Understanding and Treating Equine Recurrent Uveitis
Jacquelin Boggs, DVM, MS, Diplomate ACVIM
Area Veterinarian, Pfizer Animal Health

Objectives:
- Review of the etiology and pathophysiology of uveitis.
- Equine recurrent uveitis is multi-factorial.
- There is an association of leptospirosis and breed with the disease.
- Diagnosis, treatment and management of uveitis will be discussed.
- Current research and new therapeutic options.

Key points:
- Uveitis is the leading cause of blindness in horses worldwide.
- Equine Recurrent Uveitis (ERU) is not a single disease, but a syndrome with many subsets of disease and a variety of clinical presentations.
- ERU is an immune-mediated disease with multiple triggers. The genetic makeup of an individual’s immune system may contribute to susceptibility.
- Leptospirosis has been associated with cases of equine recurrent uveitis, but a direct cause and effect relationship has not been established.
- Certain breeds including Appaloosas and European warmbloods show a higher incidence of disease.
- Response to therapy is variable and long-term prognosis is guarded.
- Treatment is aimed at modulating the immune system, thus corticosteroids have previously been the mainstay of therapy.
- Alternative immune-modulating drugs are currently being researched and employed in the treatment of ERU.
- Ongoing research is occurring to better understand the factors that contribute to development of disease.

Introduction: By definition, uveitis is inflammation of the structures of the ocular uvea, including the iris, ciliary body and choroid. ERU is actually a complex of diseases that result in intraocular inflammation that either recurs or persists. The inflammatory process begins with compromise to the blood-ocular barrier due to some insult and is manifested as varying degrees of inflammation, degeneration and dysfunction of various intraocular structures. The precise clinical signs will vary depending on the stage of disease or type of uveitis the horse is experiencing, but miosis is the hallmark of acute inflammation. Under the “umbrella” of ERU are several clinically recognized syndromes based upon either observed inflammation or the stage of disease in the horse at the time of examination. When considering inflammation over time, experts have coined the terms “classic uveitis” and “insidious uveitis”.

“Classic uveitis” cases demonstrate repeated bouts of severe inflammation and pain in one or both eyes. This may resolve with or without treatment. In the time between bouts the eye(s) is quiet. If it is the first occurrence for the horse, the case is considered a primary case. By definition, a case is not considered “recurrent” until two or more classic episodes have occurred. Most often, the inflammation occurs primarily in the anterior chamber, however a subset of these cases have inflammation that occurs primarily in the posterior chamber resulting in severe vitreal opacity. The later is the least common and is seen mostly in Europe in warmbloods. In contrast, horses with “insidious uveitis” have historically never been observed to shown outward signs of pain, but the eye develops typical signs of chronic ERU. Ocular exam may reveal subtle degenerative changes that have occurred over time including subtle corneal haze, slight aqueous flare, change in iris color, corpora nigrans atrophy, cataracts, vitreous haze, slight miosis or retinal scarring. This has been primarily observed in European warmbloods, Appaloosas and draft horses.

An alternative classification scheme takes into consideration the severity of disease at the time of examination and is as follows: “Acute” cases demonstrate observable clinical signs associated with pain including bletharospasm, epiphora, lacrimation, or photosensitivity. In addition, chemosis, conjunctival hyperemia, corneal edema or vascularization, aqueous flare, hyphema, hypopyon, miosis or decreased ocular pressures suggest an active inflammatory process. “Quiescent” cases are pain free as they are experiencing the “quiet” stage of the disease. The horse shows no outward signs of discomfort, but slit lamp examination may reveal aqueous flare and thorough ocular examination may highlight chronic changes such as iris atrophy, synchiae, iris color change, optic disc scarring (“bullet hole” or “butterfly” lesions), cataracts, pigment on the lens or vitreous haze. In “End Stage Uveitis” obvious changes to the eye consistent with chronic and repeated bouts of inflammation are observed including, extensive corneal scarring, lens luxation, dense cataracts, glaucoma, retinal detachment or phthisis bulbi (shrunken, nonfunctional eye) and vision loss. The horse may or may not exhibit overt signs of pain in this stage.

Horses can present anywhere along the spectrum from acute to chronic stage and in either a classic or insidious form. Therefore, to aid in the diagnosis of uveitis the practitioner must take into consideration the extent of clinical signs revealed by the ocular exam, any history that may suggest a previous episode (even if not confirmed as uveitis at the time), and the horse’s breed. Furthermore, it is paramount that the practitioner rule out any other causes of uveitis, such as a corneal ulcer, stromal abscess, foreign body, neoplasia or keratitis (idiopathic or immune mediated) before arriving at a diagnosis of acute or recurrent uveitis. This is key as the mainstay of therapy for ERU is corticosteroids, which would be contra-indicated if anterior or posterior uveitis is secondary to another underlying etiology.

Pathophysiology: Uveitis starts as a blood-ocular barrier compromise. Blood vessels of the iris, ciliary body and choroid become thickened and congested. This results in leakiness of the tight fenestrations between cells of the ocular capillary walls that normally prevent cells and large molecules from passing into the aqueous and vitreous. Normally, the blood ocular barrier also isolates the intraocular structures from the immune system, thus resulting in an immune privileged site. When acute uveitis occurs,
neutrophils cross from the blood vessels into the intraocular structures and result in the observed clinical signs of hypopyon, aqueous flare and vitreous haze. Shortly thereafter lymphocytes infiltrate the connective tissue of the uveal and other ocular tissues. Lymphocytes, predominantly T lymphocytes of MHC class II, form clusters in the ciliary body that resemble follicles histologically and disrupt normal functioning of the eye. Once the immune system can recognize the proteins of the inner eye, antibodies and inflammatory cytokines are initiated resulting in the accumulation of heavy exudates. These exudates interfere with normal function of the ocular tissue. Cytokines result in tissue destruction. With repeated bouts of inflammation, chronic changes occur resulting in vision loss secondary to dense cataracts, synechiae, retina detachment, glaucoma or degeneration of the optic nerve.

While it is currently accepted that ERU is an immune-mediated disease, the exact mechanism is a topic of ongoing research. Multiple etiologies have been associated as triggering events. These include bacteria, viruses, parasites, vaccination; as well as, host conditions and individual genetics. The most notable bacterial infections include: leptospirosis, *Borrelia burgdorferi* (Lyme’s disease), brucellosis, *Streptococcus*, and *Rhodococcus equi*. Viruses such as Influenza A, equine viral arteritis and parainfluenza and parasites such as Onchocerciasis, Strongylus and Toxoplasmosis have also been variably implicated. Finally, any inflammatory condition in the host (abscesses, septicemia or severe trauma) that is overwhelming enough to cause a vasculitis and subsequent disruption of the tight junctions of the blood ocular barrier can create an environment for chronic stimulation of ocular tissues.

**Leptospirosis:** Of all the possible infectious triggers, leptospirosis is the most significant worldwide. In one report, leptospirosis was associated with at least 60% of cases of ERU in the Northeast US. According to Brooks, ERU prevalence in the USA is 1-8% or 9.2 million horses in the USA in 2005 resulting in 736,000 cases. The most significant serovars associated with disease are *L. interrogans* serovar *Pomona* (USA) and *L. interrogans* serovar *Grippotyphosa* (Germany and central Europe). It is reported that factors that increase the risk of leptospirosis in horses include: pasture access to cows, pigs and deer, close proximity to streams or ponds, use of piped pond water for drinking, heavy infestation of stable with rats and rainy season with persistent ground water. However, in the authors experience high seroprevalence of *L. interrogans* has occurred frequently on farms in MS with none or few of the above-mentioned factors.

Leptospirosis occurs when the spirochete gains access to the horse’s bloodstream through mechanical penetration of mucous membranes. Usually the infection is subclinical with mild elevations in temperature or minor “flu-like” symptoms only. While signs resolve usually uneventfully and often unnoticed, the bacteria is not eliminated from the body once resolution of disease has occurred. Leptospirae organisms colonize the renal tubules, often persisting for months and are shed in the urine. Ocular signs of classic uveitis associated with *Leptospira* do not usually occur during acute infection, but rather manifest months later. Inflammation associated with subsequent episodes may compromise the intraocular tissues.

While the exact mechanism by which *Leptospria* causes uveitis is a subject of much debate and ongoing research, several theories have been proposed based on the following
findings. Antibodies to pathogenic serovars can be found in sera, aqueous and vitreous in horses with leptospira associated uveitis. Antibodies are synthesized in the eye, and do not just “leak” across the blood-ocular barrier. *Leptospira* organisms can occasionally be cultured from the ocular media of horses with uveitis. There is genetic similarity between tissues of the equine cornea and *Leptospira* organisms. *Leptospira* may modulate the immune response of the eye as evidenced by pineal inflammation that accompanies some *Leptospria*-associated uveitis (similar to experimental models in laboratory animals). *Leptospira* organisms (lipoprotein fragments and DNA) are partially cross-reactive with equine ocular tissue.

Based on these observations, the following mechanism for inflammation and chronic stimulation by the immune system is proposed: 1) inflammation and uveitis occurs (either due to *Leptospira* or other organism) 2) a general loss of ocular immune tolerance occurs 3) Activated Antigen Presenting Cells (APC) in the uveal tract present autoantigens to the adaptive immune system, resulting in cross-reaction between infectious agents and self-antigens 4) self-antigens are recognized and processed in cytoplasmic endosomes to be presented to T cells 5) cleavage in endosomes can result in “neoepitopes” (novel confirmation or realignment of proteins) 6) intramolecular epitope spreading, which is the development of antibodies against these autoantigens, occurs 7) reactivation of APC can occur leading to reamplification of the inflammatory process. This sets the stage for recurring episodes of inflammation seen in ERU.

While there are currently many unanswered questions, this is an active area of ongoing research. While it is clear that systemic infection with pathogenic strains of *leptospira* can be a common trigger for recurrent uveitis, it is not the only factor. Not all cases of uveitis are seropositive for leptospira and there have been some cases that were seronegative however organisms were cultured. Thus, it is evident that there must be a genetic makeup of the host that contributes to susceptibility to disease. Recent research has suggested that the genetic makeup of the MHC complex of the immune system is integral to determining the susceptibility and the severity of the inflammatory episode. This is further supported by the fact that certain breeds have a higher prevalence of disease than others.

**Breed and Uveitis:** In Western, NY Appaloosas are 8.3x more likely to suffer from uveitis than other breeds. At risk individuals tend to have light coat patterns (overall roan or white), sparse pigment around the eyelids and scant manes and tails. It is theorized that these individuals have a genetic susceptibility due to aberrations in the MHC, particularly the Equine Lymphocyte Antigen subtype. Recent work in Germany further supports this theory as noted in German warmbloods at higher risk of developing ERU. Research continues on the genomic level to elucidate the components involved in the immune system and ERU interaction.

**Therapeutic options:** Treatment is aimed at decreasing inflammation, minimizing ocular damage from repeated bouts of inflammation and managing pain. Currently, there are no medications that aim to “prevent” the disease. Prior to initiating treatment owner counseling is important. Not only will there be exhaustive time and financial resources put towards treating recurrent bouts, but many uveitic horses will ultimately go blind despite therapy and some horses end up being euthanized. In addition >25% of horses
with uveitis suffer corneal ulcers over time, thus ongoing veterinarian involvement is key. However, there is an up side to the story and indeed many can lead productive lives. The inflammatory process must be minimized and the inappropriate response of the immune system controlled. Thus, corticosteroid treatment (dexamethasone HCL or Prednisolone acetate 1% topically or dexamethasone PO, IM or IV – variable doses) has been the primary modality. Furthermore, the addition of systemic NSAIDs may be necessary in cases of severe pain. Mydriasis is essential to therapy for all cases of acute uveitis. Atropine (1/4” strip or 0.1-0.3 ml, q 6-48 h) should be applied frequently until dilation of the pupil is achieved. In some chronic cases, the addition of phenylephrine can be utilized if atropine fails to dilate the pupil. However it can be epitheliotoxic so should be used judiciously. Oral doxycycline (10mg/kg PO q 12h) or enrofloxacin (7.5 mg/kg PO q 24h) have been used anecdotally in some cases of leptospiral infection. It is theorized that these drugs will be effective at eliminating the organism but no controlled studies have been done to validate these assumptions. In addition, the strong evidence to support an immune mediated disease makes efficacy of antibiotics unlikely. Bear in mind that horses with acute uveitis are very painful and can induce secondary corneal ulcers from self-trauma. In this case, corticosteroids should NOT be used, but alternative NSAIDs should be employed to address pain and inflammation; as well as, appropriate corneal ulcer treatment. Some horses may develop glaucoma and drugs such as Timolol, Dorzolamide or combination therapy are being used.

Suprachoroidal Cyclosporine A (CsA) implant surgery is becoming the treatment modality of choice in cases of clearly documented recurrent episodes when finances dictate (cost $2,000). This involves surgically instilling a small sustained-release device into the surpachoroidal space to allow direct administration of cyclosporine to the ciliary body. Cyclosporine is an immunosuppressant that blocks transcription of IL-2 production and responsiveness of T lymphocytes. The reservoir device allows long-term release of cyclosporine (or any other drug) into the bloodstream at 4ug/day continually for up to 3 years. Since CsA is hydrophobic, it has poor penetration into the intact cornea, but is highly effective when absorbed directly into the bloodstream. Clinical observations indicate that it takes 30-45 days after implantation to achieve adequate ocular levels of CsA. If recurrent episodes occur during this time, traditional therapy including atropine, systemic NSAIDs and topical steroids should be used. Early results are promising in that 81% have less inflammation and attacks and 85% were visual up to 24 months. In several recent studies, the number of uveitic flare-ups after surgery was significantly decreased (mean 0.05 flares/mo) in cases that had CsA devices implanted for ERU with a mean follow up of 29 months (1-7 years). The author’s personal experience is that horses respond favorably, quickly become comfortable and the frequency of attacks substantially diminishes or is abolished. The surgery requires an ophthalmologist or trained surgeon, but is quick and minimally invasive. The procedure is being performed at NC State, U Fla, MSU and Ohio State. Although horses in central Europe routinely undergo pars plana vitrectomy for ERU, results have been poor in the US, likely due to a variation of the disease.

Prognosis: Visual prognosis for horses suffering multiple attacks is guarded. While data on the incidence of blindness in uveitic horses is lacking, it is the leading cause of blindness in horses worldwide. In one study, following visual outcome of 160 cases over
11 years, 56% of cases lost vision in one or both eyes, 20% of cases became completely blind and 36% lost vision in one eye. Secondary complications and degeneration of ocular tissues are common sequela of uveitis. In the same study, 43 of the 160 horses (27%) with a ERU diagnosis were treated for corneal ulcers. The risk of corneal ulcers should be stressed to owners as many choose to medicate horses with painful eyes themselves, risking potentiating serious infections by applying corticosteroids and delaying proper diagnosis. Other complications include: corneal scars and calcific band keratopathy, iris atrophy and color change, posterior synechia, cataracts, lens luxation, severe vitritis, glaucoma and phthisis bulbi. In all cases, the incidence of complications was higher in Appaloosas than any other breed.

Other immunosuppressive medications that are currently being evaluated in horses with ERU are two drugs used in human medicine to prevent rejection in organ transplantation. They include tacrolimus (FK506) and rapamycin (sirolimus), which can be delivered via similar slow release delivery devices as cyclosporine. In addition, rapamycin can be delivered as a single dose intravitreal injection. Both hold promise for inducing T cell anergy in ERU horses and clinical trials are currently underway investigating their efficacy in horses.

**Summary:** Equine recurrent uveitis is a complex disease, which potentially has a variety of inciting factors and results in multiple clinical presentations. It has been established that there is an immune-mediated component to this disease, thus prompt and accurate diagnosis is necessary for improved outcomes. The mainstay of therapy has been mydriasis and immuno-suppression. The later achieved either via corticosteroids or new alternative therapies including sustained release cyclosporine A; as well as, promising new drugs like tacrolimus and rapamycin. ERU can have devastating outcomes, including significant financial costs to owners, repeated painful bouts for horses, blindness and sometimes loss of life. In addition, the associations of *Leptospira* and breed predilection in individual susceptibility are key to our understanding of the pathophysiology, treatment and prevention of this disease. The questions of whether *Leptospira* cause direct toxicity to intraocular structures, there is molecular mimicry between the organism and the host tissue, or whether the organism actually modulates the immune response in the eye are yet to be elucidated. Thus, ongoing research is necessary to continue to answer the questions regarding the roles that genetic makeup, autoantigens and immune mechanisms play in disease.

**References:** Available upon request.