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A Review of Equine Herpes Myeloencephalopathy (EHV-1)

Identification of Equine Herpes Myeloencephalopathy (EHM) (neurological form of herpes virus infection) occurs across the country every year. Occasionally clusters or outbreaks are identified. The most concerning outbreaks for the horse industry are those which occur in large shows with horses from many states and/or countries, as there is the potential for an small cluster to become a multiple location outbreak. Outbreaks lead to the cancellation of multiple shows, quarantine of multiple farms, and voluntary closure of some private and teaching hospitals.

The purpose of this article is to provide the reader with more information about Equine Herpes Virus – 1 (EHV-1), its clinical signs, transmission, biosecurity, testing, and therapy.

BACKGROUND on Equine Herpes Viruses - Five different herpes virus are commonly found in domestic horses. Equine Herpes Virus (EHV) infection is ubiquitous in the equine population and most horses are infected in the first few months of life. Following infection with an EHV, the virus is able to essentially hide from the immune system in the lymphoid or neurologic tissues; horses are then said to have a "**latent infection**." Once infected with EHV, horses are thought to be permanently infected. A latent viral infection can become reactivated via currently unknown mechanisms often during times of stress. Horses with re-activated latent infections are a source of infection for other horses.

EHV-1 was one of the first equine herpes viruses to be described. EHV-1 is an "alpha herpes virus" that can cause severe pneumonia in newborn foals, mild respiratory disease in young horses, abortion in pregnant mares, and neurologic disease in any age horse. The neurologic form of disease is a result of inflammation of the blood vessels surrounding the nervous tissues (i.e., the spinal cord and brain) leading to interrupted function and neuronal death. The neurologic form of EHV infection is generally referred to as Equine Herpes Myeoloencephalopathy (EHM) as both the brain and spinal cord can be involved. This form of herpes virus infection can cause clinical signs in any age, breed, or gender of horse. In many outbreaks (~80%) of the neurologic disease a specific mutatation of the DNA polymerase gene can be identified. EHV are specific to equid and are not known to be contagious to other species except camelids. It is believed that there has been an increase in EHM outbreaks in recent years and in 2007 the USDA-APHIS declared EHM to be a potentially emerging disease.

Our understanding of how and when an EHV-1 infection will lead to EHM is poor, but improving. It is likely that many environmental, host, and viral factors not yet elucidated are involved. The recently discovered mutation of open reading frame 30 (ORF 30) results in the presence of either an aspartic acid (D) or an asparagines (N) residue at position 752. The D_{752} variety (also referred to as the neuropathic strain) of EHV-1 is associated with 80 to 90% of the neurologic disease. Abortion outbreaks are almost exclusively N_{752} varieties. Infection with D_{752} leads to higher level of viremia, but not nasal shedding than N_{752}. How the degree of viremia is related to EHM is not known., but other factors are important in the development of EHM. Both varieties of the virus establish latency and can be detected or recrudesce in subsequent years.

PATHOGENESIS: EHV-1 infection begins in the epithelium of the respiratory tract. This leads to ulceration and nasal viral shedding for 4 – 7 days post infection. The virus spreads cell to cell and is present in the lymph nodes of the respiratory tract in 12 to 24 hours. The virus is picked up by leukocytes and the associated viremia delivers the virus to other tissues. The viremia typically persists for 5 to 7 days, and is thought to be a requirement for transport of the virus to the CNS and development of EHM. Once in the vasculature of the CNS, the endothelium is infected. The results in microvasculature damage of the CNS secondary to an inflammatory cascade including vasculitis, thrombi formation, extravasation of mononuclear cells, perivascular cuffing, and hemorrhage. Development of EHM is not a typical sequel of viremia, but the result is diffuse ischemic necrosis of the spinal cord.

EPIDEMIOLOGY: Infections with EHV-1 are common in performance horses. It is estimated that more than 80% of horses are latently infected with EHV-1. Cases of EHM are infrequent, occurring in small outbreaks with most horses showing fever and few horses developing signs of EHM. Outbreaks tend to be seasonal and are most common from late fall through spring. The index horse has often recently been transported. Signs of EHM are less common in younger horses and pony breeds. Severe signs are more commonly seen in older female horses. Outbreaks on premises in close proximity may not be related and molecular investigation of other genes, specifically ORF 68, has great value identifying different strains of EHV-1. To date ORF 68 variations have not been linked to any pathogenicity. A recent study looking at 4228 nasal swabs of horse with neurologic symptoms or fever found 2.7% tested positive for EHV-1 with most being the N_{752} variety. In that same study racing horses were over-represented in the positive group.

CLINICAL SIGNS: Infection usually develops following exposure to a horse shedding the virus but in a small percentage of cases, infection occurs by reactivation of latent virus. EHV typically causes a biphasic fever peaking on day 1 or 2 and again on day 6 or 7. With respiratory infections there is often significant nasal and ocular discharge, but not a lot of coughing. There may be some enlargement of submandibular lymph nodes. With the neurologic form there is typically minimal respiratory signs, with fever (rectal temperature greater than 102°F) being the only warning. Neurologic disease appears suddenly and is rapidly progressive reaching its peak intensity in 2-3 days. The degree of neurologic signs depend on the number, size, and location of the ischemic lesions in the spinal cord. In horses infected with EHM, clinical signs may include: nasal discharge, incoordination, hind end weakness, recumbency / paralysis, lethargy, urine dribbling, decreased tail tone, and/or head tilt. An upper motor neuron bladder is common early stages of the disease.

DIAGNOSIS: Horses that show a fever and any of these signs should be isolated and examined on the farm. Definitive diagnosis of EHM may only be possible with histologic and post mortem examination of CNS tissue. A presumptive diagnosis can be made when EHV-1 is isolated from nasal secretions or blood in combination with appropriate clinical signs. In suspicious cases where EHV-1 is a differential, a nasal swab, venous blood, serum, and CSF should be collected when possible. Samples collected from the nasal passages and whole blood (in EDTA) should be submitted for PCR analysis to evaluate for nasal shedding and viremia. Once exposed and infected with EHV the virus may be detected in blood and nasal swabs for 21 and 14 days respectively. Virus shedding maybe more transient and difficult to detect in the latter stages of disease. Horses can develop clinical signs as early as 1 day after exposure to the virus but clinical signs can be delayed up to 10 days after exposure. Nasal shedding typically peaks within 24 to 48 hours of EHV-1 infection and can quickly

become undetectable. However in outbreaks of EHM, the period of shedding is frequently prolonged, with horses shedding the virus for 21 days or longer after the appearance of clinical signs. Serum samples should be frozen and saved for paired evaluation with a convalescent sample 21 days after onset of clinical signs. A 4 fold increase in EHV-1 titers demonstrate an active infection. Cerbrospinal fluid typically show xanthrochromia and elevated protein concentrations without pleocytosis. PCR of the CSF is unrewarding, and detection of EVH-1 antibodies is not diagnostic of EHM.

Candidates for testing can be broken into three categories: non-exposed and a-clinical, clinically affected, and exposed but a-clinical. Non-exposed horses should not be tested. Clinically affected horses should be isolated and tested as described above. **Testing of a-clinical but know exposed horses is controversial.** A positive EHV-1 test result on a blood sample indicates viremia most probably resulting from an active infection, as it is unlikely that latent viral infection alone will give a positive result. However, the sensitivity and specificity of conventional PCR is typically ill defined, so the possibility of an erroneous result or interpretation is typically present. The random testing or screening of healthy horses for EHV-1 by conventional PCR should therefore be avoided. However, advances the use of real-time PCR, allow for more sensitive detection, greater specificity, and calculation of viral loads. Determination of viral load can allow for better characterization of disease stage, assessment of risk of exposure to other horses and monitoring of response to treatment. When viral loads are known, it is possible to distinguish between horses that are shedding high or low amounts of virus in nasal secretions, and to estimate the risk they pose to other horses. Similarly, the magnitude of the viremia can be determined, and inference can be made about the severity of the infection and the risk of progression.

TRANSMISSION: Horse to horse transmission of the herpes viruses is significant when horses are kept in close contact. However, contaminated equipment (e.g., water buckets, water hose handles, cleaning and grooming equipment etc) can be a source of infection and people can transmit the virus on their hands or clothes. An infected horse will excrete and aerosolize the virus in respiratory secretions. All horses with clinical signs are expected to be contagious, although horses not showing any clinical signs can shed EHV. Neurologic horses shed large quantities of virus and should be securely isolated. The virus is estimated to be viable for up to 7 days in the environment under normal circumstances but may remain viable for a maximum of one month under perfect conditions. The virus is easily killed in the environment by most disinfectants.

PREVENTION: Preventing exposure is likely to be of the greatest value as, for all of the equine herpes viruses, vaccination is not fully protective. Based on a study of the 2011 Cutting Horse outbreak, individuals who had more “at risk” activities or competed in more events had an increased chance of developing EHM. Things such as sharing water, grazing on the show grounds, using wash racks, and being tied in a barn were all considered risks.

An effective immune response requires local antibody production in the nasal mucosa, systemic antibody production, and a cell mediated immune response. No current vaccine achieves all of these measures. Current EHV vaccines may reduce the amount of the virus shed in secretions of the respiratory tract, but does not protect against the neurologic form. A recent study found both the high antigen killed vaccine and a modified live virus vaccine reduced nasal shedding, but only the killed vaccine reduced viremia.

Unfortunately, boostering well vaccinated horses during an outbreak is not helpful. While some clinicians believe that vaccination may facilitate development of EHM, evidence for this belief is lacking. **Vaccinations 14 days prior to exposure is not likely to be harmful, and may help limit the spread of the disease.**

BIOSECURITY: Horses with confirmed EHM should be isolated. Strict hygiene and biosecurity measures should be implemented because the virus can be aerosolized. Exposed horse must also be isolated to control spread of the virus. Based on an analysis of an outbreak at Colorado State, the authors concluded horses with active nasal EHV-1 shedding should be isolated in an airspace that is separate from other horses by strictly enforced biosecurity and isolation procedures. Personnel should wear protective clothing and adhere strictly to hand sanitation. Rectal temperatures should be taken on every potentially exposed case twice daily.

If it is necessary to admit a horse to a farm with ongoing cases, they should be current on EHV-1 vaccination and isolated away from the resident population. Veterinary care for suspect horses should be performed on the farm as much as possible to prevent spread of the disease. A detailed history should be provided on the movement of the patient, as well as, movement of other horses at the facility. Knowledge of the vaccination history (type and date) is also important.

As suggested by AAEP EHV control guidelines, clinically normal horses housed within the primary perimeter may be permitted segregated exercise periods outside the perimeter. Precautions should be taken, and may include: Exercise scheduled after general population's exercise period to avoid potential virus transfer to unaffected horses/barns by exercise riders. It is recommended to avoid strenuous exercise in at risk horses. Access to starting gate or similar equipment should be denied. Restricted use of ponies/outriders' horses—horses housed within the primary perimeter may only be escorted by horses housed within the same facility. Direct horse-to-horse contact is to be avoided. Prompt post-contact use of hand sanitizer by individuals having contact with horses during exercise.

Maintain isolation procedures (primary perimeter) for 28 days after the last suspected new infection resolves. Rectal temps should be taken and recorded on every horse at least once a day. Any horse with a fever should be tested by both nasal swab and whole blood PCR. In the absence of clinical disease, the risk of exposure decreases with time. A shorter quarantine period maybe justified, such as 21 days, if during this time no horse has had any fever (temperature taken at least 24 hours without treatment with non-steroidal drug), abortion or neurologic signs and all exposed horses are tested and have a negative test result using nasal swabs for EHV-1 by Real-Time-PCR. There should be compliance with requirements by state animal health officials for duration of quarantine and testing

TREATMENT: The prognosis after infection is dependent on the severity of the neurologic symptoms and the duration of recumbency. The disease spreads quickly and can have high morbidity and mortality. There is little scientific evidence to support specific therapies and treatment is mostly empirical. Most cases are treated symptomatically, although some practitioners have used antiviral therapy. Therapy for EHM cases can be broken into three stages of disease: prevention, shedding of virus with no clinical disease, and clinical signs of EHM.

Non steroidal anti-inflammatory drug therapy, including aspirin, are effective antipyretics. However it is their effect on platelets that may also be useful in horses with no clinical signs. Use of Aspirin (5mg/kg PO SID) which has a more potent effect on platelets than other NSAIDs early in the course

of disease (prevention and early exposure) may help to limit the degree of thrombus induced ischemia of the CNS. However a recent ex vivo investigation found no evidence that Aspirin altered EHV induced platelet activation. Use of aspirin in clinical cases of EHM is contraindicated as it may exacerbate hemorrhage. Other NSAIDs should be used to control inflammation and fever in all stages of the disease.

Unfractionated heparin and low molecular weight heparin have been shown in a recent ex-vivo study to reduce EHV induced platelet activation and should be considered as adjunct therapies. In this same study two phosphodiesterase inhibitors (IBMX and Cilostazol) were also effective. The commonly used phosphodiesterase inhibitor pentoxyfilline was not study, but could be considered for as an adjunct therapy.

Use of corticosteroids is controversial. Use of corticosteroids during the shedding and replication of the virus may down regulate adhesion molecules and interfere with the virus infected lymphocytes interaction with the CNS endothelial cells. Administration should be limited to 5 days and not concurrent with NSAID therapy. Longer duration of administration may interfere with tissue regeneration.

Antioxidants may help to reduce self perpetuating inflammatory cascades in the CNS. Drugs such as DMSO and vitamin E have been used. Supplementation with vitamin E at 5,000 to 10,000 IU PO SID is encouraged early and in all stages of disease.

L-lysine has been used in humans and cats for herpes infections. L-ysine competitively inhibits enteral absorption of L-arginine, which is a key amino acid in the replication of herpes viruses. It should be started early and is most likely to be effective in the early stages of the disease. A suggested dose is 15 g L-lysine PO BID.

Supplementation with zinc had a weak protective effect to reduce the risk of EHM in one study.

Acyclovir, Valcyclovir and Ganciclovir are antiviral drugs that have been studied in horses. Acyclovir is the least expensive, but the absorption is poor (<4%). The susceptibility of EHV-1 isolates varies with some susceptible at low concentrations and others requiring levels unachievable with oral dosing. Giving the drug intravenously should improve its effect, but the IV formulation is difficult to acquire. A suggested dose for Acyclovir is 20-30 mg/kg TID to QID orally. A suggested intravenous dose is 10 mg/kg TID given slowly (over 1 hour) to avoid neurologic side effects.

Valcyclovir and Ganciclovir are more effective drug but also more expensive. Based on work done at Oklahoma State Valcyclovir is recommended for prophylactic and early therapy. A loading dose of 27 mg/kg PO TID is given for 2 days, then 18 mg/kg PO BID for 7-14 days. If the horse remains febrile they may need to be maintained on the higher dose.

Ganciclovir may be more effective later in the course of disease. A loading dose of 2.5 mg/kg IV TID is given the first day and then maintained on 2.5 mg/kg IV BID. If an antiviral agent is used it should be given early in the course of the disease, preferably before the onset of neurologic symptoms.

Supportive care is critical in successfully managing recumbent and severely neurologic horses. It requires a tremendous amount of round the clock labor and specialized equipment.

PROGNOSIS: An outbreak in a stable in Findlay Ohio has been described. Of the 135 horses exposed, 117 (86%) had some clinical signs. Neurologic deficits were identified in 46 (39%) of the affected horses. 12 horses did not survive. The authors concluded being > 5 years of age, having had a rectal temperature of > 103.5 degrees F, and highest rectal temperature occurring on or after the 3rd day of the febrile period were the factors most predictive of the development of neurologic disease and death. Horses that remain standing have a good prognosis for recovery and improvement is generally seen in a few days. However it may takes months to over a year before a horse is completely recovered and returned to its previous level of performance. Some horses may be left with permanent residual neurologic deficits.

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