How to Medically Manage a Case of Equine Eosinophilic Keratoconjunctivitis

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1. Introduction
Equine eosinophilic keratitis or keratoconjunctivitis (EK) is an inflammatory disease of the conjunctiva and cornea. This disease has been described in other veterinary species, including cats,7 dogs,7 and rabbits8; however, there is a dearth of information in the veterinary literature regarding this disease in horses.9–18 The disease appears to have a seasonal component, with the majority of cases occurring in summer and early fall. EK has been reported in the Quarter Horse, Thoroughbred, Arabian, Warmblood, Mustang, and Icelandic horse breeds and in one donkey. No definitive sex or breed predisposition has been identified. The exact etiology and pathogenesis of EK are still unknown, but EK is postulated to be the result of a hypersensitivity reaction to an unknown stimulus, a theory supported by the response to treatment with immunomodulating drugs in horses and other species.1–17 In horses, parasitic causes, such as Onchocerca, Thelazia, and Habronema infections, have been investigated and have not been found to play a role in the development of EK.16 Although a wide range of treatment approaches has been used in horses, including systemic and topical medications and surgical interventions, no treatment approach has been rigorously tested and shown to be superior to any other. Irrespective of treatment, the course of the disease is often extended, and it is not unusual for treatment to extend beyond 1 month. The exception is surgical intervention with a superficial keratectomy, which results in a relatively rapid resolution once performed.

In one case series, Yamagata et al10 reported on seven horses diagnosed with EK in the Midwestern United States from 1976 to 1994. These horses were treated either medically or surgically. Time to resolution of clinical signs ranged widely, from 14 days for one horse that was treated with a superficial keratectomy, 90 days for one horse treated with topical antibiotics only, and between 45 and 106 days for five horses treated with a combination of topical medications, including antibiotics and corticosteroids. Secondary corneal bacterial or fungal infections were not identified in these cases. Although this is a small case series, it supports the hypothesis that topical corticosteroid treatment may increase the time to resolution, whereas surgical intervention with a superficial keratectomy may hasten resolution of EK.

After this case series was reported, several case reports and case series have described EK in equids.
A single case of EK in a 29-year-old donkey was reported by Jennings. The donkey presented with a 2-day history of unilateral ocular discharge and a limbal mass. After treatment with topical dexamethasone and topical antibiotics, the lesions had resolved at the time of a follow-up appointment 30 days after initiation of treatment. In another single case report of EK, bilateral conjunctival and periocular skin biopsies were performed in a 17-year-old Icelandic mare with a 4-week history of bilateral conjunctivitis. In this mare, BPV-1/2 DNA and oncogene E5 transcript were identified, suggesting a role for a viral component in the development of EK in horses.

The following year in a conference abstract, Sandberg et al reported EK in a group of three horses recurring in the summer months over a 2-year period. All three horses responded poorly to medical therapy with topical antibiotics and topical as well as systemic corticosteroids but demonstrated rapid resolution after a superficial keratectomy. Histopathology and transmission electron microscopy of the keratectomy specimens identified eosinophils in the anterior corneal stroma. Allergic dermatitis was diagnosed in two of these horses, raising the possibility of a multi-system eosinophilic disease process or general immunoglobulin E–mediated hypersensitivity disease. Kafarnik reported a single case of EK in a 7-year-old Cob gelding with a 3-month history of bilateral corneal ulcers. Superficial keratectomy led to resolution in 14 days, with no recurrence reported in 6 months of follow-up. Diamond burr debridement has been used to treat horses previously diagnosed with EK and with subsequent nonhealing corneal ulcers. Taken together, these cases support the hypothesis that superficial keratectomy may be associated with more rapid resolution of clinical signs than medical therapy alone.

Although the superficial keratectomy has shown the most promise for achieving rapid resolution of EK, surgical intervention is not the best “first-line” treatment for mild or recurrent cases. In addition, even in cases with severe and prolonged disease, surgical intervention is often declined by owners because of concerns about risks of general anesthesia and/or financial constraints. Therefore, identifying the best non-surgical approach to treatment of EK is important and useful in managing a disease that has a seasonally occurring component. The most recent insight into medical management of EK is in a retrospective study of 46 eyes in 26 horses. In this study, the signalment, history of EK, presenting signs, medical therapy, time to resolution, and recurrence during a follow-up period (mean, 1.9; standard deviation [SD], 1.6; range, 0.3–4.7 years) were evaluated in horses diagnosed with EK from 2008 to 2012. The results of this retrospective study support the use of systemic corticosteroids and a systemic histamine 1(H1)-receptor antagonist in cases of equine EK and provides additional evidence that EK is a recurrent, seasonal disease in horses.

On the basis of this literature, medical management of equine EK should include standard ulcerative keratitis regimen (described in Treatment Approach section) in addition to a short course of systemic corticosteroids to combat the plausible allergic hypersensitivity component. An H1-receptor antagonist, cetirizine, should also be prescribed as both an immediate treatment and future preventative measure. Although use of topical corticosteroids in some cases of EK may result in short-term improvement, the use of topical corticosteroids in the face of a corneal ulcer is dangerous because it may increase the incidence and severity of secondary bacterial and fungal corneal infections.

2. Clinical Signs and History

Clinical signs of EK include moderate to severe ocular pain, caseous ocular discharge, severe conjunctival hyperemia and chemosis, and pink proliferative corneal plaques, most often originating at the corneal limbal junction. White, cellular plaques may be present overlying the pink proliferative lesions. Individual cases of EK can present with clinical signs at any point along the clinical spectrum, from severe conjunctivitis and blepharitis with or without corneal ulceration, to geographic corneal ulceration with secondary bacterial and/or fungal involvement. The majority of horses are exquisitely painful on presentation with moderate to severe epiphora and blepharospasm. The disease can present unilaterally or bilaterally, and severity can differ between left eye and right eye when bilateral. Reflex uveitis is often present. There was a clear seasonal component, with 92% of cases in one study having developed clinical signs from June through October.

Many horses present with a history of similar ophthalmic clinical signs observed by the owner during the summer and early fall months of previous years. In one study, 44% of horses diagnosed with EK had a 1- to 5-year history of confirmed EK. An owner may also report that within a single year, their horse exhibits repeated bouts of conjunctivitis, blepharitis, and corneal ulceration, which respond poorly to routine corneal ulcer management, including topical antibiotics and antifungals, systemic non-steroidal anti-inflammatory drug (NSAID) medication, and topical mydriatic/cycloplegic treatment. Although in many cases the definitive diagnosis of EK cannot be made for previous episodes, awareness of a possible recurrent disease process may raise a red flag to the clinician that this is not a typical case of ulcerative keratitis.

3. Examination and Diagnosis

A complete ophthalmic examination should be performed to rule out other causes of conjunctivitis, blepharitis, corneal ulceration, and anterior uveitis, if present. Differential diagnoses for EK include
other infiltrative, potentially ulcerative corneal diseases, including fungal, bacterial, parasitic, or viral keratitis, neoplasia, and calcific band keratopathy. A definitive diagnosis of EK is made on the basis of predominance of eosinophils on corneal or conjunctival cytology in conjunction with clinical signs. Eosinophils may be accompanied by smaller numbers of mast cells, lymphocytes, plasma cells, and neutrophils, in addition to bacteria or fungal hyphae, depending on whether a secondary corneal infection is present. A brightly eosinophilic, acellular, granular material may surround the corneal plaques. On the basis of the results of a general ophthalmic examination and cytological evaluation, additional microbial diagnostics should be performed, including bacterial culture and antimicrobial susceptibility and fungal culture, because the risk of secondary corneal infection is high in any case of ulcerative corneal disease in horses.

Corneal cytological evaluation is critical to making the diagnosis of EK. The easiest way to initially misdiagnose a case of EK as a case of “simple” ulcerative keratitis or conjunctivitis of another etiology is to fail to perform cytology.

4. Medical Treatment Approach

On the basis of data from a retrospective study of 46 eyes in 27 horses,17 the most effective medical treatment regimen includes a short, tapering regimen of systemic dexamethasone; systemic H1-receptor antagonist (cetirizine); topical antibiotic and antifungal treatment to prevent and/or treat secondary corneal infection; topical mydriatic/cycloplegic to address reflex uveitis; and systemic NSAIDs after cessation of systemic dexamethasone.17

Eosinophilic keratoconjunctivitis cases are at risk for secondary corneal infection, with 51% of eyes having a positive bacterial or fungal culture in one study.17 Therefore, topical antimicrobial therapy is critical. The medical management of horses diagnosed with EK is routine with respect to treating corneal ulceration and reflex uveitis. Treatment should include a topical antibiotic and antifungal, topical mydriatic/cycloplegic, and systemic NSAIDs. With the exception of mild cases of EK, a tapering regimen of systemic dexamethasone is used as follows: 0.04 mg/kg for 1 day, 0.03 mg/kg for 2 days, and 0.02 mg/kg for 3 to 5 days.17 The initial dose is typically administered intravenously, with all subsequent doses given orally. After treatment with systemic dexamethasone, a significant improvement in conjunctivitis and blepharitis is typically observed within 24 to 48 hours.

Horses diagnosed with EK are also treated with systemic cetirizine given orally at a dose of 0.4 mg/kg twice daily.17 Cetirizine is an H1-receptor antagonist used for the treatment of seasonal allergies in humans. It acts by blocking the H1-receptor and preventing the histamine-dependent increase in adherence and migration of eosinophils.21 Blocking additional eosinophils from being recruited and migrating to the conjunctiva and cornea could help alleviate the clinical signs of EK in horses. This is supported by in vitro research in an epithelial cell culture model in which epithelial cells showed signs of toxicity and a decrease in the rate of wound repair after treatment with the major eosinophil granule product, major basic protein.19,20 On the basis of these studies, it can be hypothesized that the presence of degranulating eosinophils on the equine cornea could lead to corneal ulceration and failure of normal corneal healing.20 Therefore, preventing additional eosinophil recruitment and migration to the corneal surface could benefit horses diagnosed with EK. Pharmacokinetic studies have identified a safe oral dose in horses that achieves similar plasma concentrations to those achieved in humans.21 In a histamine-induced cutaneous wheal formation study in horses, it was shown that pretreatment with cetirizine inhibited wheal formation.22 These studies support the use of cetirizine in cases of EK as a way to reduce the severity of clinical signs while the horse is having an active bout of EK or during at-risk times of year, in an effort to reduce the recurrence rate.17

Extended treatment is the reality for the majority of cases of equine EK, with more than 80% of cases requiring medical treatment for at least 3 months.17 In one retrospective study, time to resolution was significantly shorter for horses treated with systemic corticosteroids (mean, 2.23; SD, 1.13 months), relative to patients that were not so treated (mean, 4.20; SD, 1.47 months).17 Recurrence is common in this disease, with a 33% recurrence rate; however, horses treated with cetirizine are significantly less likely to have recurrence during the following year.17 In one study, recurrence of EK was reported for only one of 13 horses (8%) treated with cetirizine, relative to recurrence in eight of 14 horses (57%) that had not been treated with cetirizine.17

5. Monitoring and Follow-Up

It is imperative that frequent re-evaluations are performed on horses diagnosed with EK, just as with any case of equine ulcerative keratitis. However, following up with owners dealing with equine EK is perhaps even more important compared with uncomplicated ulcerative keratitis because of the prolonged treatment time often required to achieve resolution of clinical signs. As many veterinarians have probably seen in other cases of ophthalmic disease requiring frequent daily treatments, an owner’s inability to treat ulcerative keratitis in their horse can lead to significant worsening of the disease in a short period of time if not reported to or appreciated by the veterinarian. A subpalpebral lavage delivery system is often necessary to permit extended treatment of horses with EK. Additionally, serum total protein should be monitored weekly and serum creatinine every 2 weeks because of the well-established gastrointestinal and renal
adverse effects associated with chronic NSAID administration.

6. Environmental Management
The role of environmental management in the development and duration of clinical signs of EK is not completely understood. Controlling EK by environmental modification is predicated on the hypothesis that EK is a hypersensitivity reaction to an environmental allergen. The role of environmental modification in controlling EK was reported by Utter\(^6\) on a single farm in July to August 2009. Utter reported the incidence of EK in 19 Standardbred broodmares, representing an incidence of 10% on the farm in a single year. With the addition of specific management changes, including the use of fly masks, fly repellent, night turnout, keeping pasture cut close to the ground, and longer periods of time housed in stalls, fewer horses had EK the following year, and overall clinical signs were less severe than during the previous year. This approach to controlling recurrence of EK is especially significant in horses not treated with cetirizine because of financial constraints.

7. Conclusions
Eosinophilic keratoconjunctivitis in horses is a disease that can be frustrating for veterinarians, owners, and horses alike because of the severity of clinical signs and prolonged treatment often required to achieve resolution. Additionally, it is not uncommon for horses to have additional bouts of disease during the same year or later years because of the high recurrence and seasonality of the disease. Correctly diagnosing the disease as EK is the first step to beginning an appropriate therapeutic plan with the best chance of success. Treating the disease with systemic dexamethasone and cetirizine, in addition to topical antibacterial, antifungal, and mydriatic/cycloplegic medications, has proved to be the best medical treatment option currently available. Additionally, continuing treatment with cetirizine during future summer and early fall months and recommending environmental modification can help to decrease recurrence and severity of clinical signs in horses that have repeated bouts of confirmed EK.

References