1. Introduction

Equine herpesvirus-1 (EHV-1) belongs to the family of herpesviruses and the subfamily of Alphaherpesvirinae. EHV-1 is ubiquitous in horses worldwide, and most horses are infected with EHV-1 early in life with overall low morbidity. Following this primary infection, a life-long latency is established, and it is currently estimated that ~80% of horses are latently infected with EHV-1. Combined with frequent reactivation, this is the dominant feature ensuring the virus' survival in the horse population. In addition, viral survival depends on a number of immune evasive and suppressive mechanisms that are initiated by the virus and prevent the host's immune system from establishing long-term protective immunity.

2. Clinical Disease Manifestations

Clinically, EHV-1 is the cause of viral respiratory disease, late-term abortions, neonatal foal death, equine herpesvirus myeloencephalopathy (EHM), and chorioretinopathy. EHV-1 has also been shown to infect the male reproductive tract, residing in the testicular vasculature and seminal fluid following infection. However, the clinical relevance of these findings has yet to be determined. Differences in the pathogenic potential of viral strains can influence clinical outcome, as do several additional host and environmental factors.

Respiratory Disease

Respiratory disease caused by EHV-1 can be mild or subclinical in older or previously infected horses. In contrast, the respiratory disease observed in young immunologically naïve horses can be severe, lasting for 2 to 3 weeks. This form is characterized by a biphasic fever, lethargy, anorexia, coughing, and nasal and ocular discharge that is initially serous and then becomes mucopurulent.

Abortions and Neonatal Foal Death

EHV-1 is also the cause of late-term abortions in the third trimester of pregnancy, in addition to the premature delivery of foals that die soon after birth. Mares infected with EHV-1 can appear healthy and abort 2 weeks to several months after infection or reactivation of the virus. Sporadic abortions in individual mares are most common, but EHV-1 outbreaks with high attack rates (so-called abortion storms) have been reported and depend on herd management, immune status, and viral factors.

EHV-1 Myeloencephalopathy

In addition to respiratory disease and reproductive consequences, EHV-1 also causes a neurological disease apparent in up to ~10% of infected horses in
outbreak situations. Onset of EHM typically occurs between 9 to 13 days after primary infection following a secondary fever response that is associated with a cell-associated viremia. Clinical signs range from mild, temporary ataxia to paralysis that can lead to recumbency and urinary incontinence, bladder dysfunction, and sensory deficits in the perineal area.

EHV-1 Chorioretinopathy

EHV-1 infection can lead to chorioretinopathy, causing permanent “shotgun” lesions of the retina in a substantial proportion of infected horses (Fig. 1). Ocular lesions primarily affect the choroidal vasculature and appear between 4 weeks and 3 months after primary infection. Clinically, lesions do not have a significant effect most of the time, but histopathological changes mirror those observed in the central nervous system (CNS) and uterus.

3. Pathogenesis of EHV-1 and EHM
Pathogenesis of Infection

Initial infection with EHV-1 commonly occurs within the first few months of life via respiratory secretions, fomites, or exposure to placental or fetal materials containing the virus. After infection, a life-long latency is established in the trigeminal ganglion and lymphoid tissues and reactivation can occur during periods of stress and lead to renewed shedding, clinical disease, and infection of other horses. Primary infection with EHV-1 occurs via the respiratory tract and results in replication, shedding, and spread of the virus via the basement membrane to the underlying tissues and local lymph nodes of the head. After further replication and infection of leukocytes, a cell-associated viremia is established between days 4 and 10 postinfection. This cell-associated viremia is central in the pathogenesis of EHV-1 because peripheral blood mononuclear cells are a robust immune and inflammatory cell population in the vasculature, as well as carriers of EHV-1, and transport the virus to sites of secondary infection including the CNS. In the vasculature of the CNS, contact between infected leukocytes and the vascular endothelium leads to endothelial cell infection, inflammation, thrombosis, tissue necrosis, and ultimately EHM directly after viremia on day 9 to 13 postinfection.

Viral and Host Factors

A number of recent studies have examined viral and host factors that contribute to the establishment of viremia, virus and host interaction during viremia, and transfer of virus to vascular endothelial cells of the spinal cord. For viral factors, the identification of a single nucleotide polymorphism in the viral polymerase gene that results in a coding change (D752 vs. N752), is the most studied and has been shown to be strongly associated with an increased duration and magnitude of viremia and neuropathogenicity. Other viral proteins that have thus far been identified to be directly involved in viral spread and cell-to-cell transfer in vitro include ORF2, ORF17, gB, gD, gp2, and UL3. For host factors, increased age, breed (Standardbred, Warmblood, Thoroughbred, Quarter Horse, Paint, Appaloosa, Spanish horses, Fjord, Draft, and Lipizzaner), female sex, increased magnitude and duration of viremia, and pregnancy or nursing have been identified with an increased incidence of clinical EHM. In addition, more recent in vitro studies have shown that cellular mechanisms that contribute to EHM pathogenesis include the induction of interferons, chemokine responses, activation of the mitogen-activated protein kinase (MAPK) pathway, regulation of adhesion molecules, and cell-to-cell contact. In addition, a dysregulation of hemostasis after EHV-1 infection has been shown in vitro and in vivo and is thought to play an important role in the neuropathogenesis of EHV-1.

4. Control of EHV-1 and EHM

Vaccination and Immunity

Currently, there are a number of inactivated and modified live vaccines for EHV-1 commercially available. Vaccination regimens are commonly implemented in large breeding or stud operations and in the racing industry to reduce viral spread. However, although current vaccines can limit viral nasal shedding and clinical signs of respiratory disease, the reduction of viremia is more limited, as is prevention of abortion. Currently only two vaccines are licensed for providing some protection from abortion, and none of the current vaccines appear to reduce the incidence of EHM.
recommend vaccination after the initial series at 6-month intervals for horses younger than 5 years of age, horses on breeding farms or exposed to pregnant mares, horses on premises with frequent movement, and performance or show horses (https://aaep.org/guidelines/vaccination-guidelines/risk-based-vaccination-guidelines/equine-herpesvirus-rhinopneumonitis). However, in the face of an outbreak, vaccination of sick or already exposed animals is not recommended. Vaccination of healthy horses in neighboring premises may aid in the limit of viral spread but should not be performed with the expectation of preventing EHM. Furthermore, in light of some reports suggesting an increased incidence of EHM as a result of frequent vaccination, initiation of EHV-1 vaccination should be carefully considered.24,32 Some of the problems related to developing better vaccines for herpesviruses are the establishment of latency and the fact that herpesviruses use many immune evasion mechanisms to subvert induction of protective immunity. In addition, EHV-1 affects multiple sites of the body, and a better understanding is needed to define what protection entails. This includes whether the goal is to protect from respiratory disease, abortions, and EHM or whether also trying to prevent viral nasal shedding, viremia, and possibly establishment or reactivation from latency. In order to achieve any of these goals, it is vital to understand what is required for protection from these different aspects of EHV-1 infection. After natural infection, a short period of immunity protects against reinfection, and horses are likely protected from all clinical disease manifestations as well as shedding and viremia.33 This immunity includes a combination of virus-neutralizing antibodies, which play a role in reducing nasal viral shedding;33 and cytotoxic T-lymphocytes (CTLs), which are most critical for protection from secondary clinical disease and viremia,19,34 as well as multiple components of mucosal and systemic innate immunity.35,36 However, the only identified reliable correlate of immunity for protection from EHM is precursor frequencies of CTLs (pCTL).19,34 Unfortunately, good laboratory assay systems for regularly evaluating pCTL are lacking. Some studies have also identified high preinfection EHV-1-specific IgG and IgG3/7 (IgGb) titers in serum as well as a rapid induction of IgG3/7 in the absence of interferons and chemokines in nasal secretions after infection as an indicator of protection from respiratory disease, shedding, and viremia,37 but these studies did not include horses that showed clinical EHM or abortions. Consequently, predictions may not apply the same way to secondary EHV-1 manifestations. An earlier study found that protection from EHM was associated with increased IgG3/7 (IgGb) and decreased IgG3/5 (IgGT) levels and lower IgG3/5 to IgG3/7 or IgG1(IgGa) ratios in serum prechallenge.38 A third study that used the neuropathic strain Ab4 and induced clinical EHM in 3 out of 8 yearling horses identified decreased induction of interferon (IFN) alpha and increased induction of interleukin (IL)-10 in nasal secretions collected from horses that went on to develop clinical EHM.7 Together, these results suggest that a shift from a T-helper 1 type cellular immunity to a T-helper 2 type immunity may correlate with an increased risk for developing EHM. These data are supported by a study evaluating host risk factors correlated with EHM by using the “aged mare model.”39 However, studies that include horses of all ages, sexes, and breeds that are affected by clinical EHM would be needed to further confirm host risk factors for EHM, correlates for protection from EHM, and ultimately development of more efficacious vaccines.

Management and Biosecurity

In the absence of better vaccines, current measures to protect horses from EHV-1 and EHM outbreaks should rely on the implementation of effective management practices aimed at reducing the likelihood of introducing and disseminating EHV-1 infection.10 On a day-to-day basis, this means quarantine for new incoming horses or horses returning from an on-site event. At a show or event, this means avoiding sharing food/water buckets or other equipment that could be contaminated, washing hands, limiting stress as much as possible, and generally keeping horses away from others that are not from the same cohort. Horses presenting with fevers and nonspecific symptoms that may or may not include neurological signs should be isolated until a diagnosis is secured. If an acute EHV-1 infection and shedding have been diagnosed on the premises, stringent biosecurity measures should be taken, including isolation of potentially infected horses for 21 to 28 days after the last new infection (https://aaep.org/sites/default/files/Documents/EHV1_4_Final.pdf).10 In an outbreak situation, all animals on the premises should be monitored for clinical signs which includes taking temperatures twice daily. Sick or exposed animals with a confirmed diagnosis should be segregated using distance, airspace, or a separate building and supported by separate personnel and equipment. Foot traffic should be kept out of the primary biosecurity perimeter, and hygiene measures should be implemented (i.e., foot baths, hand washing, and protective clothing). Other horses on the premises that have not been diagnosed and appear clinically healthy should be monitored daily for fevers, respiratory signs, submandibular lymph node enlargement/sensitivity, signs of limb/ventral edema, or neurological signs and tested for viral nasal shedding and viremia if any clinical signs suggestive of EHV-1 are detected. Quarantined healthy horses should only be lightly exercised separately from nonquarantined horses, preferably outdoors. Furthermore, exposed horses should not be moved until it is determined they are not going to develop disease or pose a risk to unexposed horses. Vaccination of sick or already exposed animals on the premises is not recommended. For diagnosis, a combination of nasal swabs and whole blood collected in ethylenediaminetetraacetic acid (EDTA) tubes is recommended to
evaluate nasal shedding and viremia associated with EHV-1 infection. Testing of asymptomatic horses is done to verify the absence of shedding at the end of the quarantine period. Virus isolation is considered the “gold standard” test for making a laboratory diagnosis of EHV-1 infection and should be attempted, especially during epidemics of EHM, concurrent with use of rapid diagnostic tests such as quantitative polymerase chain reaction (qPCR), to achieve retrospective biological evaluation of EHV-1 infection or vaccination offers limited protection in particular regarding EHM. This lack of an induction of protective immunity to EHV-1 is likely due to immunomodulatory properties of the virus and latency establishment. Thus, early detection of suspected cases and monitoring of high-risk horses, as well as stringent biosecurity measures, currently represent the most reliable means of preventing outbreaks of EHM.

5. Summary
In conclusion, EHV-1 is ubiquitous in horses worldwide, and >80% of horses are estimated to be latently infected with the virus. EHM is a relatively rare but devastating sequela of EHV-1 infection that can occur in up to ~10% of infected horses in outbreak situations. The mechanism underlying CNS endothelial infection is unknown, as are the risk factors that determine its occurrence. Although viral factors are certain to be important, host factors including age, breed, sex, pregnancy, and magnitude and duration of viremia as well as environmental factors are also critical. Immunity after infection or vaccination offers limited protection in particular regarding EHM. This lack of an induction of protective immunity to EHV-1 is likely due to immunomodulatory properties of the virus and latency establishment. Thus, early recognition and diagnosis of suspected cases and monitoring of high-risk horses, as well as stringent biosecurity measures, currently represent the most reliable means of preventing outbreaks of EHM.

Acknowledgments

Declaration of Ethics
The Author has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

Conflict of Interest
The Author has no conflicts of interest.

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