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## Ulcerative Keratitis in the Horse

By Lynne Sandmeyer, DVM, DVSc, Diplomate ACVO

**Corneal ulceration is one of the most common ocular diseases in the horse. Equine corneal ulceration has the potential to threaten vision and, as a result, requires early clinical detection, appropriate classification, and rapid initiation of therapy. This issue of *Large Animal Veterinary Rounds* discusses the diagnosis and therapeutic principles for equine corneal ulcers.**

### Ulcerative keratitis

The equine cornea is predisposed to corneal ulceration because of its large size and propensity for trauma. Trauma may occur from environmental hazards such as tree branches, feed material, hardware, as well as dirt or stones kicked-up into the eye during races. The horses' environment is such that there is constant exposure to bacteria and fungi. Normal conjunctival flora varies, depending on the season and geographic region,<sup>1-3</sup> and many bacteria and fungi that constitute normal flora can become potential pathogens. Usually, the epithelium is a strong barrier against pathogens, but a defect in the epithelium may allow bacteria and fungi to adhere to the cornea and initiate infection. The development of infection should be a concern in every equine ulcer, no matter how minor the initial appearance.

### Diagnostic techniques in corneal ulceration

A complete ophthalmic examination is necessary to diagnose any ophthalmic disease. A more detailed review of ophthalmic examination techniques is outlined in *Ophthalmic Disease in Veterinary Medicine* by Charles L. Martin.<sup>4</sup>

The ophthalmic examination must be performed in a consistent and systematic manner and both eyes should be examined in all cases. A safe and thorough ocular examination usually requires sedation. Xylazine, at a dose of 0.5 -1.1 mg/kg intravenously (iv), will sedate the animal and lower the head, facilitating access to the eye. Blockade of the auriculopalpebral nerve, a branch of the facial nerve (cranial nerve VII), aids the examination, especially when blepharospasm is present. The ophthalmic examination should consist of a neuro-ophthalmic examination (menace response, palpebral reflexes, and direct and consensual pupillary light reflexes), ocular diagnostic tests (Schirmer tear test, fluorescein staining, and intraocular pressure measurement, if the equipment is available), followed by a detailed examination of all ocular structures. A darkened room is best for intraocular examination and dilation of the pupils with 1% tropicamide will facilitate examination of the lens and posterior segment.

When ulcerative keratitis is present, special attention should be paid to investigating the underlying causes, as well as the severity of disease. Inspect the periocular area for evidence of trauma and evaluate the eyelids for conditions that may contribute to corneal ulceration, such as impaired motion (eg, facial nerve paralysis), irregularities in the lid margins, or aberrant hairs. The conjunctiva and third eyelid should be inspected for foreign bodies. Note the location, size, and approximate depth of the corneal lesion. The presence of infiltrates within the defect and the extent of corneal edema and vascularization should be evaluated. Examine the anterior chamber for the presence of exudates (eg, aqueous flare, fibrin, hypopyon, or hyphema) and note the size of the pupil and its reactivity to light as compared to the contralateral eye.

Corneal culture and scrapings for cytology are necessary in complex ulcers (see below) and in any ulcer not responding to therapy. Corneal cultures are obtained by rubbing the swab along the edges and base of the ulcer while avoiding contamination from adjacent structures (eg, eyelids and conjunctiva). For best results, moisten the culturette with the nutrient broth prior to obtaining the samples and avoid the use of topical anesthetics prior to sample collection. If infection is suspected, aerobic and anaerobic



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**Table 1: Summary of ulcer classification, manifestations, diagnosis, and treatment**

Ulcer classification	Features	Clinical manifestations	Diagnosis	Therapy
<b>Simple</b>	Acute, superficial	Blepharospasm, Lacrimation, Corneal edema at ulcer site, +/- mild uveitis: miosis, aqueous flare	Appearance, Fluorescein positive	<b>Medical:</b> Prophylactic topical antibiotic; 4 times daily until fluorescein is negative
<b>Indolent</b>	Chronic, non-responsive, superficial, non-adherent epithelial margins	Blepharospasm, Lacrimation, Corneal edema at ulcer site, Loose epithelial edges, +/- Corneal vascularization, +/- Mild uveitis: miosis, aqueous flare	Appearance, Fluorescein positive: leaks below non-adherent epithelial margin	<b>Surgical:</b> Debridement, or debridement and superficial striate keratotomy <b>Medical:</b> Prophylactic topical antibiotic; 4 times daily until fluorescein is negative
<b>Complex</b>	Acute or chronic	Blepharospasm, Lacrimation, Corneal edema at ulcer site, +/- corneal vascularization, Moderate to severe uveitis: miosis, aqueous flare (+/- fibrin, hypopion, hyphema), diffuse corneal edema	Appearance, Fluorescein positive Cytology, culture: aerobic and anaerobic bacterial and fungal	<b>Surgical:</b> May require keratectomy and grafting procedure (referral to ophthalmologist) <b>Medical:</b> Specific topical antibiotic or antifungal based on cytology and culture; 1-6 times daily <b>For uveitis:</b> Topical atropine 1-4 times daily, Topical NSAID 1-4 times daily, Systemic NSAID
Deep	Stromal loss	Visible corneal defect, +/- purulent ocular discharge	As above	As above
Infected	Stromal inflammatory cell infiltration	Yellow-white infiltrate in ulcer bed, Purulent ocular discharge	As above	As above
Melting	Stromal liquifaction	Opaque, soft/liquid stroma, Purulent ocular discharge	As above	As above Also: Anticollagenase (eg, serum) every hour until liquefaction halted

bacterial, as well as fungal cultures, are recommended. Corneal cytology can be obtained with the blunt handle-end of a sterile scalpel blade following application of topical anesthesia (0.5% proparacaine). Vigorous corneal scrapings at the edge and base of the lesion are needed to detect bacteria and deep fungal elements. The material collected is transferred to a glass slide, air-dried, and fixed; it is then stained with a modified Wright's-Giemsa (eg, Diff-Quick) or a Gram stain.

### Classification of ulcerative keratitis

Corneal ulcers are classified as simple, indolent, and complex. The clinical manifestations and diagnosis of each are described below and Table 1 summarizes the clinical manifestations, diagnosis, and therapy of these ulcers.

#### Simple ulcers

Simple ulcers usually develop secondary to superficial ocular trauma and remain superficial and noninfected. Clinical manifestations include photophobia, blepharospasm, lacrimation, corneal edema due to entry of the tear film into the exposed stroma, and an irregular corneal surface. The diagnosis is made with fluorescein stain uptake by the exposed stroma. Healing of simple ulcers occurs by migration of surrounding epithelial cells and mitosis, as long as they do not become infected.

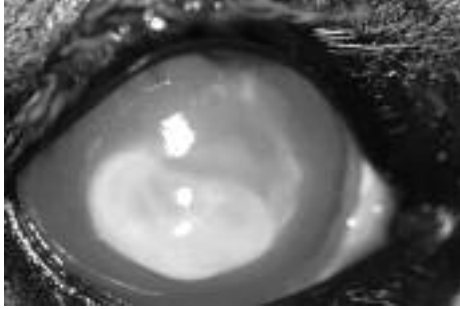
#### Indolent ulcers

Clinical manifestations of the indolent ulcer comprise a superficial corneal ulcer that is nonresponsive to appropriate medical therapy. These ulcers are surrounded by loose, non-adherent epithelial margins and lacrimation and blepharospasm are often present. Corneal vascularization may develop with chronicity. The diagnosis of an indolent ulcer is confirmed with positive fluorescein staining that continues under the loose, nonadherent edge of the ulcer. It is important to assess the horse for other causes of a non-healing ulcer such as dry eye, ectopic cilia, and conjunctival and corneal foreign bodies, since correction of these factors are necessary for healing.

#### Complex ulcers

Complex ulcers are those that are infected, melting, and/or deep. All ulcers have the potential to become infected by opportunistic environmental and periocular bacteria or fungi. Melting ulcers occur due to enzymatic breakdown of the cornea. Microbial enzymes (eg, collagenases and proteases) incite dissolution of the corneal intercellular ground substance and collagen lamellae. Neutrophils, attracted by chemotactic factors, invade the corneal stroma and degranulate, releasing additional degradative proteases.<sup>5</sup> Progressive stromal necrosis can result in an increased depth of the stromal lesion.

**Figure 1: Photograph of a melting ulcer in a horse.** The affected stroma appears opaque, soft, and liquefied. The surrounding cornea is diffusely edematous making visualization of the iris difficult. The peripheral cornea has a 1 mm in-growth of blood vessels. The ventral anterior chamber has a brighter appearance due to fibrin accumulation from secondary uveitis.



Clinical manifestations of infected ulcers include photophobia, blepharospasm, corneal edema, lacrimation and, often, a purulent ocular discharge. Additionally, the ulcer may have rough edges and there is frequently a yellow/white infiltrate of inflammatory cells in the ulcer bed. Corneal vascularization will develop with chronicity. Infection may occur with bacteria or fungi and the manifestations are similar; however, fungal keratitis will not respond to conventional antibiotic therapy.<sup>6</sup> Melting ulcers have similar clinical manifestations as those mentioned above, since most melting ulcers are also infected with bacteria and/or fungi. In addition, the corneal stroma becomes opaque, soft, and liquid-like (Figure 1). Melting ulcers are true ocular emergencies because progression may result in loss of the eye within 24 to 48 hours. With deep ulcers, the loss of corneal stroma causes a visible depression or defect in the cornea (Figure 2). If stromal loss extends all the way down to Descemet's membrane, this is called a descemetocele. Progression of melting and deep ulcers may result in corneal perforation and septic endophthalmitis.

The diagnosis of a complex ulcer is based on clinical manifestations and fluorescein staining, which is always positive. If a descemetocele is present, there will be no uptake by Descemet's membrane, but the surrounding ulcerated stroma

**Figure 2: Photograph of a deep and infected ulcer in a horse.** There is an obvious depression in the region of the ulcer. The stroma around the ulcer contains an infiltrate of inflammatory cells. The cornea has diffuse edema and blood vessels are extending several mm toward the ulcer.



**Figure 3: Photograph of a perforated corneal ulcer with iris prolapse in a horse.** The central corneal defect has a protrusion of brown iris. The stroma near the defect contains an infiltrate of inflammatory cells. The surrounding cornea is diffusely edematous making visualization of the iris difficult.



will be fluorescein positive. When a complex ulcer is diagnosed, further testing should include aerobic and anaerobic bacterial and fungal culture and sensitivity, as well as scrapings for cytology. In fungal keratitis, histopathology of keratectomy specimens may be required for diagnosis.

### **Corneal perforation**

Corneal perforation falls under the classification of a complex ulcer. This full-thickness defect in the cornea exposes the intraocular contents to the environment. It can occur due to progression of a deep stromal ulcer or a penetrating trauma. The clinical manifestations of corneal perforation include blepharospasm, serous to purulent ocular discharge, corneal defect, corneal edema, and iris prolapse. Iris prolapse appears as a protrusion from the corneal surface that may be brown (due to the color of the iris itself) or tan/pink (due to fibrin accumulation on the surface; Figure 3). Aqueous humor may leak from the corneal defect, or fibrin and the iris itself may seal the wound.

The diagnosis of a corneal perforation is made based on clinical signs and fluorescein staining. A Sidel test for aqueous leakage can be performed by placing concentrated fluorescein on the eye and determining whether rivulets of dilute fluorescein flow from the perforation. It is important to evaluate for lens rupture in cases of traumatic perforation. This requires dilation of the pupil and careful examination of the lens surface. Penetration of the lens will cause leakage of lens material and cataract development, and can lead to severe uveitis. Diagnostic testing in the case of corneal perforation should include aerobic and anaerobic bacterial and fungal culture and sensitivity, and cytology. In some cases, an ocular ultrasound may be performed to assess intraocular structures.

### **Ulcers and uveitis**

Corneal ulcers in the horse are frequently accompanied by anterior uveitis. Two basic mechanisms may cause anterior uveitis to occur secondary to corneal ulceration.

- The first is by an “axon reflex” between the sensory nerve fibers in the cornea and the anterior uveal blood vessels. When stimulated by corneal injury, this reflex results in miosis (constricted pupil) and increased protein levels in the aqueous humor.

- The second mechanism occurs when ulcers become infected or infiltrated with inflammatory cells, and inflammatory mediators in the cornea stimulate uveal inflammation.<sup>7,8</sup>

The severity of anterior uveitis is worse with complex ulcers and reflects the severity of the corneal disease. Manifestations of anterior uveitis in the horse include miosis, ciliary spasm causing pain and photophobia, lacrimation, aqueous flare, and a lowered intraocular pressure. Fibrin may appear in the anterior chamber as a yellow web-like mass. Leakage of white and red blood cells may occur from uveal blood vessels into the anterior chamber (hypopyon and hyphema, respectively). Despite the presence of these elements, the aqueous humor is usually sterile unless the cornea has become perforated.<sup>9</sup> Because the constricted pupil is in contact with the anterior lens surface, adhesions of the iris to the lens or posterior synechia may occur. These adhesions can become permanent in chronic conditions. Simple and indolent ulcers may exhibit minimal signs of uveitis or mild miosis and aqueous flare only. Increasing severity of uveitis is a sign that the ulcer is more serious and may indicate progression to a complex ulcer.

### Principles of ulcer therapy

All ulcers require antimicrobial therapy and most equine ulcers require treatment of secondary uveitis. In addition to medical therapy, complex and indolent ulcers frequently require surgical intervention. In complex ulcers, referral to an ophthalmologist is recommended; however, appropriate medical therapy should be initiated as soon as possible to halt the progression of disease.

### Antimicrobial therapy for ulcers

The choice of antimicrobial agent and the frequency of administration will depend on the type of ulcer. Topical administration of antibiotics is required, since systemically-administered medications will fail to reach adequate levels in the cornea. There are several commercially-available ophthalmic antibiotic preparations. However, some antimicrobials (eg, the cephalosporins) are not available as ophthalmic preparations. In these cases, an injectable form of the drug may be formulated for ophthalmic application, if required, based on sensitivity testing.

Antibiotic therapy for simple ulcers consists of a prophylactic topical broad-spectrum antibiotic to reduce the potential for infection by pathogens in the environment and conjunctival flora. The resident microflora of the conjunctival sac are predominantly Gram-positive aerobes while Gram-negative aerobes are isolated less frequently.<sup>10</sup> An excellent broad-spectrum prophylactic antibiotic is a triple antibiotic ointment or solution, typically containing neomycin, polymyxin B, and bacitracin or gramicidin.<sup>11</sup> A minimum application of 4 times daily is required for prophylactic therapy of simple ulcers. Antimicrobial therapy of indolent ulcers is similar to that of simple ulcers and includes prophylactic antibiotic ointments or solutions at a frequency of 4 times daily. Antibiotic therapy must continue until the ulcer has healed and healing has been confirmed with a fluorescein stain.

Antimicrobial therapy of complex ulcers must be more aggressive. The best choice of antimicrobial agent is based upon results of culture and sensitivity; however, these results are often not available for 48 to 72 hours after obtaining the culture. Cytology is reported to accurately identify organisms in only 60% to 70% of bacterial or fungal keratitis, but may be useful for directing initial therapy while awaiting culture results.<sup>12</sup> Rods are most often Gram-negative and *Pseudomonas* sp. and *Escherichia coli* are the most commonly isolated Gram-negative bacteria from equine ulcers.<sup>13</sup> *Pseudomonas* sp. is the most notorious organism associated with melting ulcers. Cocci are most often Gram-positive and those most commonly isolated from horses with ocular disease are *Staphylococcus* sp. and *Streptococcus* sp.<sup>2,13</sup>

In complex ulcers, topical antibiotics should be administered every 1 to 4 hours, with the higher frequencies used in severely infected or melting ulcers. Appropriate choices for suspected Gram-negative infections include: tobramycin, amikacin (10 mg/mL of injectable solution) ciprofloxacin, or ofloxacin.<sup>11</sup> Tobramycin and amikacin are the best choices in a melting ulcer due to the susceptibility of *Pseudomonas* sp. to these agents.<sup>14</sup> Although *Pseudomonas* sp. are often sensitive to gentamicin initially, resistance to this antibiotic can develop rapidly; therefore, gentamicin is not recommended as therapy for melting ulcers.<sup>13,14</sup> Good choices for suspected Gram-positive infections include: cephazolin (50 mg/mL of injectable solution), erythromycin, ciprofloxacin, or ofloxacin.<sup>11</sup> When the cytology is nondiagnostic and infection is suspected, the use of ciprofloxacin or ofloxacin is reasonable due to their broad-spectrum coverage. However, routine use of these agents is discouraged due to their potential to promote microbial resistance.

### Antifungal agents

Most cases of equine keratomycoses involve *Aspergillus* sp. or *Fusarium* sp.; however, many other fungal agents may be identified.<sup>1</sup> The only commercially-available ophthalmic antifungal preparation is natamycin, which has a broad-spectrum action against filamentous fungi and yeast. Natamycin use has been limited somewhat by cost in veterinary medicine. Miconazole is recommended for topical use as the initial choice for treating confirmed or suspected fungal keratitis in horses.<sup>15</sup> Although an ophthalmic preparation is unavailable, miconazole 10 mg/mL intravenous solution may be formulated for use on the eye. Alternatively, miconazole 2% vaginal preparations are also well-tolerated by the eye.<sup>11</sup> Silver sulfadiazine is a topical antimicrobial agent with both antifungal and antibacterial activity and has been used in equine eyes.<sup>15</sup> Itraconazole, combined with dimethyl sulfoxide (DMSO), has also been used successfully in treating equine fungal keratitis.<sup>16</sup> The frequency of application of antifungal agents is every 2 to 4 hours depending on severity.

### Anticollagenase therapy for melting ulcers

Anticollagenases are required for treating melting ulcers. Several different anticollagenases have been used to treat melting ulcers, including autologous serum, 10% acetylcysteine, and 0.05% potassium ethylenediaminete-

traacetic acid (EDTA).<sup>9,12,17</sup> However, the most commonly used, readily available, and effective anticollagenase is autologous serum. Serum must be stored and handled in a sterile manner to prevent bacterial growth. It should be refrigerated and replaced with fresh serum every 3 days. Anticollagenases are applied every hour for the first 24 hours or until stromal liquefaction is halted; at that point, the frequency of administration is tapered.

### **Therapy for secondary uveitis**

The mainstay of treatment for uveitis is a combination of anti-inflammatory and anticholinergic therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used to reduce pain and help control the secondary uveitis associated with ulcerative keratitis. Flunixin meglumine (1.1 mg/kg iv or orally 1-2 times daily) or phenylbutazone (2.2 to 4.4 mg/kg iv or orally, once or twice daily) is used systemically. Topical NSAIDs, such as diclofenac or flurbiprofen, may also be used up to 4 times daily to reduce anterior uveitis. The application frequency of topical NSAIDs and the dose of systemic NSAIDs required to control uveitis will decrease as the corneal disease resolves. Topically applied anticholinergics (1%-2% atropine) are used to:

- reduce proteinaceous and cellular leakage from inflamed uveal blood vessels
- dilate the pupil, which protects eye from the development of posterior synechia
- relax ciliary muscle spasm, which is a major factor in the discomfort associated with corneal ulcers and uveitis.

Atropine should be applied 1-4 times daily, as needed, to maintain pupil dilation. The frequency of application required to maintain pupil dilation will be higher when uveitis is more pronounced and will decrease as the corneal disease and uveitis resolve. Caution is advised when treating horses with topical atropine, since gastrointestinal stasis and subsequent colic may occur.<sup>18</sup>

### **Contraindicated therapy**

Corticosteroids are contraindicated in the treatment of ulcers. Corticosteroids will suppress the local immune response and impair ulcer healing; in addition, they can promote collagenolysis of the cornea.<sup>19</sup> The use of corticosteroids in ulcers is a well-known predisposing factor in the development of fungal keratitis.<sup>1</sup> Corticosteroids have been promoted for decreasing the vascularization and scarring following the reepithelialization of ulcers; however, this author does not recommend the practice. Corneal vascularization is a vital part of the healing process in corneal disease and interfering with this process may be detrimental. Vascularization regresses naturally after the ulcer has resolved.

### **Delivery of ophthalmic medications to the eye**

In addition to the type of medications used and the frequency of administration, the method of delivery should also be considered. When >1 solution is delivered to the eye, a minimum of 5 minutes should be allowed between the application of each medication to avoid dilution or chemical incompatibility. This should be extended to 30 minutes if ointments are used. Horses with severe corneal

disease are often in extreme discomfort and may become resistant to manual opening of the eye to apply medications. In these cases, a subpalpebral lavage (SPL) system can be used to facilitate ocular therapy. SPL systems can be purchased commercially (eg, Mila International, Florence, Kentucky) or manufactured by the practitioner using polyethylene tubing. They can be placed in the dorsal or ventromedial conjunctival fornix.<sup>20</sup>

### **Surgical treatment of indolent ulcers**

Debridement of the loose, nonadherent epithelium and superficial stroma, with or without a superficial striate keratotomy, are performed in treating indolent ulcers. The superficial striate keratotomy is specific to the indolent ulcer and should not be performed on infected, melting, or deep ulcers. Descriptions of this surgical procedure are found in most ophthalmic texts. Following surgery, medical therapy is continued as directed for the simple ulcer until the ulcer has healed, which may take 2-3 weeks, depending on the affected surface area. Re-debridement is discouraged during this time.

### **Surgical treatment of complex ulcers**

Most complex ulcers require surgical intervention and, in these cases, referral to a veterinary ophthalmologist is recommended. Ulcers that are  $\geq 50\%$  of the depth of the cornea are at risk for perforation and should be treated with a grafting procedure (eg, a conjunctival or corneal graft) to provide support for the cornea. Infected and melting ulcers benefit from a keratectomy to remove infected and necrotic cornea; this is usually followed by placement of a conjunctival or corneal graft.<sup>17</sup> The most commonly-performed grafting procedure is the conjunctival pedicle graft, in which the base of the graft retains a connection to the bulbar conjunctiva. The benefits of the conjunctival pedicle graft include replacement of tissue to strengthen the corneal defect and a continued blood supply that will provide the lesion with the antibacterial, antifungal, antiprotease, and anticollagenase properties of serum. The deeper layers of the graft provide immediate fibroblasts and collagen that help to rebuild the corneal stroma.<sup>17</sup> A degree of corneal scarring should be expected following the healing of a conjunctival graft. Medical therapy is initiated to stabilize the corneal disease prior to surgery (usually 12- 24 hours before surgery and continued after surgery for 3 to 4 weeks).

### **Other surgical procedures**

Temporary tarsorrhaphy, in which the eyelids are temporarily sutured either partially or completely closed, or a third eyelid flap, in which the third eyelid is sutured to the dorsolateral eyelid or sclera to cover the cornea, are rarely used for ulcer management in the horse. They may be useful, however, in the treatment of simple and indolent ulcers to provide increased warmth, moisture, and protection for healing or, in the case of acute facial nerve (cranial nerve VII) paralysis, to protect the cornea. They are also useful to prevent further corneal trauma if a horse is being referred to an ophthalmologist for surgical repair and must be transported over a long distance. Otherwise, these surgeries are contraindicated in the treatment of

complex corneal ulcers because they cover the defect and prevent frequent evaluation. In addition, they reduce the penetration of topical medications and fail to provide structural support for the cornea.

## Summary

Ulcerative keratitis can be classified into 3 forms based on the clinical manifestations — simple, indolent, and complex. Diagnosis requires a complete and thorough ophthalmic examination, and culture and cytology are indicated in complex ulceration. The appropriate therapy will differ based the classification. Medical therapy is adequate for treatment of simple ulcers, but indolent and complex ulcers usually require a combination of medical and surgical therapy. Any ulcer can develop into a serious vision threatening condition, therefore, prompt diagnosis and initiation of appropriate treatment is crucial.

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Please note the following correction in: Caron JP. Therapy for Equine Joint Disease. *Large Animal Veterinary Rounds* 2006;6:1-5.

In Table 4 - MAP-5 is currently marketed for cryopreservation of mammalian embryos, not as a topical preparation for wounds.

— Editor

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