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Equine eosinophilic keratoconjunctivitis in California: retrospective study of 47 eyes from 29 cases (1993–2017)

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Abstract

Objective—(1) To evaluate the epidemiology of equine eosinophilic keratoconjunctivitis (EK) in the western United States, (2) to ascertain the efficacy of keratectomy and diamond burr debridement versus medical management alone, (3) to determine the efficacy of various medical therapies, and (4) to further characterize the histopathologic findings of the disease in horses.

Animals studied—Twenty-nine horses (47 eyes) diagnosed with EK from 1993 to 2017.

Procedure—Retrospective medical record review; owner questionnaire.

Results—Average age of presentation was 11 ± 4 years. Warmbloods were significantly overrepresented (P=0.024). Twenty horses were treated with medical therapy alone, five were treated with superficial lamellar keratectomy, and four were treated with diamond burr debridement. Follow-up data was available for 38 eyes of 23 horses. Median time to resolution for horses treated with either superficial keratectomy or diamond burr debridement (62 days) was not statistically significantly different from those that underwent medical therapy alone (46 days; P=0.33). Eyes treated with topical steroids had a statistically significant longer median time to resolution (61 days) compared to those that did not receive topical steroid (44 days; P=0.023). Common histopathologic findings in keratectomy samples included the presence of eosinophils, vascularization, and an eosinophilic membrane spanning areas of ulceration.

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Conclusion.—In this population, time to EK resolution was similar for horses treated with medical and surgical management. The use of topical steroids was associated with a prolonged time to resolution. Keratectomy samples from horses with EK had similar findings to those reported in other species.

Keywords

corneal ulcer; keratectomy; granulocyte; allergy; horse

INTRODUCTION

Eosinophilic keratoconjunctivitis (EK) is an inflammatory disease of the cornea and conjunctiva that is becoming more frequently recognized in horses.[1] Numerous etiologies have been postulated, although the direct pathogenesis is unknown. A type IV hypersensitivity response (i.e. a delayed hypersensitivity response) is suspected and may be associated with an environmental or parasitic allergen.[1, 2] Eosinophilic keratoconjunctivitis has been reported in several domestic species, including horses, donkeys, cats, and rabbits.[3–7] An apparently similar disease process, vernal keratoconjunctivitis (VKC), affects people and is defined as a chronic, bilateral, allergic conjunctivitis in patients that often have a history of atopic disease. This condition is most prevalent in young males.[8] Definitive diagnosis of EK is based on the presence of eosinophils on cytologic or histopathologic examination of corneal or conjunctival samples.[1, 9] While in most cases of VKC eosinophils are identified in scrapings, their absence does not entirely rule out the disease and other diagnostics including measurement of total and immunoglobulin E (IgE) concentrations in both serum and tears may provide further support of the diagnosis.[10] While feline herpesvirus-1 infection has been associated with feline eosinophilic keratoconjunctivitis,[11] no similar herpetic cause has been shown in the horse, nor in humans with VKC.

Eosinophilic keratoconjunctivitis typically presents with a combination of caseous ocular discharge, blepharospasm, chemosis, conjunctival hyperemia, white corneal plaques, and/or corneal ulceration.[1] Cytology and histopathology often reveal numerous eosinophils within the corneal plaque, although other inflammatory cells, including mast cells, lymphocytes, plasma cells, and neutrophils, may be present.[1] Recent studies have reviewed the effects of husbandry and environmental conditions on disease prevalence, as well as the clinical findings and treatment of EK.[2, 12] Retrospective studies conducted in the Mid-Atlantic region of the United States as well as in the state of North Carolina have shown the disease to have a seasonal occurrence, although no associations with husbandry, humidity or environmental temperature have been found.[2, 12]

Medical management is the mainstay of treatment in horses and has primarily been directed at modulating the inflammatory response and treating or preventing infection.[2, 13, 14] Treatment of corneal plaques or regions of non-healing ulceration via superficial keratectomy or diamond burr debridement have been reported,[4, 6, 14, 15] and these procedures may speed time to healing.[1, 15] Treatment with the systemic antihistamine cetirizine has been associated with decreased risk of recurrence.[2]

The primary aims of this study were to describe the epidemiologic factors associated with development of eosinophilic keratoconjunctivitis in the western United States, to present the clinical appearance of EK in this population of horses, to determine the efficacy of various approaches to medical management and to compare combined keratectomy and medical therapy with medical therapy alone. The characteristic histologic findings of corneal and conjunctival tissue from horses with EK are also described.

MATERIALS AND METHODS

Case selection

Electronic and hardcopy medical records at the William R. Pritchard Veterinary Medical Teaching Hospital at the University of California, Davis were reviewed for horses diagnosed with eosinophilic keratoconjunctivitis from January 1st, 1983 through December 31st, 2017. Definitive diagnosis of eosinophilic keratoconjunctivitis was based on clinical signs and the presence of eosinophils on corneal cytology and/or histopathology. The general hospital population for the same time-frame was used as a control population for comparison of patient signalment.

Data collection

Parameters obtained included patient signalment, clinical signs and duration, diagnostic tests performed, surgical and/or medical treatment, and time to resolution. Information regarding recurrence and patients' clinical status, as well as husbandry prior to disease onset was obtained from owners via telephone or email questionnaire. Atmospheric data was reviewed for the regions where patients were housed prior to disease onset. This data was obtained via the Quality Controlled Local Climatological Database in collaboration with the National Oceanic and Atmospheric Administration.

Statistical Analysis

Data was tested for normality using the Shapiro-Wilk normality test. Descriptive statistics included means and standard deviations for normally distributed data, and medians and ranges for data that were not normally distributed. Differences between medians were inferred using a Mann-Whitney U test. Differences in breed between the affected population and general hospital population were determined using a Fisher's exact test. All statistics were performed in GraphPad Prism v7.04.

RESULTS

Signalment

Twenty-nine horses with clinical examination findings and cytology or histopathology to confirm a diagnosis of EK were identified (Table 1). A diagnosis of EK was not made prior to the year 1993. Four cases were presented between the years of 1993–2002, 11 cases were presented between 2003–2012, and 14 cases were presented between 2013–2017. The mean age of affected horses was 11 ± 4 years. Sixteen of 29 horses (55.2%) were female, 12 of 29 horses (41.4%) were geldings, and one affected horse was an intact male (3.4%). The affected horses included eight Warmbloods (27.6%), six Thoroughbreds (20.7%), five

Quarter Horses (17.2%), four American Paint Horses (13.8%), three Morgan-Arabian crosses (10.3%), two Arabians (6.9%), and one Percheron (3.4%). Warmbloods were significantly over-represented in the affected population compared to the general hospital population for the same period (1993–2017) (27.6% versus 12.6%, P=0.024). No other breed was found to be over-represented compared to the general hospital population.

Seasonality

Disease onset was characterized by month, with 82.8% of cases presented between the first of May and the 31st of August (Fig. 1).

Environmental Factors

Average local temperature and precipitation in the county where the horses were kept at the time of diagnosis were evaluated. Mean daily temperature in the three months prior to disease onset was 18.8 ± 4.3 degrees Celsius. Mean precipitation in the three months prior to disease onset was 1.8 ± 2.3 centimeters. Housing information was available for 11 horses. Three horses (27.3%) lived in a box stall prior to disease onset and eight horses (72.7%) lived on pasture. Previous medical history via owner questionnaire was available for 10 horses, of which six were reported to have episodes of urticaria during the horse's ownership.

Examination Findings

Clinical signs were noted in one eye of 11 horses (37.9%) and in both eyes of 18 horses (62.1%), for a total of 47 affected eyes. Of the unilateral cases, the right eye was affected in six horses and the left eye was affected in five. Commonly observed findings at the initial examination included conjunctival hyperemia in 32/47 eyes (68.1%), corneal fluorescein stain uptake in 31/47 eyes (66.0%), blepharospasm in 23/47 eyes (48.9%), caseous or mucoid ocular discharge in 30/47 (61.2%), corneal plaques in 22/47 eyes (46.8%), and corneal vascularization in 20 of 47 eyes (42.6%). Other clinical signs included chemosis in 20/47 eyes (42.6%), corneal edema in 12/47 eyes (25.5%), epiphora in 4 of 47 eyes (8.5%), and a stromal cellular infiltrate in 3 of 47 eyes (6.7%). Notably, 14 of 29 horses (48.2%) were described as being pruritic immediately prior to or during hospitalization.

Treatment

Eight eyes of five horses underwent surgical treatment via superficial keratectomy, and four eyes of four horses underwent diamond burr debridement of the affected cornea. The remaining 35 eyes were treated medically (Fig. 2 & 3). Follow-up including time to resolution, defined as healing of ulceration and/or resolution of the corneal plaque, was available for 38 eyes of 23 horses. The median time to resolution for 11 eyes of eight horses treated with either superficial keratectomy or diamond burr debridement was 62 days (range: 17–203) and was not significantly different from the median time to resolution for 27 eyes of 15 horses treated with medical therapy alone (46 days; range: 13–401 days) (U=57, P = 0.33). Follow up was not available for one eye treated with diamond burr debridement.

The most commonly prescribed therapies included a topical steroid-antibiotic combination ointment and topical atropine ointment (Fig. 4). Systemic medications included flunixin

meglumine (≤1.1mg/kg IV or PO q12h) in 22 horses (75.8%), dexamethasone sodium phosphate (0.05–0.2mg/kg IV q12h) in seven horses (24.1%), hydroxyzine pamoate (1 mg/kg PO q8–12h) in five horses (17.2%), cetirizine hydrochloride (0.2–0.4 mg/kg PO q12h) in five horses (17.2%), and prednisolone (1mg/kg PO q24h) in one horse (3.4%).

The median time to resolution was significantly longer for the 26 eyes of 16 horses that were treated with a topical steroid (61 days; range: 17–401 days) compared to the 12 eyes of seven horses that did not receive a topical steroid (44 days; range: 13–91 days, U=85, P=0.023). Three horses that received topical steroids developed secondary infectious keratitis in one eye each (fungal keratitis in two eyes, stromal abscess in one eye), while these complications were not seen in eyes not treated with topical steroids. One of the fungal keratitis cases was enucleated subsequent to corneal perforation and the other had the longest time to healing (401 days). The eye that developed a stromal abscess took approximately 6.5 months (194 days) to heal. Fifteen eyes of nine horses that received topical lodoxamide did not have a significantly different median time to healing (median=57 days, range=13–203) than the 23 eyes of 14 horses that did not (median=49 days, range=20–401) (U=155; P=0.85). The eight horses that received a systemic steroid did not have a significantly different median time to healing (median=48 days, range= 41–91) than the 15 horses that did not (median=59 days, range=20–401)(U=44; P=0.64).

Histopathology

Histopathologic analysis of biopsy samples was available from nine eyes of six horses. Six corneal samples were available from lamellar keratectomy in four horses, with the procedure performed bilaterally in two. The remaining three samples were obtained via conjunctival biopsy from two horses. Analysis of keratectomy samples revealed the presence of eosinophils in five of the six samples. The sample in which eosinophils were not present was positive on staining with Luna stain, selective for eosinophils, and highlighted eosinophilic granules incorporated into a superficial membrane. Lymphocytes were present in each of the examined corneal tissues and one of the conjunctival tissues, neutrophils were present in all keratectomy samples and two of the conjunctival samples, and plasma cells were identified in three of the six keratectomy samples. Mast cells were not identified in any of the samples. Ulceration was evident histologically in each of the keratectomy samples as well as two of the conjunctival biopsy samples. An eosinophilic membrane associated with areas of ulceration was present in each keratectomy sample (Fig 5). Corneal stromal vascularization and hemorrhage were common findings, and stromal necrosis suggestive of sequestrum formation was observed in one case. Periodic acid-Schiff and Luna stains were performed on three corneal samples and all were positive for both stains. One horse that developed secondary fungal keratitis which resulted in perforation of the globe underwent enucleation as well as removal of a focal, movable mass which was identified between the globe and dorsal orbital rim at the time of surgery. Histologic examination of the mass revealed the tissue to be consistent with severe, chronic, eosinophilic dacryoadenitis with a focal granuloma composed of a large mass of eosinophils surrounded by macrophages, lymphocytes, and plasma cells (Fig. 6).

DISCUSSION

In recent years, EK has become a more prevalent diagnosis among equine patients.[2, 4] Nearly fifty percent of the cases described here were presented in the most recent four years, while the remainder were presented over the 20-year period prior to this. Whether EK is truly increasing in incidence or is simply now recognized more routinely by veterinarians is unclear. The cases described here were similar to previous reports of equine EK in that laterality was not seen, and seasonality of disease occurrence was appreciated with the majority of cases presenting in the summer months of June-August.[2, 12] The descriptive nature of this study did not allow statistical analysis of environmental factors in regards to development of clinical disease and further studies are required to fully analyze environmental factors as they relate to onset of EK. The majority of horses for which housing information was available were reported to live on pasture, which arguably may predispose to contact with environmental allergens. However, a previous study revealed that most horses diagnosed with EK were stalled during the day and on pasture at night.[12]

The over-representation of Warmblood horses in the EK-affected population versus the general hospital population is an interesting finding which has not been previously reported. Dermal allergies have been described in Warmblood horses,[16–19] and therefore a potential genetic predisposition for the development of allergic disease including EK may exist in these breeds. Further studies are warranted to investigate this hypothesis. As many of the horses in the population were reported to have urticaria or to be notably pruritic, it is possible that the ocular lesions of equine EK are a manifestation of systemic allergic disease. In people with VKC, the presence of increased serum concentrations of cytokines, enzymes, eosinophil-derived mediators, neuropeptides, and neurotrophins suggest a systemic cause of the local ocular disease.[8] Eczema, asthmas, and rhinitis have been reported in up to 41.5% of human VKC patients.[10] In support of a systemic allergic response being present in horses with EK is the evidence that systemic medications such as cetirizine can prolong the time to or prevent recurrence.[2]

Additional evidence that supports EK having a systemic etiology is that a case within this population is the second horse documented to have eosinophilic dacryoadenitis accompanied by keratitis. In 1989, Spiess et al described a yearling Thoroughbred colt with clinical signs consistent with EK and bilateral enlargement of the lacrimal glands.[20] Histology revealed the lacrimal glands in this yearling to be severely atrophic and essentially replaced by eosinophilic granulomas. While a parasitic etiology was proposed, no infectious agents were identified despite thorough investigation,[20] and thus this may have been a case of primary eosinophilic disease. Further studies are warranted to investigate lacrimal gland involvement in cases of equine EK, with ultrasonography perhaps providing the best non-invasive imaging modality.[21] Schirmer Tear Tests should be performed to evaluate aqueous tear production in suspected and confirmed cases, and tear supplementation should be provided to those patients with low aqueous tear production.

A significant difference in median time to disease resolution was not observed for the five horses that underwent superficial lamellar keratectomy under general anesthesia, nor the four horses that underwent standing diamond burr debridement when compared to the horses

that were treated with medical management alone. It is possible that those in which keratectomy was utilized were either more severe or refractory cases, which may have resulted in bias involving resolution. Anecdotally, clinicians report improved response to medical management following superficial keratectomy or diamond burr debridement in cases refractory to medical management prior to these interventions.

Horses treated with topical steroids had a significantly prolonged time to healing relative to those that were not treated with topical steroids. Secondary infection has been previously associated with an increased time to resolution in equine EK,[2] and in this population, each of the horses that developed secondary fungal keratitis were being treated with neomycin-polymixin B-dexamethasone ophthalmic ointment. One of the horses that developed secondary fungal keratitis had the longest time to resolution (401 days), and the other required enucleation subsequent to corneal perforation. A third horse treated with topical steroids developed a stromal abscess. The use of topical corticosteroids as treatment for EK in horses must be selective and closely monitored due to the propensity of the horse to develop infectious keratitis, particularly keratomycoses in endemic areas.[22, 23] The prevalence of corneal ulceration in this disease process (31 of 47 eyes in this population) in addition to the frequency of corneal vascularization (20 of 47 eyes at initial examination) suggests that systemic rather than topical corticosteroid treatment should be considered as an alternative in appropriate cases. The identification of a case of severe eosinophilic dacryoadenitis with eosinophilic granuloma formation further supports the role of systemically administered anti-inflammatory or immunomodulatory agents to address potential non-ocular tissue involvement in the disease process. While use of systemic steroids in this population was not associated with an increased time to healing as has been previously reported,[2] some horses received both systemic and topical steroids, which may have led to this result. The calcineurin inhibitor cyclosporine, which inhibits eosinophil and mast cell activation in addition to T cell proliferation, has been used widely to treat VKC in people, with varying success.[10, 24, 25] The drug has also been shown to be safe and efficacious in managing eosinophilic keratitis in cats.[26] Few horses within this population were treated with this drug, and thus statistical assessment of its efficacy was not investigated. Determination of the safety and efficacy of this drug for use in horses with EK should be carried out, particularly given the risk of infectious keratitis development associated with treatment with topical corticosteroids.

The histologic attributes of feline eosinophilic keratitis have been previously described and include infiltrates of mast cells and eosinophils in the corneal epithelium and stroma, vascularization, hypertrophy/hyperplasia of the corneal epithelium, a periodic acid Schiff reagent positive thickened basement membrane corresponding to areas of ulceration, and corneal excrescences composed of amorphous nuclear debris and eosinophilic material as well as eosinophils and free eosinophilic granules.[27] The histologic findings reported here are similar, and the thickened eosinophilic basement membrane was a consistent finding in each of the equine keratectomy samples examined. The morphologic findings of leukocytic infiltration, vascularization, and a superficial stromal acellular hyaline area corresponding to regions of ulceration as has been described in keratectomy samples from dogs with SCCEDs, are strikingly similar to the histologic findings in these cases of equine EK.[28] The abnormal eosinophilic membrane may prevent proper adherence of the corneal

epithelium to the basement membrane and the underlying stroma. This supports the utility of diamond burr debridement or lamellar keratectomy in the treatment of equine EK, as either would allow for disruption and removal of the membrane, allowing for proper re-epithelialization to occur. Interestingly, while mast cells were a common attribute of feline keratectomy samples,[27] none were seen in the equine corneas evaluated histologically in this study.

Limitations of this study include those associated with a retrospective study, including biased treatment, small sample size, choice of reference population, and variability in clinician experience and case management. Eosinophilic keratoconjunctivitis is an important equine ophthalmic disease affecting horses throughout North America. Despite numerous reports from the eastern United States, this is the first report of the disease occurring in the western United States. The morphologic aspects of EK beyond corneal cytology are described in keratectomy samples, revealing the presence of an abnormal anterior stromal membrane which may be the defining feature of the disease and explains prolonged time to healing of corneal ulceration. While the horses that underwent superficial keratectomy or anterior stromal puncture did not have a significantly shorter time to healing than those managed medically, the presence of this membrane supports these procedures as important treatment methods for equine EK. Future studies are required to further evaluate the etiologic as well as genetic factors that may play a role in the development of EK in horses.

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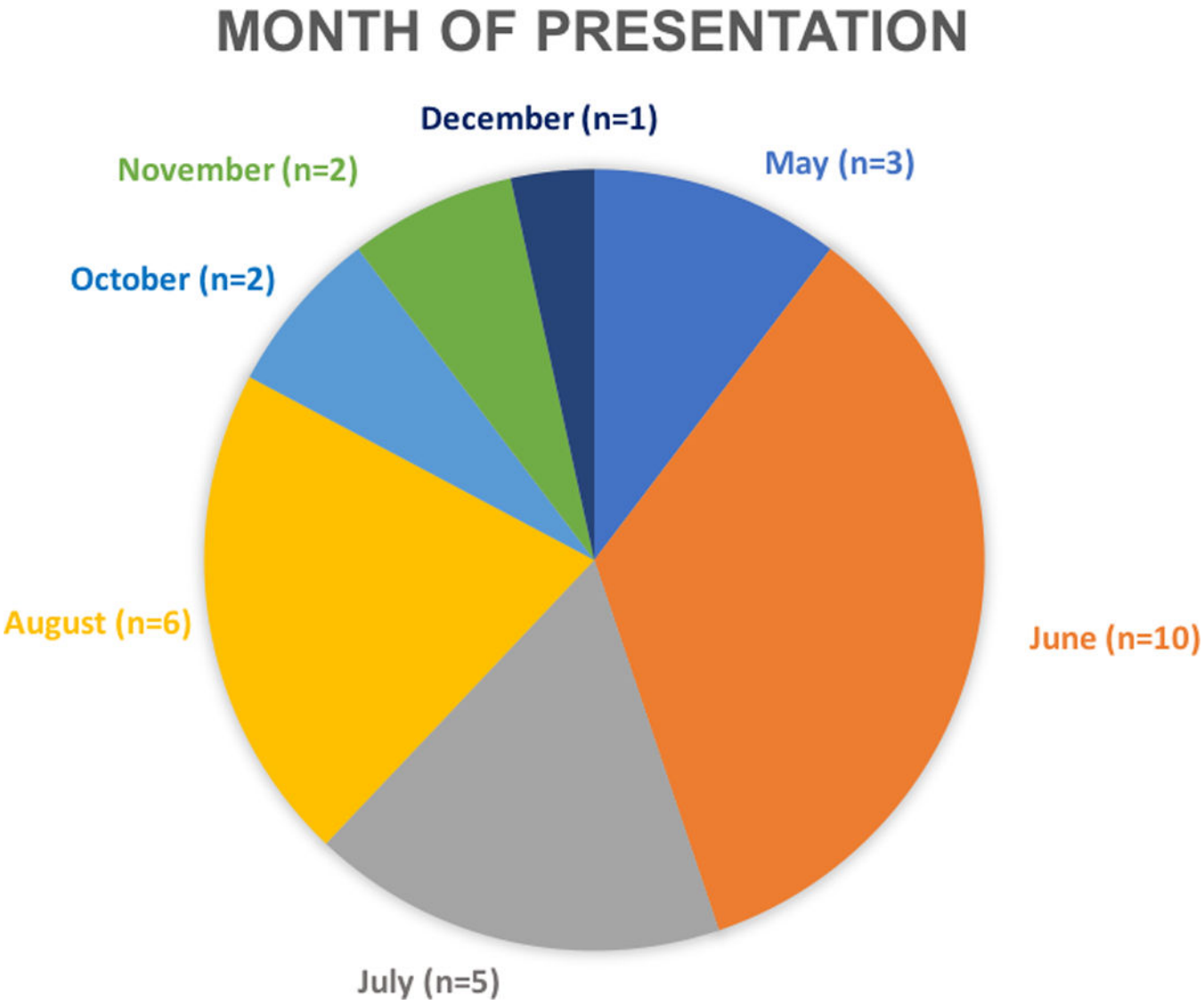

Figure 1.

Number of equine eosinophilic keratoconjunctivitis cases by month of presentation from 1993–2017 (n=29). Twenty-four of the 29 cases presented between May and August, accounting for 82.8% of case presentations. No cases were presented in January through April or in September.

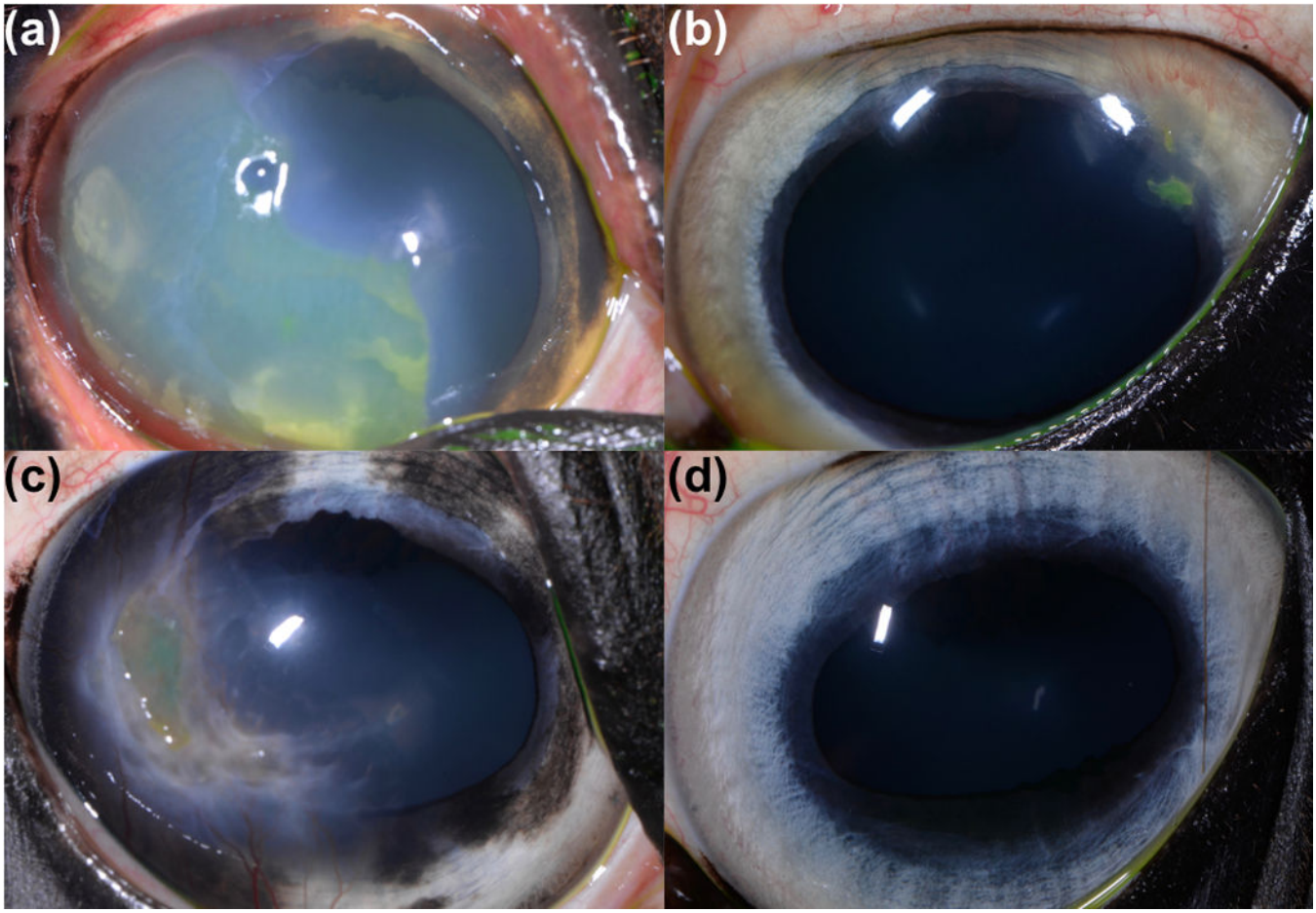

Figure 2.

Clinical photographs of a 7-year-old Paint mare diagnosed with eosinophilic keratoconjunctivitis OU. In (a) OD and (b) OS, note the conjunctival hyperemia, corneal vascularization, corneal plaques and ulceration which have stained green with fluorescein, and reflex anterior uveitis indicated by serum staining of the normally blue iris. Photographs (c) OD and (d) OS were obtained 8 weeks into medical therapy with a topical antibiotic, antifungal, and atropine OD and topical antibiotic and atropine OS. Systemic therapy included flunixin meglumine, dexamethasone SP, and cetirizine. The mare underwent a single diamond burr debridement OD. Time to healing was 3 months OD and 1 month OS.

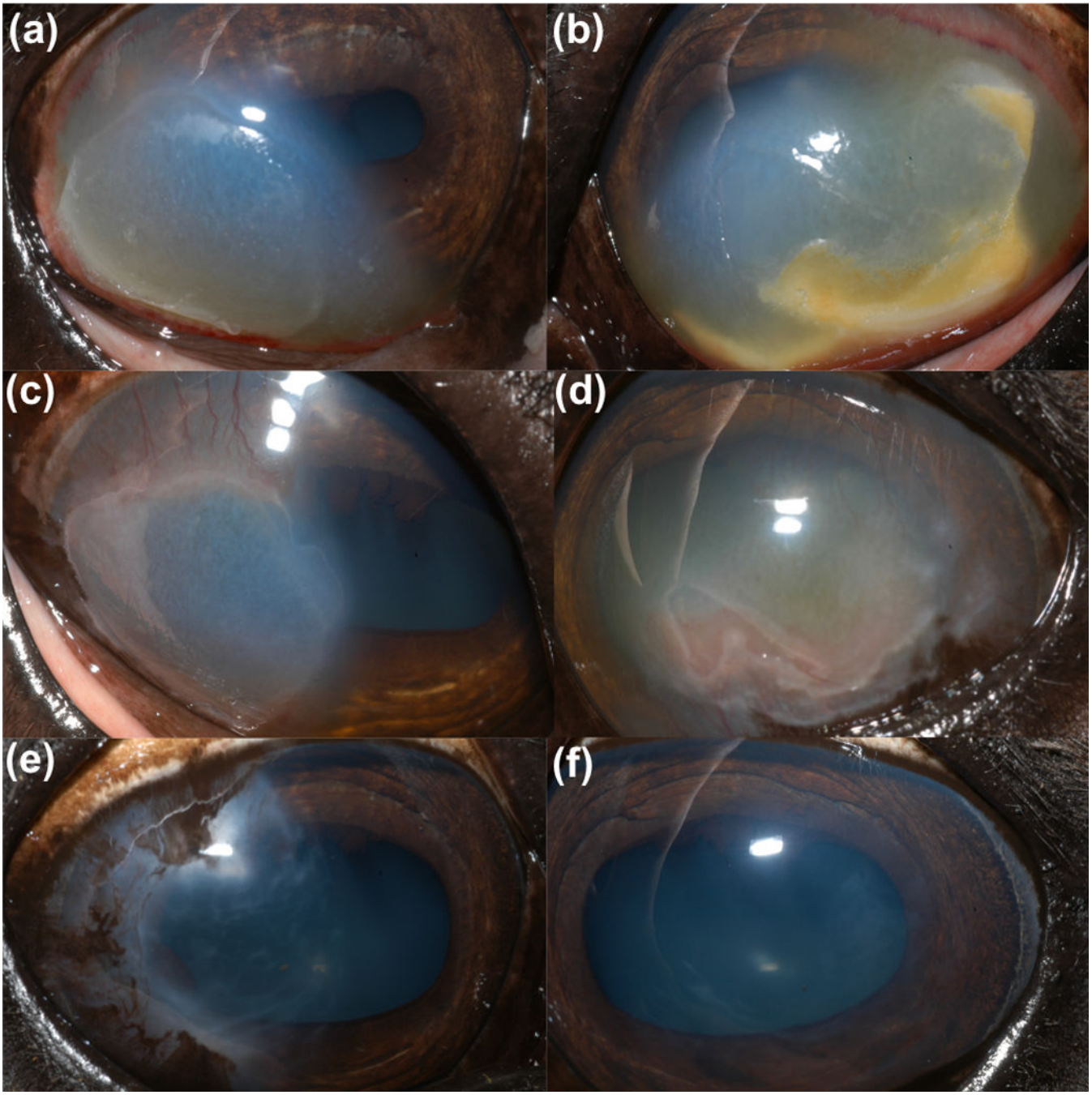

Figure 3.

Clinical images of a 13-year-old Oldenburg mare diagnosed with eosinophilic keratoconjunctivitis OU. Photographs (a) OD and (b) OS were obtained at the time of diagnosis. Photographs (c) OD and (d) OS were obtained 6 weeks into medical therapy with neomycin-polymixin-dexamethasone, atropine, amikacin, and cefazolin and subsequently cyclosporine, prednisolone acetate, and lodoxamide. Nine weeks following initiation of medical management a superficial keratectomy was performed OD due to failure of corneal

ulceration to heal. The right eye healed four months following diagnosis (e) and the left eye healed with medical management alone 3 months following diagnosis (f).

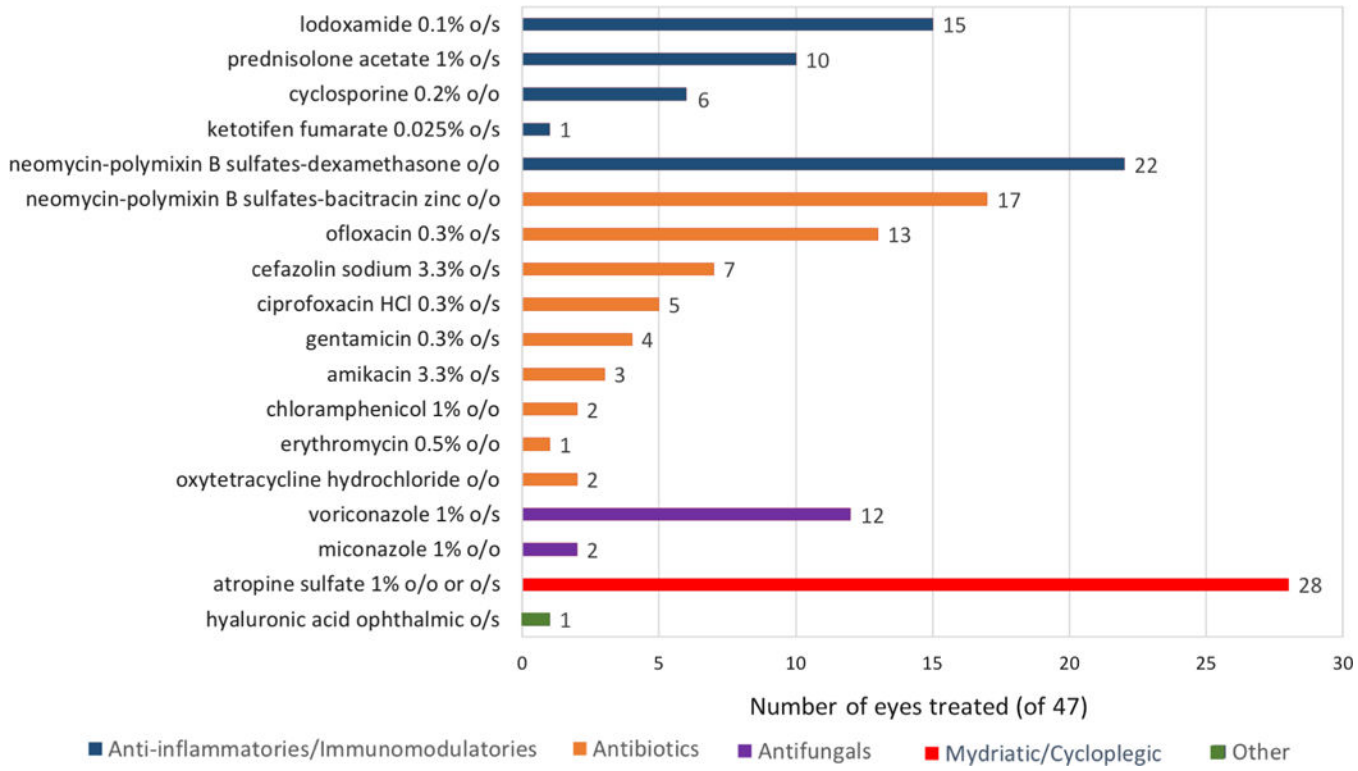

Figure 4.

Topical ophthalmic medications used in the treatment of equine eosinophilic keratoconjunctivitis in 47 eyes of 29 horses. (o/o= ophthalmic ointment; o/s=ophthalmic solution).

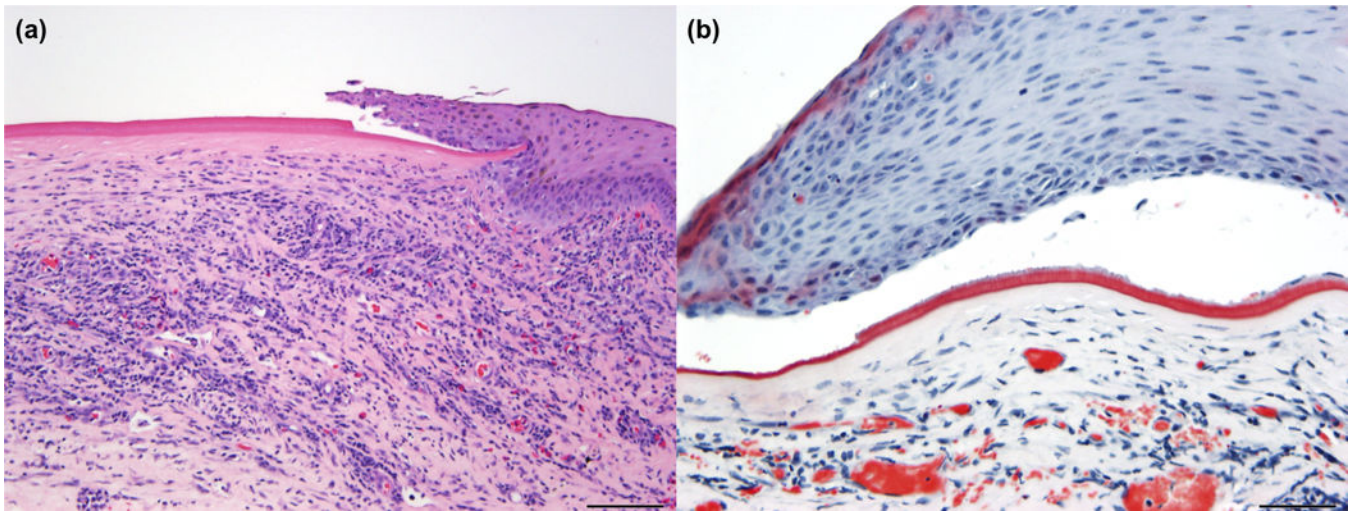

Figure 5.

Photomicrographs of keratectomy samples from a horse with eosinophilic keratoconjunctivitis. (a) Note the eosinophilic membrane which abuts the edge of the corneal ulcer and the abundance of neutrophils and blood vessels in the underlying corneal stroma. H&E (bar = 100 um). (b) The thick membrane beneath the non-adherent corneal epithelium stains Luna positive (red). Luna stain (bar = 200 um).

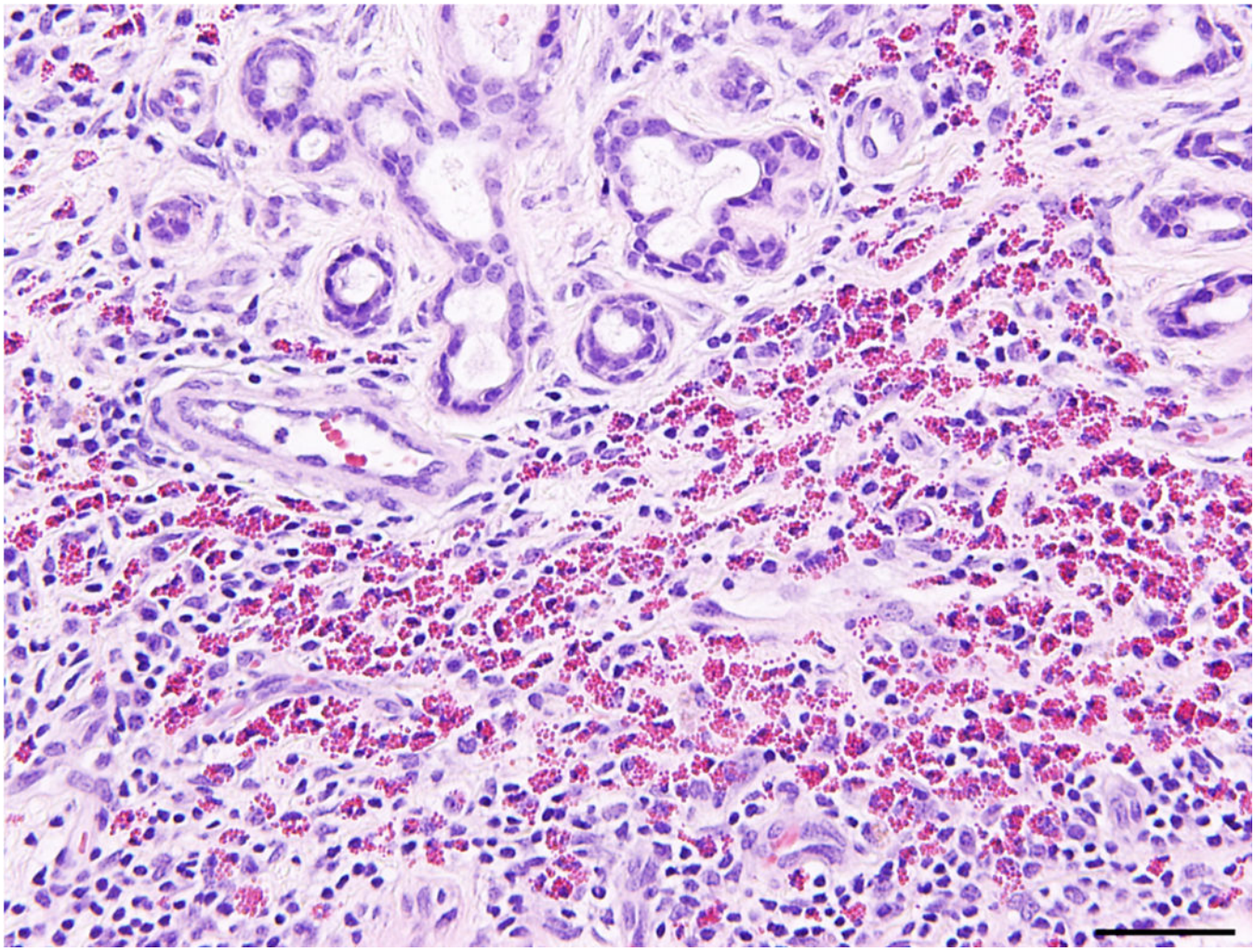

Figure 6.

Photomicrograph of the lacrimal gland from a horse with severe eosinophilic dacryoadenitis and keratoconjunctivitis. Atrophic acini in fibrotic stroma are to the top of the image. Small lymphocytes are scattered amongst the eosinophils. H&E (bar = 50 um).

Table 1.

Cases of equine eosinophilic keratoconjunctivitis treated by an ophthalmology specialty service in California (1993–2017)

Case	Breed	Age (years)	Sex	Eye(s) affected	Therapy	Time to resolution (days)	Comments
1	Thoroughbred	7	gelding	OU	keratectomy OU	OD-62, OS-81	
2	Thoroughbred	1	colt	OS	medical	NA	
3	Arabian	13	mare	OU	medical	OD-59, OS-13	
4	Quarter Horse	10	gelding	OU	medical	OU-76	
5	Thoroughbred	10	gelding	OD	medical	401	fungal keratitis OD following treatment with NeoPolyDex
6	Thoroughbred	16	gelding	OS	medical	21	
7	Quarter Horse	7	mare	OU	medical	OD-20, OS-enucleated	enucleation OS due to fungal keratitis with corneal perforation following treatment with NeoPolyDex, left-sided eosinophilic dacryoadenitis
8	Thoroughbred	5	gelding	OU	medical	OD-49, OS-20	
9	American Paint Horse	5	gelding	OU	medical	OD-194, OS-109	stromal abscess OD following treatment with NePolyDex
10	Morgan-Arabian cross	10	gelding	OU	medical	NA	
11	Percheron	5	mare	OD	medical	28	
12	Oldenburg	13	mare	OU	keratectomy OD, medical OS	OD-126, OS-111	horse pictured in Figure 3
13	Morgan-Arabian cross	15	mare	OU	keratectomy OU	OD-17, OS-203	
14	American Paint Horse	13	mare	OD	medical	365	
15	Swedish Warmblood	10	mare	OU	keratectomy OU	OU-55	
16	Warmblood	14	gelding	OS	keratectomy OS	41	
17	Arabian	18	mare	OU	medical	OU-50	
18	Holsteiner	3	filly	OU	medical	OU-100	
19	Quarter Horse	14	mare	OD	medical	47	
20	Thoroughbred	18	gelding	OS	diamond burr debridement OS	63	
21	Selle Francais	13	mare	OU	medical	OU-38	
22	American Paint Horse	10	gelding	OU	medical	OU-44	
23	Quarter Horse	10	mare	OU	medical	OU-21	
24	Warmblood	15	gelding	OS	medical	NA	
25	Warmblood	17	mare	OU	medical	NA	
26	Morgan-Arabian cross	13	gelding	OU	medical	NA	
27	Quarter Horse	10	mare	OD	diamond burr debridement OD	28	

Case	Breed	Age (years)	Sex	Eye(s) affected	Therapy	Time to resolution (days)	Comments
28	Warmblood	17	mare	OD	diamond burr debridement OD	NA	
29	American Paint Horse	7	mare	OU	diamond burr debridement OD, medical OS	OD-91, OS-35	horse pictured in Figure 2