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The pathogenesis of many nonulcerative keratopathies of horses is believed to be mediated by a dramatic corneal immune response to a foreign protein, microbial antigen or a self-antigen. Such suspected immune-mediated keratitis (IMMK) of horses has been classified primarily according to the apparent depth of the inflammatory response. Geographic differences in primary corneal insult, antigen exposure and in the duration of the IMMK prior to its recognition have led to some discrepancy in the clinical presentations and responses to therapy. It does seem that the more chronic the duration of IMMK the poorer response to medical therapy.

Epithelial keratopathy
This is a unilateral disease affecting horses of any age. Vascularisation is not a prominent feature of the disease. There is a diffuse, central, superficial corneal opacity usually associated with very slight blepharospasm and discomfort. There may be some slight associated conjunctival hyperaemia or chemosis. The superficial opacity represents irregular coalescing clumps or islands of thickened epithelium with no underlying stromal oedema. The unaffected areas of cornea appear normal. Fluorescein is weakly uptaken occurs. The apposing palpebral conjunctiva is moderately hyperaemic.

A NOTE OF CAUTION
Subepithelial keratomycosis has recently been identified in Florida. It looks identical to some cases of the epithelial keratitis form of IMMK. Biopsy and response to topical antifungal therapy are factors in making the diagnosis. It does seem capable of self-resolution in a few cases, which is quite confounding!

Chronic superficial keratitis
This disease is characterised by an insidious onset with affected eyes showing only slight to moderate discomfort. The lesions appear to be initially restricted to the area under the upper lid, and less frequently, the third eyelid and lower lid. The paracentral cornea is commonly involved in the USA. There is prominent subepithelial arborising vascularisation from the limbus, perivascular epithelial oedema, and a superficial yellow-white stromal cell infiltrate. Tear production is normal and no fluorescein uptake occurs. The apposing palpebral conjunctiva is moderately hyperaemic.

The disease is initially unilateral but the contralateral eye may become affected with time. Topical treatment with Cyclosporine A (CsA) twice daily usually results in clearing of the cornea in 7–10 days in cases of short duration. Long standing cases may be refractory to CsA. Most cases of chronic superficial keratitis are not responsive to topical corticosteroids. Successful resolution of refractory cases of chronic superficial keratitis in the USA required superficial keratectomy and conjunctival grafting.

Chronic deep keratitis
This is an episodic keratitis recurring at irregular intervals of up to several years. There is frequently history of initiating ocular trauma, and the disease may derive from a local adaptive response to autoantigen in an immunocompetent cornea.

In the acute or active phase of the disease there is an extensive and dense, deep, stromal oedema, white cellular infiltrate and fibrovascular response with isolated blood vessels encroaching on the affected stroma at various levels. The intensity of the stromal changes varies between cases and between episodes. Despite the dramatic appearance of affected eyes the disease is associated with no ocular pain. Subepithelial bullae may form and rupture, however, to create fluorescein positive superficial erosions that are associated with transient ocular discomfort. In some eyes a yellow-green tinged coloration may appear within the midstromal central and paracentral cornea. The ventral paracentral cornea is most commonly affected. Subepithelial calcium deposition may occur in some eyes. In the quiescent or inactive phase of the disease there is a modest diffuse stromal fibrosis with some superficial vascularisation.

The therapeutic benefit of topical corticosteroids is very limited in acute episodes of chronic deep keratitis although they may slowly accelerate clearing of the cornea. Topical cyclosporine A twice daily results in significant suppression of the acute corneal reaction and clearing of the cornea within 10–14 days in eyes with chronic deep keratitis. However, treatment may need to be maintained for long periods to prevent recrudescence of the disease. Spontaneous clearing of the cornea can also occur. Topical and/or systemic doxycycline aids healing of chronic deep keratitis with the yellow-green stroma. Topical NSAIDs are also often beneficial. Superficial keratectomy and conjunctival grafting are necessary for healing of cases of chronic deep keratitis in a few cases.

Endotheliitis
This type of IMMK is characterised by acute, unilateral, central oedema and deep vascularisation. Endothelial immunoreactivity to a persistent, possibly viral, heteroantigen may be involved in the pathogenesis. Affected eyes are nonpainful with no evidence of anterior uveitis. There is a deep, diffuse fibrocellular infiltrate, opacification, and stromal oedema in the central cornea, which may evolve rapidly into bullous keratopathy. Isolated arborising blood vessels encroach upon the affected area at the level of Descemet’s membrane and/or endothelium. In some cases, dense
clumps of cells may be evident adherent to the endothelium in the region of the terminal blood vessels. In long standing cases stromal mineralisation can occur. Rapid clearing of the cornea and regression of the blood vessels using topical dexamethasone occurs in many cases of endotheliitis in the UK. Treatment should continue for a 5–7 days following the corneal clearing. Recurrence of the disease is possible in a small number of long standing cases. A successful outcome following penetrating keratoplasty has been reported in the USA.

NOTES

Further reading
Equine glaucoma: Pathogenesis and management

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Background and pathogenesis
Glaucoma is a group of diseases, associated with an elevated intraocular pressure (IOP), producing retinal and optic nerve damage and blindness. Although primary glaucoma (inherent iridocorneal angle [ICA] defect) may occur in horses, it is most frequently associated with either traumatic, infectious, neoplastic, or immune-mediated (equine recurrent uveitis) anterior uveitis.

Following formation in the ciliary body (CB), aqueous humour (AH) flows from the posterior chamber through the pupil to the anterior chamber, exiting at the ICA (conventional outflow) or through the suprachoroidal and supraciliary spaces (uveoscleral, unconventional outflow). IOP increases (>35 mmHg) when AH flow is obstructed: lens, vitreous, pre-iridal fibrovascular membranes (PIFVM), or posterior synechia block flow through the pupil, while inflammatory or neoplastic cells, peripheral anterior synechia, PIFVM, or trabecular compression may block the ICA. The IOP increase compresses the optic nerve and reduces axoplasmic flow at the lamina cribrosa, leading to retinal ganglion cell death and vision deficits. Clinical signs of glaucoma include blepharospasm, corneal oedema, Haab’s striae, mydriasis, lens luxation, buphthalmia, exposure keratitis and blindness. These signs are often more subtle in horses, and vision may be retained until later in the disease process, than in dogs.

Management
Topical ocular anti-glaucoma drugs decrease AH formation or increase AH outflow. Beta-blockers (timolol maleate 0.5%) inhibit intraocular cAMP production, decreasing formation and lowering IOP by 27% (6.8 mmHg) in normal horses on a twice-daily dosing schedule (van der Woerdt et al. 2000). Carbonic anhydrase inhibitors decrease formation by inhibiting carbonic anhydrase in the CB epithelium. With twice-daily dosing to normal horses, topical dorzolamide (2%), administered alone or in combination with timolol, reduced IOP by 10% (2 mmHg) (Willis et al. 2001a), while topical brinzolamide (1%) decreased IOP by 5 mmHg (21%) (Germann et al. 2008). Topical prostaglandin analogues (i.e. latanoprost 0.005%) increase uveoscleral outflow, theoretically having a potentially large effect on IOP in heavily uveoscleral outflow-dependent equine eyes. Once-daily latanoprost administered to normal horses, decreased IOP by 3 mmHg (17%) in mares; however, the side effects (blepharospasm, epiphora, conjunctival hyperaemia) and potentiation of uveitis were significant enough to negate its use in glaucomatous horses (Willis et al. 2001b). To date, other prostaglandin analogues have not been evaluated in the equine eye.

Surgical management may maintain a positive response to medical therapy and preserve vision, or restore comfort to a blind eye. Visual patients may be candidates for transscleral laser cyclophotocoagulation (TSCP) to decrease production by selective destruction of CB epithelium and stroma. Localisation of the pars plicata is necessary for effective laser placement, identified at 4 mm posterior to the limbus in the dorso temporal and ventro temporal quadrants, avoiding the 3 or 9 o’clock positions, in nonbuphthalmic equine eyes (Miller et al. 2001; Morreale et al. 2007). The diode laser wavelength of 780-850 nm is better absorbed by melanin and can be utilised with lower total energy doses (~150 J/eye) than the Nd:YAG laser wavelength of 1064 nm (~250 J/eye) to achieve similar clinical effect. Based on desired histological damage produced by diode TSCP in normal eyes, a starting energy of 2.25 J/site (1500 mw x 1500 msec) for 60 sites was defined as appropriate (Morreale et al. 2007). Clinically, 42 eyes of 36 horses treated with diode TSCP (mean 183 J/eye, range 99–397 J) followed as long as 68 weeks, had good IOP control and 59% were sighted at final follow-up, however 100% (8/8) of eyes surviving to 20–68 weeks required medical therapy (Annear et al. 2008). Evaluation of Nd:YAG TSCP in 23 eyes of 16 horses identified a 70% success rate, defined as IOP <30 mmHg, for eyes surviving longer than 20 weeks post procedure (Whigham et al. 1999). Of those eyes, 60% were visual, and 45% were not receiving topical ocular anti-glaucoma medications. Common complications of both lasers include hyphaema (11%), conjunctival hyperaemia (22%), and corneal ulceration (13%). As determined by this study, an appropriate protocol was a power setting of 11W, duration 0.4 sec, for 60 sites (264 J/eye).

Additional procedures currently utilised in glaucomatous canine patients that may find use in equine patients include gonioimplants and endoscopic cyclophotonacoagulation (ECP). Gonioimplants in the anterior chamber create alternate AH drainage routes, and are commonly placed in dogs at the same time as laser cyclophotocoagulation is performed. While they may extend the duration of IOP control with or without adjunctive medical therapy, common complications include shunt occlusion, cataract development, and endothelial touch (Sapienza and van der Woerdt 2005). No published reports exist on use of this procedure in the horse, however. ECP, in which a diode laser is inserted into the globe either at the limbus or the pars plana, allows precise targeting and visualisation of laser application to the pars plicata. Complications may include intraocular haemorrhage, cataract development and phthisis; however, no published reports exist on use of this procedure in veterinary patients.

References
Willis, A.M., Robbin, T.E., Hoshaw-Woodard, S., Wilkie, D.A. and Schmall, M.L. (2001a) Effect of topical administration of 0.5% dorzolamide hydrochloride or 2% dorzolamide hydrochloride-0.5% timolol maleate on intraocular pressure in clinically normal horses. Am. J. vet. Res. 62, 709-713.
When to use adjunctive treatments for equine keratopathies

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Keratopathies may be ulcerative or nonulcerative in the horse. Ulcerative keratopathies may be infectious or sterile but are always associated with increased tear film protease activity. Ulcerative infectious keratopathies in horses may be caused by bacteria, fungi and possibly viruses. Sterile ulcers may be caused by foreign bodies, tear film problems, denervation, or basement membrane corneal dystrophies.

Nonulcerative keratopathies may also be infectious or sterile, and range from cellular invasions of the stroma by inflammatory or neoplastic cells to persistent corneal oedema. Infectious stromal abscesses, glaucoma induced stria, uveitis associated endothelial oedema, eosinophilic keratitis, calcific band keratopathy, neoplasia, and immune mediated keratitis (IMMK) are major concerns.

Medical standards of care

Ulcers
The current medical standard of care of treatment of ulcerative keratitis in the horse is a topical broad spectrum, nonirritating antibiotic, careful utilisation of a mydriatic/cycloplegic and an antiprotease compound such as serum. A systemically administered nonsteroidal drug is also beneficial.

Ulcer expectations
If the ulcer does not diminish in size at a rate of 1 mm/day, the cornea does not vascularise, and/or the signs of uveitis do not improve, then consider culture and/or cytology to document a change in antimicrobials. If the ulcer deepens, then amnion, conjunctival or corneal grafting surgery is recommended.

Stromal abscesses (SA)
The current medical standard of care of treatment of stromal abscesses is topical antimicrobials (including antifungals), atropine, and systemic antimicrobials and NSAIDs.

SA expectations
Stromal abscesses must vascularise to heal. Therapy may take weeks. Vascularisation and a reduction in the associated uveitis are signs of improvement. Surgery may be necessary to remove the abscess if medical therapy fails to resolve the inflammation in 2–4 weeks.

Persistent corneal oedema
The current medical standard of care of treatment of corneal oedema due to uveitis or endothelial disease is hypertonic saline.

Oedema expectations
If clearing of the oedema from the limbus does not occur, consider thermokeratoplasty.

Corneal neoplasia
The current medical standard of care of treatment of epithelial dysplasia is topical 1% 5-fluorouracil. Corneal squamous cell carcinoma requires keratectomy, and cryotherapy or radiotherapy. The keratectomy should be covered with an amnion graft preferably but conjunctiva can be used.

Neoplasia expectations
Scarring of the cornea may be difficult to differentiate from tumour recurrence. Keratectomy and adjunctive therapies are needed for carcinoma in situ and SCC. Rapidly progressive and invasive SCC may necessitate enucleation.

Eosinophilic keratitis (EK)
The current medical standard of care of treatment of eosinophilic keratitis is topical steroids and antimicrobials. Ulcers can complicate the treatment.

EK expectations
These lesions are typically slow to heal. Scarring of the cornea occurs. 03% phospholine iodide (b.i.d.) in combination with systemic nonsteroidal anti-inflammatory drugs are indicated. Topical cromolyn sodium (4.0% t.i.d.) or loroxamide (0.1% t.i.d.) can also aid healing. Systemic corticosteroids may be necessary. Horses should be dewormed twice with ivermectin 10 days apart. Switching to moxidectin may also be beneficial. Superficial lamellar keratectomy to remove plaques speeds corneal healing.

Immune mediated keratitis (IMMK)
The current medical standard of care of treatment of IMMK is topical corticosteroids.

IMMK expectations
Topical dexamethasone rapidly resolves many of these eyes, but infection is always a concern. Consider adding topical cyclosporine, and systemic steroids and/or doxycycline to difficult cases. Corneal biopsy is recommended for recalcitrant eyes. Topical NSAIDS are also indicated for IMMK eyes that recur.

Calcific band keratopathy (CBK)
The current medical standard of care of treatment of calcific band keratopathy is topical 0.2% EDTA. Any accompanying ulcers are also treated with antimicrobials and antiproteases. Many of these horses also have ERU and the topical steroids may have induced the calcium deposition.

CBK expectations
The calcium is generally chelated in a manner of days, but superficial keratectomy may be necessary if the calcium deposition is deeper in the stroma.

Herpes and viral keratitis
Multiple, superficial, white, punctate or linear opacities of the cornea, with or without fluorescein dye retention, are found associated with equine herpes virus 2 and perhaps other viruses. The focal punctate corneal opacities may be found at the end of superficial corneal vessels, and may retain rose bengal stain. Varying amounts of ocular pain, conjunctivitis, and iridocyclitis are present.

Herpes expectation
Viral keratitis is overdiagnosed. The response to therapy can be quite variable and the clinician may become frustrated. Further diagnostic workups and cultures of ulcerated lesions can be helpful. Topical NSAIDs for treatment of equine herpes ulcers may have benefit.