

Compendium

Equine Recurrent Uveitis: Treatment

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Abstract: Equine recurrent uveitis has traditionally been treated with medical management to reduce ocular inflammation and control pain during a single episode. Newer management methods include surgical options such as cyclosporine implantation and vitrectomy. These methods were developed not only to control inflammation but also to eliminate the underlying cause of uveitis in order to prevent recurrence.

For more information, please see companion article, "Equine Recurrent Uveitis: Classification, Etiology, and Pathogenesis."

Medical Management

Treatment of equine recurrent uveitis is aimed at reducing ocular inflammation to control pain, minimizing production and release of inflammatory mediators, blocking immunologic mechanisms to reestablish the blood–ocular barrier, and limiting recurrence to prevent further intraocular damage. Because vision loss is a common long-term manifestation of equine recurrent uveitis, initial therapy must be aggressive.¹ Therapy should be directed at the etiologic cause, whether a primary ophthalmic disease or secondary to a systemic problem. Nonspecific therapy (TABLE 1) should include mydriatic cycloplegics, such as topical 1% atropine, which dilates the pupil, decreases the pain of ciliary muscle spasms, and reduces inflammation, decreasing synechiae formation. As the iris is repositioned, vascular fenestrations are narrowed, decreasing the leakage of protein and inflammatory cells into the anterior chamber.¹ The dosage frequency depends on the response of the iris to mydriasis; once the pupil is dilated, 1% atropine should be used only as needed to maintain dilation of the pupil (once-daily topical dosing is usually sufficient until inflammation has subsided). If 1% atropine is not effective, 3% atropine can be used; however, patients should be monitored for signs of colic because administration of high doses of atropine can cause decreased intestinal motility, potentially leading to ileus, gas distention, or cecal or large colon impaction. If dilation cannot be achieved with atropine alone, 10% phenylephrine hydrochloride can be used in combination with atropine.

Topical corticosteroids are most commonly used to suppress inflammation. Prednisolone acetate has the best corneal penetration; dexamethasone HCl is the next best option.² Application frequency (ranging from twice daily to eight times daily) depends on the severity of the uveitis and should be tapered slowly once clinical

signs have resolved. Adverse effects of topical steroids include potentiation of infectious agents and collagenase enzymes. Application of topical steroids when corneal ulceration is present may result in corneal melting and perforation or delayed epithelialization and healing of ulcers. Subconjunctival injection can provide a therapeutic intraocular level of corticosteroid, especially if application frequency is not conducive to owner compliance. Topical NSAIDs such as flurbiprofen and diclofenac can be used with fewer adverse effects and less concern when an ulcer is present; however, they can also delay epithelialization and are not as effective as corticosteroids in reducing intraocular inflammation.²

Systemic therapy is the most effective method of managing equine recurrent uveitis.² Intravenous flunixin meglumine is reportedly the most effective NSAID.² Phenylbutazone, aspirin, and ketoprofen may also be used according to the situation.² Systemic dexamethasone or prednisolone is highly effective for reducing inflammation; however, the adverse effects of steroids in horses may outweigh the benefits. Systemic steroids are reserved for severe cases that are unresponsive to NSAIDs or for cases involving corneal ulceration.

Topical, intravitreal, or systemic antimicrobials are indicated when uveitis is due to bacterial infection. When possible, the antimicrobial should be chosen according to sensitivity patterns of bacteria. Tetracycline or doxycycline is generally not indicated to treat horses with leptospirosis because systemic administration of

Table 1.
Common Topical Medications

Medication	Dosage
Mydriatics Atropine HCl 1% Phenylephrine HCl 10%	q6–48h q6–12h
Steroids Prednisolone acetate Dexamethasone HCl	q1–6h q1–6h
NSAIDs Flurbiprofen Diclofenac	q1–6h q1–6h

these drugs does not result in therapeutic levels in the eyes. Systemically administered enrofloxacin (7.5 mg/kg IV q24h) has achieved intraocular therapeutic levels against *Leptospira interrogans* serovar *pomona*; therefore, this drug should be considered if uveitis has been documented to be associated with leptospiral infection.³ Medical management of uveitis should be continued for several weeks or even months after remission of clinical signs because rapid tapering of topical or systemic antiinflammatories frequently leads to flare-ups of uveitis.

Vaccination against leptospirosis (multivalent inactivated strands of *L. interrogans* serovars *bratislava*, *canicola*, *hardjo*, *icterohaemorrhagiae*, and *pomona* as well as *Leptospira kirschneri* serovar *grippotyphosa*, all of which are labeled for use in swine and cattle only) in horses with nontraumatic uveitis was shown to significantly increase the time to first recurrence after the second vaccination; however, there was no effect on future recurrences after the second vaccination.⁴ Vaccination also failed to slow the progression of uveitis and seemed to speed progression in the vaccinated group versus the control group. Comparison of antibody titers in vaccinated horses versus unvaccinated horses demonstrated no difference. Therefore, the use of vaccination as an adjunct therapy for equine recurrent uveitis is not supported at this time.⁴

Surgical Management

Newer therapies aimed at preventing recurrence of equine recurrent uveitis and providing long-term control of the disease include implantation of a cyclosporine A-releasing device and pars plana vitrectomy. Cyclosporine A is an immunosuppressant that focuses on cell-mediated immune responses and has some effect on humoral immunity. Cyclosporine's exact mechanism of action is not fully known, but the drug is known to inhibit T-cell responsiveness and block the release of interleukin (IL)-2 and T-cell growth factor.⁵ Because high numbers of T cells and IL-2 have been found in eyes with equine recurrent uveitis, cyclosporine A may be ideal in preventing T-cell activation and uveitis recurrences.⁶

Cyclosporine A may be applied topically; however, it is hydrophobic and does not penetrate the cornea well. Therefore, it does not obtain a therapeutic concentration within the eye. A device containing cyclosporine A was evaluated for intravitreal implantation in horses after it demonstrated a sustained drug level in the ocular tissue of rabbits with experimentally induced uveitis.^{7,8} In experimentally and naturally affected horses, intravitreal cyclosporine A decreased the severity and duration of clinical signs, cellular infiltrate, and T cell numbers and significantly decreased IL-2 and interferon- γ .⁶ The cyclosporine A device, which is designed to release 4 $\mu\text{g}/\text{d}$ for up to 5 years, (1) limited the recurrence of uveitis in most horses and (2) decreased the severity of recurrence and length of active inflammation and increased the response to topical medications in the other horses; however, complications associated with intravitreal placement included glaucoma, cataract formation, and retinal detachment, leading to vision loss.⁹

Because of the risk of such serious complications when the vitreous cavity is entered, a biodegradable cyclosporine A implant

was manufactured for placement in the deep scleral lamella of horses with uveitis. The deep sclera lamella is situated under the sclera but above the choroid and allows cyclosporine A to be delivered to the choroid without surgical entry into the vitreous cavity. This technique provided sustained delivery of cyclosporine A to the deep sclera-suprachoroidal space and achieved a high intraocular level of drug, resulting in significant reduction of postoperative uveitis flare-ups and rates of vision loss.¹⁰ No toxicoses or severe complications were associated with the implant itself. However, the selection of appropriate candidates to receive cyclosporine A implants is important for long-term success. For example, irreversible changes due to chronic uveitis eventually result in vision loss and decreased success of the implantation device.¹¹ Candidates should be in the quiescent phase of the disease to help prevent severe inflammation after surgery.¹⁰

Vitrectomy has been evaluated for removing immune mediators, antigens, and inflammatory debris within the vitreous, possibly reducing the recurrence of equine recurrent uveitis.¹² Vitrectomy does not completely remove all the vitreous; therefore, interaction between the uvea and vitreous is not completely eliminated. However, reduced interaction between the uvea and vitreous seems to be sufficient in halting the recurrence of episodes.¹² Other reports claim that the goal of vitrectomy is not to eliminate inflammatory episodes, but to clear the vitreal opacities to improve vision.¹³ This is the main goal in humans and is typically achieved in more than half of cases, although anterior uveitis is a common complication after vitrectomy in human patients with posterior uveitis.¹³

The goal in equine patients is first to halt progressive globe destruction and recurrence of pain. Vision is usually stabilized secondarily. Vitrectomy has been performed in Europe for almost 2 decades, and most European studies report a decrease in vision over time, coupled with a decrease or cessation of uveitis

Key Facts

- Systemic antimicrobials can be administered for leptospiral-induced uveitis. The distribution of tetracyclines to the eye has been shown to be below the therapeutic level; however, enrofloxacin can achieve a therapeutic level against *Leptospira interrogans* serovar *pomona* within the eye.
- No vaccine exists for leptospiral-induced uveitis in horses. Vaccination of horses using swine- or bovine-labeled vaccine is not recommended.
- Implantation of a cyclosporine-releasing device has been shown to decrease the recurrence of uveitis, decrease the severity and length of episodes, and increase the response to topical medications in patients with recurrent episodes by suppressing immunity and blocking inflammatory cytokines.
- Vitrectomy can clear inflammatory debris from within the vitreous to improve vision and decrease inflammatory mediators that may perpetuate episodes of equine recurrent uveitis.



attacks.^{14,15} Vision loss was primarily due to progressive cataract formation, especially in patients that had lens damage before surgery; however, this rate was low. In the United States, vitrectomy is still fairly new, and only a few ophthalmologists perform it. Results in the United States seem to be less favorable than those in Europe, but this could be due to the use of different instrumentation, leading to more complications, such as intraocular hemorrhage and cataract formation.¹⁶ Affected horses in Europe tend to be Warmbloods with posterior uveitis, whereas affected horses in the United States tend to be Appaloosas and Quarter horses with panuveitis.¹⁶ Posterior uveitis may respond to vitrectomy better than panuveitis. In addition, US and European horses have different leptospiral organisms. *L. interrogans* serovar *pomona* predominates in the United States, whereas uveitis caused by *L. kirschneri* serovar *grippotyphosa* is more common in Europe.¹⁶

The Future

Further research is needed to fully understand the following regarding equine recurrent uveitis: (1) what predisposes certain horses to it, (2) the role of autoantigens and immune mechanisms in inflammation and the immune response, and (3) the role of infectious agents. Research is being conducted to further determine the genetic predisposition to recurrent uveitis in certain equine breeds. The results may allow genetic selection of unaffected individuals, thereby improving the breed and decreasing the prevalence of equine recurrent uveitis. Research is also being conducted on the role of leptospire in equine recurrent uveitis, the use of leptospirosis vaccines in horses, and newer immunosuppressive therapies. Because severe recurrent uveitis leads to vision loss and, often, euthanasia, this disease results in large economic losses worldwide. Continued research should lead to a

better understanding of equine recurrent uveitis, improved therapies, and reduced vision loss in horses.

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1. Initial therapy for equine recurrent uveitis must be aggressive to

- a. limit the number of flare-ups.
- b. reestablish the blood–ocular barrier.
- c. halt progressive globe destruction, which results in blindness.
- d. all of the above

2. Nonspecific topical therapy for equine recurrent uveitis does not include

- a. mydriatic cycloplegics (e.g., atropine).
- b. cyclosporine.
- c. corticosteroids (e.g., prednisolone).
- d. NSAIDs (e.g., flurbiprofen).

3. Topical corticosteroids should not be used when

- a. concurrent corneal ulceration is suspected.
- b. the pupil is dilated.
- c. the retina is detached.
- d. a synechia has formed.

4. Which treatment route is the most effective for managing equine recurrent uveitis?

- a. topical
- b. systemic
- c. subconjunctival
- d. intrapalpebral

5. Vaccination (against leptospirosis) of horses with equine recurrent uveitis has resulted in all of the following except

- a. elimination of recurrence.
- b. increased time to recurrence after the second vaccination.
- c. increased progression of the disease.
- d. no difference in antibody levels compared with those of unvaccinated horses.

6. Cyclosporine A has not been shown to act by

- a. inhibiting T-cell responsiveness.
- b. blocking the release of IL-2.
- c. inhibiting B-cell responsiveness.
- d. blocking the release of T-cell growth factor.

7. Documented complications of intravitreal cyclosporine implantation include

- a. retinal detachment.
- b. cataract formation.
- c. glaucoma.
- d. all of the above

8. _____ is not a reason why suprachoroidal placement of cyclosporine A is preferred for surgical implantation.

- a. A decreased rate of vision loss
- b. Surgical entry into the vitreal cavity
- c. Sustained delivery of cyclosporine A to the suprachoroidal space
- d. Achievement of a high intraocular drug level

9. Removal of _____ is not an advantage of vitrectomy.

- a. antibodies
- b. immune mediators
- c. inciting antigens
- d. inflammatory debris

10. Which of the following is shared (or similar) between European and US horses with recurrent uveitis?

- a. the most affected breed
- b. the leptospiral organism
- c. the goal of treating affected patients
- d. the type of uveitis and its response to vitrectomy