Equine Herpesvirus: What do we know?

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Equine herpesviruses are DNA enveloped viruses. They can cause respiratory disease, neurological disease, abortion, neonatal disease and genital lesions with latent lifelong infection which can re-activate and result in renewed viral shedding at any time of a horse’s life. To date, 11 equine herpesviruses have been identified worldwide. Four of these: EHV-1, EHV-3, EHV-4 and EHV-5 can pose serious health risks for domesticated horses with a significant economic impact, while EHV-2 infection is mostly suspected of predisposing to disease. Equine herpesvirus-1 and EHV-4 belong to the sub-family Alphaherpesvirinae, while EHV-2, EHV-3 and EHV-5 are Gammaherpesvirinae. \(^2\)

**EHV-1 & 4**

Equine herpesvirus (EHV)-1 is ubiquitous in most equine populations around the world. In 2009, the estimated prevalence was greater than 60%. \(^3\) It is primarily a highly contagious respiratory pathogen associated with a variety of clinical conditions in the horse. Of the herpes viruses, EHV-1 has the greater potential to cause severe disease, which includes abortion, neurological disorders, neonatal foal death or death by peracute pulmonary vasculitis.

Most commonly, young performance horses acquire the infection within the first weeks or months of life. The three most common major effects on the equine population are: \(^2\)

1. **Mild respiratory disease** associated with fever and loss of performance, which mainly affects younger horses.
2. **Late term abortions** (in the third trimester), or neonatal disease which can be responsible for significant economic losses.
3. **Neurological disease** (equine herpes myeloencephalopathy or EHM) that can occur in outbreaks, leading to high morbidity and mortality as well as economically debilitating movement restrictions.

The majority of EHM outbreaks have been associated with EHV-1 strains that have a single point mutation in the DNA polymerase gene at amino acid 752, which results in replacement of arginine (N) with aspartic acid (D). It is important to note that either form of the virus can cause neurological disease, but it is much more common for the D\(_{752}\) isolates than the N\(_{752}\) isolates. Viral genetics is not the only determinant of the development of neurological disease, but environmental and host factors also play an important role. \(^2,3\)

To the author’s knowledge there are no confirmed reports of EHM outbreaks in South Africa at the time of this publication (Pubmed database search and personal communication with Dr June Williams and Prof. Montague Saulez at the Onderstepoort Veterinary Academic Hospital). Latency and reactivation, either from EHV-1 strains currently in the country or from imported horses, places the horses in South Africa at risk of developing EHM. This manifestation of EHV-1 was designated a potentially emerging disease by the USDA in 2007 and has lead to devastating losses to the equine industry in Europe and North America due to outbreaks at riding schools, racetracks and veterinary hospitals. \(^4\)

Equine herpes myeloencephalopathy usually occurs in outbreaks of neurological disease \(^2\) and is unique amongst the causes of infectious neurological disease in that it does not require a vector. It is spread from horse to horse, unlike West Nile Virus, which is emerging as an important cause of neurological disease in South Africa \(^6,7\) and the equine encephalitis alphaviruses that are foreign to South Africa.

Equine herpesvirus-4 was the most commonly identified pathogen in a surveillance programme for important infectious respiratory pathogens in the USA. \(^8\) It most commonly causes respiratory disease (rhinopneumonitis) or poor performance, but has also been associated with incidental abortions and rarely with neurological disease. \(^9\)

The principal reservoir of infection for EHV is latently infected horses. It usually spreads from horse to horse, but environmental transmission becomes important in outbreak situations. It usually survives for less than 7 days in the environment, but has been detected for up to 35 days and is easily inactivated by heat and disinfectants. \(^10\) Equine herpesvirus spreads through aerosolised secretions from coughing horses and direct and indirect contact with nasal secretions and aborted foetuses or foetal fluids. In one outbreak of EHM, asymptomatic mules had significantly higher viral loads in nasal secretions than asymptomatic horses and are therefore important silent shedders of the disease. \(^11\) Anecdotally, both donkeys and mules have been clinically affected by EHM.

Pathophysiology and clinical signs

Primary infection of both EHV-1 and EHV-4 is at the respiratory epithelium following inhalation or direct contact with an infected fomite. Viral replication causes death of epithelial cells, with resultant epithelial erosions. Virus spreads from cell to cell in plaque-like fashion to reach the respiratory tract lymph nodes within 24 to 48 hours. It is at this point in the pathogenesis that there appears to be a fundamental difference between EHV-1 and EHV-4. In EHV-1 infections, an extensive predominantly CD8+ lymphocyte-associated viraemia is established, which delivers the virus to tissues around the body. \(^12,13\) This is how it reaches the blood vessels of the pregnant uterus and endothelial cells in the central nervous system (CNS).

The virus also reaches the neurons of the trigeminal ganglion within 48 hours, where latency is established. \(^14\) In one study, 30 trigeminal ganglia...
collected from 19 horses undergoing routine post-mortem examinations for a variety of conditions were PCR-positive for either neurotropic EHV-1 strains, non-neurotropic EHV-1 strains or both. A much lower proportion of submandibular lump nodes contained EHV-1 DNA.15

In contrast, infection of mononuclear leukocytes is rare in EHV-4 infections and may only occur with specific strains of EHV-4. This may explain the rarity of EHV-4 induced viraemia, abortion and EHM.13

In the pregnant uterus, infection of endothelial cells results in an inflammatory cascade and vasculitis with resultant thrombo-ischaemia leading to abortion.16 Attack rates can vary from isolated cases to above 50%.9

Neurological disease is caused by vasculitis and thrombo-ischaeemia of sections of the CNS subsequent to endothelial infection, which has also been referred to as ‘equine stroke’.17 The spinal cord gray and white matter is most commonly affected, with the brainstem being infrequently affected. During EHM outbreaks, approximately 10% of infected horses have developed neurological signs.18

Experimentally, vireamia can persist for 21 days,19 and the duration of EHV-4 shedding is usually shorter than for EHV-1.9

In young and naive horses, herpesvirus infection can cause severe pneumonitis leading to secondary bacterial infection and bronchopneumonia. In older horses, EHV infections or reactivation rarely causes clinically apparent respiratory disease. It is therefore not helpful to monitor for respiratory disease as a sign of impending abortion or neurological disease, as was sometimes done in the past. The only premonitory sign that is seen in most cases of EHV-1 abortion or neurological disease is pyrexia, and this often goes undetected unless horses are monitored very closely. Sudden late-term abortion with the foetus still in the allantochorion is suggestive of EHV infection. Infected foals that survive to term are born weak with marked, rapidly progressive lower respiratory tract disease and generalized lymphoid depletion.9

Clinical signs of EHM may include various degrees of ataxia and paresis, loss of anal tone, flaccid paralysis of the tail, distal limb edema, head tilt and urinary incontinence.9,20

Immunity

Protective immunity to EHV-1 and EHV-4 after natural or experimental infection lasts for 3-6 months. During this time, horses are not only protected from reinfection but also do not shed the virus or develop viraemia after exposure. Infection with EHV induces a strong humoral immune response but this response does not adequately protect against disease in isolation, because antibody titers are not correlated to protection from infection. High viral antibody titers are associated with decreased nasal shedding but do not affect the extent and duration of viraemia.21 In addition to IgM and IgG, mucosal IgA is important as a first-line defense mechanism. Protective immunity requires multiple immune components, with cellular immunity possibly playing the most important role. Cellular immunity is mediated through CD 8+ cytotoxic T-lymphocytes (CTL’s). These CTL’s mediate recovery from infection and their numbers are also correlated to protective immunity.22,23

The half-life of maternally derived antibody is less than 4 weeks, which suggests that vaccination of foals may need to commence prior to the currently recommended 4-6 months of age.24

Diagnosis

Clinicopathologically, infection with EHV-1 and EHV-4 is characterised by initial leukopaenia (lymphopaenia and neutropenia) from 7-14 days of infection, followed by lymphocytosis up to day 28 after infection.9

A diagnosis of EHV-1 or EHV-4 can be confirmed through immunofluorescence, polymerase chain reaction (PCR) or viral isolation from nasopharyngeal swabs or blood, histopathology, PCR or immunohistochemistry of infected tissues (especially foetal tissues), or serology. False negatives can occur for a variety of reasons. It is important to recognise that viral shedding from the respiratory tract may be short-lived and intermittent. The best cases to sample are those with very early infection (possibly prior to clinical signs) and therefore horses who have had contact with the index case(s) and are showing pyrexia but no other clinical signs, are the best candidates to test. In EHM, clinical signs may only start to appear at the end of viraemia, which can lead to false negatives if nasopharyngeal swabs or blood are tested. In addition, seroconversion may already have occurred by the time a horse presents for investigation of neurological disease which further complicates diagnosis.

Cerebrospinal fluid of horses with EHM will typically have a mononuclear pleocytosis with elevated protein and xanthochromia. This is suggestive of, but not diagnostic for EHM. Accurate, definitive, antemortem diagnosis of latent infection is not currently possible, but would be of great value in control programmes.9

Treatment and prognosis

Treatment for EHV is symptomatic and supportive. Young horses with respiratory infections should be rested for at least 7 days past clinical resolution. Antibiotics are usually not necessary, unless secondary bacterial infection has set in.

Mares who abort generally do not require treatment, however they should be evaluated to ensure that foetal membranes are not retained (which is rare in EHV abortion) and rapidly treated if this is the case.

Horses with EHM may require prolonged intensive and supportive care. Most horses that survive will recover fully by one year after infection. The use of acyclovir has been reported, but subsequently found to only have 2.8% oral bioavailability in the horse.20,25

Valacyclovir and penciclovir have better oral bioavailability in the horse and would therefore be better choices if antiviral treatment is pursued.26,27 In one small experimental study, despite high concentrations in plasma and mucous, no effect was seen of the treatment with valacyclovir on clinical signs, viral shedding and viremia of EHV-1-infected ponies.28
Prevention and control
A large majority of recovered horses carry latent EHV infections for prolonged periods, potentially for life and therefore all horses are at risk for developing disease.9 Reactivation can occur at any time and has been observed after transport, handling, re-housing and weaning as well as after corticosteroid administration.14-30 The goal of vaccination is to limit the severity of clinical signs and more importantly, to decrease shedding which decreases the risk of infection propagation. Vaccination is therefore useful in an outbreak and as part of a comprehensive preventative health programme. One study in healthy breeding stallions illustrates the effect of regular whole herd vaccination: 13-55% of healthy unvaccinated breeding stallions were found to shed EHV-1 in their semen prior to routine whole herd vaccination. This number decreased to 0% after implementation of regular vaccination of all horses on a breeding farm, but a decrease in EHV-1 shedding was not apparent on farms where the entire herd was not vaccinated. By vaccinating the entire herd, the amount of virus circulating between animals is significantly reduced.31,32

Due to the short duration of immunity to EHV, frequent vaccination is required to maintain maximal protection. There is partial cross protection to EHV-4 after vaccination against EHV-1.9

The American Association of Equine Practitioners currently recommends the following vaccination schedule to protect against equine herpesvirus (www.aaeep.org/ehv.htm): See Table 1.

The AAEP guidelines for infectious disease outbreak control provides a comprehensive plan for implementing control measures of EHV-1 (www.aaeep.org). Important factors in outbreak control include early identification of cases, appropriate isolation and timely quarantine measures. Horses showing clinical signs as well as in contact horses should be completely isolated from at risk horses, ideally in separate airspaces.33 Serial PCR of nasal secretions is important to try to abbreviate quarantine, because the severity of clinical signs cannot predict the duration of shedding.34

EHV-2
The significance of EHV-2 infection remains unclear, since it is frequently isolated from both healthy and diseased horses. It is mostly thought to predispose to secondary infections. In one study, equine herpesvirus infections were significantly more prevalent in the trans-tracheal wash fluid of horses suffering from respiratory disease compared to a healthy control group, but interestingly EHV-2 had the highest prevalence in the diseased group.35

The EHV-2 load was also significantly larger in foals suspected to have Rhodococcus equi pneumonia compared to normal foals of a certain age, but further study is required to fully understand the role of this virus in equine health and disease.36

Keratitis with superficial punctate or dendritic lesions has been associated with EHV-2 infection. Herpetic keratitis in the horse may be treated with topical antiviral drugs such as 0.1% idoxuridine, 4-12 times daily. Non-steroidal anti-inflammatory drugs such as 0.03% flurbiprofen should be used with caution. Oral L-lysine is helpful in treating human and feline herpetic keratitis but there is limited information available on its use in horses.9

EHV-3
Equine coital exanthema, also known as genital horse pox, equine venereal vulvitis or balanitis and coital vesicular exanthema is caused by EHV-3. It is endemic in most equine breeding populations and causes papules, vesicles, pustules and ulcers on the penis and prepuce of infected stallions and the vaginal and vestibular mucosa and perineal skin of infected mares. The virus is venereally transmitted and labile in the environment but can be transmitted iatrogenically. An outbreak of unilateral rhinitis (an atypical manifestation) was ascribed to iatrogenic EHV-3 transmission through a contaminated endoscope. Viral replication is limited to epidermal skin or muco-cutaneous margins. Epithelium is destroyed when the lytic viral infection induces a pronounced localised inflammatory response. As with other herpesviruses, latency is established with re-activation resulting in reactivation and re-excretion. Re-infection can occur in subsequent breeding seasons but the severity of lesions tends to decrease with subsequent infections.37-39

The biggest impact of EHV-3 is in the suspension of breeding activity in an attempt to limit disease transmission, which can result in substantial

<table>
<thead>
<tr>
<th>Table 1: Equine Herpsevirus Vaccination Schedule</th>
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<tbody>
<tr>
<td><strong>Group of horses</strong></td>
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<tr>
<td><strong>Recommended vaccination schedule</strong></td>
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<tr>
<td>Non-breeding previously vaccinated horses</td>
</tr>
<tr>
<td>• less than 5 years</td>
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<tr>
<td>• all horses on breeding farms where there are pregnant mares</td>
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<tr>
<td>• at facilities with frequent movement on and off premises</td>
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<tr>
<td>• show horses</td>
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<tr>
<td>Re-vaccination every 6 months</td>
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<tr>
<td>Adult horses with unknown vaccination history</td>
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<tr>
<td>3 vaccinations, 4-6 weeks apart</td>
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<tr>
<td>Pregnant mares</td>
</tr>
<tr>
<td>5th, 7th and 9th month of gestation</td>
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<tr>
<td>Barren mares at a breeding facility</td>
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<tr>
<td>At the onset of the breeding season</td>
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<tr>
<td>Stallions and teasers</td>
</tr>
<tr>
<td>Before the start of the breeding season</td>
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<tr>
<td>Foals</td>
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<tr>
<td>First vaccination at 4-6 months of age, second vaccination 4-6 weeks later and third vaccination at 10-12 months of age. Re-vaccinate every 6 months after the primary series.</td>
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<tr>
<td>In an outbreak</td>
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<td>Re-vaccinate horses at risk of exposure</td>
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economic loss. Painful lesions can also lead to loss of libido. Affected mares can still be artificially inseminated while symptomatic, because EHV-3 infection does not affect the outcome of pregnancy.38

Diagnosis of EHV-3 is through identification of characteristic clinical signs and viral isolation or PCR of swabs or scrapes from the edges of fresh lesions, or a fourfold increase in serum antibody titer.38

The treatment for equine coital exanthema is sexual rest until the lesions have healed, but daily cleansing, anti-inflammatory and antibiotics (to prevent secondary bacterial infection) may shorten the recovery period. The use of a 5% acyclovir cream in both stallions and mares has been reported.38

EHV-5
Equine herpesvirus 5 is highly prevalent in healthy equine populations. One Lipizzaner population in Italy was found to have a 73% and 80% prevalence in nasal swabs and blood respectively for EHV-5, while symptomatic, because EHV-3 can still be artificially inseminated and abortion in mare infected with lineage 1 west nile virus, south africa. Emerg Infect Dis. 2011 Jun;180(3):279-89.


Horses present with fever, cough, decreased appetite, weight loss, tachypnoea and respiratory distress. Thoracic radiographs and ultrasound typically reveal a severe nodular interstitial pattern. Trans-tracheal aspirates will be negative for bacterial and fungal growth, unless secondary infection has set in. Bronchoalveolar lavage (BAL) may contain increased numbers of degenerate and non-degenerate neutrophils. Histology of lung biopsy specimens have shown interstitial expansion of alveolar parenchyma with collagen (interstitial fibrosis), interstitial inflammatory infiltrate, hyperplastic and hypertrophied type 2 pneumocytes lining the alveoli, intraluminal accumulation of neutrophils and macrophages within the alveoli as well as degenerate type 2 pneumocytes and occasional intranuclear inclusions in the alveolar macrophages.5,44 Equine herpesvirus 5 can be detected in lung tissue, bronchoalveolar lavage fluid or both using PCR.

Treatments that have been used include corticosteroids and antiviral drugs. In one case report of 5 EMPF cases, 2 of the 5 horses survived and returned to their previous level of performance.44

References

References 21 - 44 available on request.
Pneumabort-K+1b
Your Aid in Prevention of Respiratory Disease and Abortion

P. O. Box 783720, Sandton, 2146, South Africa. Website: www.pfizeranimalhealth.co.za