. Keratomalacia has a gelatinous appearance, especially at the ulcer’s leading edge, due to (1) degradation of stromal collagen fibers from cytokines released from pathogenic organisms and (2) cell death.

All corneal ulcerations are accompanied by clinical signs of anterior uveitis, including one or more of the following: miosis, aqueous flare, keratitic precipitates, hypopyon, hyphema, and/or intraocular fibrin. Low intraocular pressure (<15 mm Hg) is a common examination finding; however, if uveitis is severe, high intraocular pressures (>25 mm Hg) can also be detected due to the presence of secondary glaucoma. While examining an ulcerated eye, the attending veterinarian must remember that the greater the severity of corneal disease, the more pronounced anterior uveitis will be.

Corneal ulcers are often classified to aid in description, diagnosis, and treatment. A simple classification scheme categorizes ulcers as (1) simple, (2) recurrent (refractory), or (3) complex. Simple ulcers are acute and superficial, involving the corneal epithelium and possibly up to one-third of the anterior stroma (FIGURE 2). To the naked eye, these ulcers may not be noticeable, but they take up fluorescein stain. Corneal edema is generally absent to mild, and neovascularization is not present. Although simple ulcers are probably contaminated with microorganisms, deep infection has not yet occurred.10

Recurrent or refractory ulcers are often described as indolent. These superficial ulcers persist because the corneal epithelium is unable to adhere to the underlying stroma (FIGURE 3). Indolent ulcers stain similarly to simple ulcers; however, staining can be observed underneath the periphery of the corneal epithelium, indicating detachment from the underlying stroma. Furthermore, the edges

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**Figure 2.** A horse with a simple corneal ulcer. This superficial ulcer could not be readily seen without application of fluorescein stain.
of these ulcers can be easily debrided to reveal a significantly larger corneal defect. In these cases, the presence of corneal edema and neovascularization is variable. Although no obvious cause can be found in most cases, microbial infection of the superficial layers of exposed stroma, abnormalities of tear production, or primary epithelial failure may be responsible. As continuous mechanical disruption of the corneal epithelium can also be associated with indolent ulcers, a thorough examination of the eyelids, conjunctival fornix, and third eyelid should be performed.

Complex corneal ulcers include a wide variety of ulcerations in which deep layers of stroma are involved and infection (bacterial and/or fungal) is well established (FIGURE 4; FIGURE 5; FIGURE 6). Corneal edema may be moderate to severe, depending on the severity of the ulceration. Corneal neovascularization is not present at the time of initial injury but often develops due to various corneal angiogenic agents, such as PMN leukocytes. As disease progresses, microorganisms migrate into the deeper stromal layers by secreting collagenolytic enzymes such as matrix metalloproteinases, elastase, and alkaline protease. These enzymes may lead to a “melting” appearance of some corneal ulcers. Significant corneal destruction and, possibly, perforation will likely result if the caustic process is not halted through medical therapy or surgical intervention.

Corneal lacerations have a variable prognosis, depending on the depth and length of the laceration, involvement of other intraocular structures, and the degree of inflammation. Lacerations that are longer than 15 mm, cross the limbus, or involve keratomalacia and/or hyphema are generally associated with a poor prognosis for salvaging the vision of the affected eye.

Figure 3. A horse with a chronic (indolent) corneal ulcer. This superficial ulcer has been present for more than 30 days after the initial trauma that caused it. The margins of the true ulcer extend beyond the edges; this is demonstrated by the fluorescein stain extending past the visible edges of the ulcer. Courtesy of Christine Lim, DVM, DACVO; University of Minnesota.

Figure 4. A horse with a complex corneal ulcer infected with Streptococcus equi zooepidemicus. A plaque-like lesion is found at the center of a midstromal depression. Extensive conjunctivitis is present.

Figure 5. A horse with a melting corneal ulcer infected with mixed bacteria. Histopathology revealed severe, chronic ulcerative and suppurative keratitis and keratomalacia with intralesional bacteria and mild anterior uveitis.

Figure 6. A horse with a deep corneal ulcer that almost reaches the Descemet membrane. Aggressive medical therapy was administered for 24 hours before placement of a conjunctival graft.
negative prognosticators include chronic wounds, iris prolapse, lens capsule rupture, and lens luxation.\textsuperscript{14}

**Diagnosis**

Diagnosis of a corneal ulcer should always be accompanied by a complete ophthalmic examination. Intravenous sedation (xylazine, 0.25 to 0.5 mg/kg; romifidine, 20 to 40 µg/kg; detomidine, 5 to 10 µg/kg) in combination with butorphanol (10 to 20 µg/kg) and an auriculopalpebral nerve block (2 to 3 mL of 2\% lidocaine via a 25-gauge needle inserted at the level of the zygomatic arch) should be performed before examination of a painful eye (\textbf{FIGURE 7}). Additionally, a frontal nerve block can be performed at the level of the supraorbital foramen for supplementary analgesia (\textbf{FIGURE 8}). Manual restraint and forced opening of the eyelids is contraindicated due to the potential for converting a deep corneal ulcer into a perforating ulcer.

Ocular examination should be performed in a dark room with a focal bright light to compensate for the reflective quality of the cornea. The eyelids, especially the margins, should be examined with magnification to ensure that no defects are contributing to the corneal ulcer. Incomplete or weak palpebral reflexes should be documented because they can impair corneal healing due to improper distribution and the washing effect of the tear film. The cornea should be closely evaluated from several angles for clarity, luster, and defects. If the cornea appears dull, a Schirmer tear test is warranted to detect keratoconjunctivitis sicca (KCS). Schirmer tear test results of 15 mm/min or less with accompanying clinical signs (conjunctivitis, superficial corneal blood vessels, and/or mild corneal edema) are suggestive of a tear production disorder.\textsuperscript{15} If a low Schirmer tear test result is detected, it is recommended to recheck tear production after resolution of the corneal ulcer in order to confirm a diagnosis of KCS. Although KCS is very uncommon in horses, it may be a significant contributing factor in indolent ulcers. Corneal neovascularization can help establish a timeline from injury to examination: budding of blood vessels at the limbus takes approximately 4 days, and blood vessels migrate toward the corneal ulcer at a maximum rate of 1 mm/d. Although indolent ulcers may initially appear similar to simple ulcers, gentle debridement with a cotton applicator after application of topical anesthesia can reveal a significantly larger superficial corneal defect (double or triple the size of the ulcer's original visible area); simple ulcers will reveal minimal corneal epithelial debridement (1 to 2 mm).

Corneal cytology in addition to corneal aerobic bacterial and fungal culture and sensitivity testing should be performed on all chronic (indolent) and complex corneal ulcers. If possible, these samples should be taken before corneal staining. Before sending the samples, it is recommended to contact the testing laboratory to select for sensitivities of commercially available topical ophthalmic antimicrobial solutions; by doing so, the veterinarian will have a more tailored list of readily available medications. After topical anesthesia, corneal cytology samples are obtained using a small cytobrush, a Kimura spatula, or the blunt end of a scalpel blade.\textsuperscript{16} Cytology is easy, quick, and inexpensive and can be helpful in determining the type of bacteria (i.e., rods versus cocci) or whether fungal organisms are present (\textbf{TABLE 1}). Cytology slides can be stained with Diff-Quik or gram stains.

Eyes that appear painful should be stained to further evaluate the corneal surface; however, if a deep corneal ulcer is detected, staining should not be performed because manipulation of the eye could worsen the condition. Fluorescein and rose bengal
stains are commonly used. Uptake of fluorescein suggests the presence of a full-thickness defect in the corneal epithelium, as the stain is easily absorbed by exposed stroma. As a secondary stain, rose bengal is useful for evaluating partial-thickness epithelial defects or tear film deficiencies. The stain is best evaluated using a bright white light in dim lighting. Viral keratitis and early fungal keratitis may be more easily diagnosed using rose bengal stain.17 Although specific applications exist, rose bengal staining should not be routinely performed due to the potential for irritation and toxicity to the corneal epithelium.18

Treatment
Treatment of all corneal ulcers includes medical therapy, with appropriate surgical intervention when needed. Physical protection (i.e., fly mask, cup mask) is often needed to allow optimal healing. Placement of a subpalpebral lavage system is frequently necessary to allow repeated, practical, and potentially long-term therapy. Although reevaluation of a corneal ulcer is at the discretion of each equine practitioner, the general recommendations are to reevaluate simple ulcers within 3 to 5 days, indolent ulcers within 5 to 7 days, and complex ulcers within 24 to 48 hours. If the patient is hospitalized due to a severe corneal ulcer, frequent administration of medication, and/or management decisions (e.g., inability to medicate the patient), the affected eye should be reevaluated every day. Corneal ulcers should be reevaluated any time they worsen (i.e., become deeper or larger and/or mucopurulent discharge does not subside or recurs during therapy), anterior uveitis is not well controlled (i.e., ocular pain worsens, as indicated by an increase in blepharospasm, tearing, or enophthalmia), or owner or patient compliance is problematic. The attending veterinarian should recommend a same-day recheck if the owner notices an increase in blinking and tearing or that the eye becomes more sunken and more painful to treat, the ocular discharge becomes yellow green, or the appearance of the corneal defect changes.

Medical Therapy
The goals of medical therapy for superficial corneal ulcers include reducing contamination and preventing bacterial colonization of the exposed corneal stroma until reepithelialization has occurred. For all types of ulcers, topical antibiotic therapy should be continued until fluorescein stain uptake is negative.

Initial empirical therapy for simple ulcers includes application of a broad-spectrum antibiotic (bacitracin-neomycin-polymyxin B ophthalmic ointment) four times daily. Antibiotics such as gentamicin and ciprofloxacin are usually not warranted in these cases.

For indolent ulcers, correction of eyelid, conjunctival, or third eyelid anomalies is recommended, followed by superficial debridement with dry cotton swabs and keratotomy (described below). Topical antibiotic therapy should be selected based on cytology and culture results, if available; otherwise, indolent ulcers can be treated in the same manner as simple ulcers.

The main goals of treating complex ulcers include administering aggressive antimicrobial therapy, halting keratomalacia (if present), and treating uveitis. Using a combination of topical antibiotics, such as alternating between cefazolin (intravenous powder mixed with artificial tears as a 55-mg/mL solution)19 and an aminoglycoside (i.e., ophthalmic solution or an ointment preparation of gentamicin or tobramycin) every other hour, or using a fluoroquinolone (i.e., ophthalmic solution of ofloxacin or an ointment preparation of ciprofloxacin) can increase the spectrum of antimicrobial activity until culture and sensitivity results are known.1 The frequency of application can vary from every 2 to 4 hours7,20 for a severely affected ulcer to every 6 hours.

It is not uncommon to have a mixed bacterial and fungal corneal infection. Presence of fungal hyphae on cytology or positive growth on culture necessitates antifungal therapy. Antifungal therapy should also be considered if the ulcer appears to be unresponsive to antibiotic therapy; the presence of fungus may be difficult to ascertain due to the corneal depth that the organism can reach (i.e., Descemet membrane). Common topical antifungals include 5% natamycin,21 1% miconazole,22 1% itraconazole in 30% dimethyl sulfoxide,23 and 1% voriconazole.24 Sensitivity of fungal organisms may vary dramatically by geographic region, and knowledge of regionally effective antifungals is important in drug selection. As it is quite common for accompanying anterior uveitis to worsen after the start of antifungal therapy, the recommended frequency of initial administration is every 6 hours. The maintenance application of topical antifungals is four to six times daily for a minimum of 2 to 4 weeks; for deep infections, this may need to be extended to 6 to 8 weeks.

Treating keratomalacia is crucial to preventing further loss of corneal tissue. Studies have reported that elevated proteinase levels have been observed in the tear film of eyes with corneal ulcers,5,25 and are associated with increased incidence of keratomalacia.4 Autologous serum, 0.2% EDTA, 0.1% doxycycline, and 10% N-acetylcysteine have been shown to significantly reduce proteinase levels within equine tear film.5,25 Antiproteinase therapy has given the clinical impression of slowing or stopping keratomalacia and providing a healthier cornea for surgical grafts.5 Therefore, application of autologous serum every 2 to 4 hours is recommended in all cases with keratomalacia and is continued until the cornea appears firm or the ulcer is reepithelialized.

As anterior uveitis accompanies all corneal ulcers, treatment with topical atropine and systemic NSAIDs is required. Treating the affected eye with 1% atropine twice daily significantly increases a
horse's comfort by decreasing ciliary body spasm associated with uveitis. Atropine is also speculated to help stabilize the compromised blood-aqueous barrier associated with uveitis. Atropine administration can be used as needed once pupillary dilation has occurred. Care should be taken to monitor gastrointestinal motility in patients treated with atropine, as decreased gastrointestinal motility has been reported. Oral or intravenous NSAID therapy (i.e., flunixin meglumine [1 mg/kg q12–24h IV or PO], phenylbutazone [2 mg/kg q12–24h PO]) can also be given to address signs of ocular pain. Flunixin meglumine is preferred in cases of moderate to severe uveitis. Close attention should be paid to horses treated with a systemic NSAID, as early signs of impaction colic may be missed. Long-term therapy (>7 days) with systemic NSAIDs should be monitored because renal toxicity and gastric ulceration are possible; however, if the patient continues to eat and drink normally, systemic NSAIDs can be administered long-term if anterior uveitis persists. Topical or systemic corticosteroids should be avoided due to their immunosuppressive effects. Topical NSAIDs should not be used because their use has been linked to delayed epithelial healing.

**Surgical Therapy**

**Corneal Debridement and Keratotomy for Chronic (Indolent) Ulcers**

Intravenous sedation, auriculopalpebral and frontal nerve blocks, and topical anesthesia are administered before corneal debridement and keratotomy for chronic (indolent) ulcers. The cornea is superficially debrided with dry, sterile cotton swabs, and the ulcer bed is significantly enlarged. A grid or punctate superficial keratotomy is then performed using a 25-gauge needle. The keratotomy exposes healthy corneal stroma by disrupting the overlying hyaline membrane, which prevents epithelial adherence. Corneal cytology and culture results should be known before this procedure, as proceeding with a grid keratotomy could implant bacterial or fungal organisms deeper into the corneal stroma. It is imperative that a deep or an infected ulcer not be treated with a grid keratotomy.

**Corneal Grafts**

A corneal ulcer that fails to respond to appropriate medical therapy and/or advances deeper than one-third of the thickness of the corneal stroma likely requires surgical therapy. Deep corneal ulcers and lacerations, descemetoceles, and corneal perforations should immediately be considered surgical cases. Surgical procedures are always associated with aggressive preoperative and postoperative medical therapy. Although corneal surgeries are generally limited to referral centers due to the technical expertise and specialized instruments required, knowledge of available surgical procedures is beneficial when referring clients. Conjunctival grafting, one of the most commonly performed surgeries for corneal ulcers, involves creation of a thin flap of highly vascular conjunctiva that is sutured over the freshly debrided corneal defect to provide a blood supply, fibroblasts, anticolagenases, and protection. Conjunctival grafting can offer excellent ocular survival in cases with corneal lacerations as well as bacterial and fungal corneal ulcers.

Corneal transplantation (keratoplasty) may be indicated for deep or perforating corneal ulcers, descemetoceles, and deep stromal abscesses. Although corneal transplantation generally does not result in transparency over the defect, it allows preservation of globe integrity and complete removal of diseased tissue. Partial-thickness (lamellar) or full-thickness (penetrating) keratoplasty has been reported to have an overall good success rate. Equine amnion and porcine small intestinal submucosa are commonly used as biologic bandages for covering freshly debrided corneal defects, or for additional support of corneal repairs. Equine amnion, which is harvested during cesarean section, can be prepared and frozen for later use in clinical cases. Equine amnion is well suited as a biologic bandage for the cornea due to its transparent and avascular nature and inherent properties. Porcine small intestinal submucosa has been reported to similarly aid successful repair of full-thickness corneal defects in horses. It can also be sutured between the cornea and a conjunctival graft to support penetrating keratoplasties. The major benefits of porcine intestinal submucosa are its commercial availability (BioSIS, Benson Medical, Markham, Ontario, Canada; ACell Vet Corneal Discs, Columbia, MD), shelf life, and ease of storage.

In cases in which surgical intervention is required but proximity or financial reasons prevent referral, enucleation of the diseased eye should be considered to prevent ongoing ocular pain. Euthanasia with the horse under general anesthesia or standing and sedated has been well described.

**Summary**

Corneal ulceration is the most common disease process affecting the equine eye and is often seen in general practice. Corneal cytology, in addition to bacterial and fungal culture and sensitivity testing, should be performed on chronic and complex ulcers. After diagnosis, frequent monitoring of an ulcer is indicated to ensure proper progression of healing. Aggressive medical therapy should be instituted, and referral for surgery should be considered if the ulcer fails to heal, shows signs of keratomalacia, is at significant
risk of perforation, or has already perforated. In cases in which aggressive medical and/or surgical therapy fails or referral is not possible, enucleation should be strongly considered.

References
1. Which of the following nerve blocks is most commonly used to examine a painful equine eye?
   a. an auriculopalpebral nerve block
   b. a modified Peterson nerve block
   c. an infraorbital nerve block
   d. a retrobulbar nerve block

2. Which tests have a direct therapeutic effect on infected corneal ulcers?
   a. the maze test and the pupillary light reflex test
   b. the Seidel and Jones tests
   c. corneal bacterial and fungal culture and sensitivity testing
   d. a conjunctival cytology and biopsy

3. Which of the following factors can have the greatest influence on initial antimicrobial selection for treating complicated corneal ulcers?
   a. geographic region
   b. corneal cytology
   c. breed of horse
   d. time of year

4. A superficial, uncomplicated corneal ulcer appears to be 9 mm in diameter. If no complications develop, complete reepithelialization would be anticipated after ___ days.
   a. 4
   b. 9
   c. 12
   d. 15

5. Which of the following is the most appropriate treatment for a superficial, uninfected corneal ulcer that has not healed after 6 weeks of appropriate antibiotic therapy?
   a. superficial debridement and grid keratotomy
   b. changing the antibiotic class and increasing the frequency of treatment to every 4 hours
   c. adding topical antifungal and corticosteroid therapy
   d. superficial keratectomy and amniotic membrane transplantation

6. A fluorescein-positive eye is being examined for the first time. Vascularization around the periphery of the cornea extends approximately 3 mm onto the surface of the cornea. How long has this ulcer been present?
   a. 3 days
   b. 7 days
   c. 14 days
   d. 20 days

7. Which of the following is considered an important therapeutic agent if signs of corneal melting are present?
   a. topical prednisolone acetate 1%
   b. bacitracin-neomycin–polymyxin B ointment
   c. autologous serum
   d. topical 0.1% diclofenac

8. After a diagnosis of corneal laceration, which of the following clinical signs is a negative prognosticator for ocular globe retention?
   a. miosis
   b. aqueous flare
   c. blepharospasm
   d. iris protrusion

9. Which of the following is not a sign of anterior uveitis?
   a. hypopyon
   b. low intraocular pressure
   c. lens luxation
   d. miosis

10. Cytology of a 3-mm diameter, moderately deep corneal ulcer reveals fungal hyphae. Which topical medication would be most appropriate to administer as part of a treatment plan?
    a. natamycin
    b. tropicamide
    c. tobramycin
    d. dexamethasone