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Respiratory Infections by Equine Herpesvirus Types 1 and 4 (28-Feb-2002)

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Summary

Equine respiratory disease associated with infection of the upper airway mucosal epithelium by equine herpesvirus type 1 or type 4 is a condition seen primarily in young horses. The two herpesviruses are remarkably ubiquitous, and infection is enzootic in most horse populations. Exposure to the viruses occurs early in life with an estimated 80 - 90% of horses being infected by 2 years of age. The majority of such respiratory infections run a subclinical or mild course, and a large number of foals seroconvert without manifesting clinical signs. Clinical respiratory disease caused by the equine herpesviruses is acute, treatment is palliative, prognosis is favorable, and sequelae are rare. However, widespread outbreaks of herpesvirus respiratory disease may occur, and infection spreads rapidly within susceptible horse populations. Natural transmission is readily accomplished by contact with another infected horse, its aerosolized respiratory secretions, or virus-contaminated fomites. The fraction of all viral upper respiratory tract disease in horses that is attributable to EHV-1 and EHV-4 is unknown. The two herpesviruses are closely related genetically and antigenically and share many epizootiologic, clinical and pathologic features. Of the two viruses, equine herpesvirus-4 is by far more commonly isolated from cases of herpesvirus respiratory disease, while respiratory infection by equine herpesvirus-1 has the greater potential for clinically severe sequelae (abortion, neurological disorders, neonatal foal death, ocular disease, or death by peracute pulmonary vasculitis). Diagnosis of herpesvirus respiratory disease in horses cannot be made on the basis of presenting clinical signs alone and requires laboratory assistance.

Introduction

Two equine herpesviruses (EHV), EHV-1 and EHV-4, are among the large spectrum of respiratory pathogens capable of causing clinically significant upper respiratory tract disease (URTD) in the domestic horse [1-6]. EHV-1 and EHV-4 are remarkably ubiquitous in the world's horse population and are primary respiratory pathogens that can cause respiratory tract disease without major predisposing factors. Evidence suggests that the two herpesviruses circulate and are transmitted year round. While respiratory infections of horses with EHV-1 and EHV-4 are often subclinical, both viruses have the potential for causing widespread outbreaks of severe upper respiratory tract disease. The greatest burden of herpesvirus respiratory disease is borne by young horses, with the window of highest risk for infection between weaning and two years of age.

EHV-1 and EHV-4 have large (150 kb), double-stranded DNA genomes enclosed within an icosahedral protein capsid and surrounded by a delicate lipid envelope containing a dozen different glycoproteins (Fig. 1). The fragility of the envelope limits the survival of the herpesviruses in the environment and makes them highly susceptible to destruction by common disinfectants. Both EHV-1 and EHV-4 genomes contain 76 homologous, co-linear genes whose spatial arrangements are illustrated in Fig. 2.

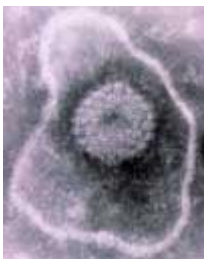


Figure 1. Electron photomicrograph of a negatively stained virion particle of equine herpesvirus type 4 (EHV-4). The central nucleocapsid structure, comprised of 162 hollow capsomeres arranged as an icosahedral shell, encloses the viral DNA. The nucleocapsid is surrounded by a flexible lipid membrane (envelope) containing numerous virus-encoded glycoproteins. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 2. Spatial arrangement, relative size and direction of transcription of the 76 genes contained within the genomes of EHV-1 and EHV-4. - To view this image in full size go to the IVIS website at www.ivis.org . -

Within each of the two herpesvirus types, isolates worldwide comprise a remarkably homogeneous group with minimal genetic or antigenic diversity [2,6-8]. Nucleotide sequence diversity within each virus type can be demonstrated, but is limited. Comparison of the complete genomic sequence of two unrelated isolates of EHV-1 has revealed only 42 nucleotide differences that give rise to amino acid coding changes (Davis-Pointer N. Personal communication). As such, EHV-1 and EHV-4 each consists of multiple, co-circulating strains with minimal genetic heterogeneity but detectable and quite dramatic differences in pathogenic potential. Nucleotide sequence diversity between EHV-1 and EHV-4 within individual homologous genes ranges from 55% to 84% [9,10], and the two herpesviruses are easily distinguished by differences in the electrophoretic profiles of their DNA restriction endonuclease fragments (Fig. 3).

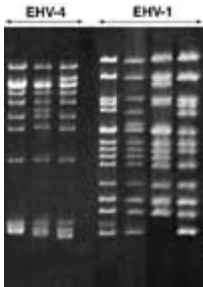


Figure 3. Agarose gel electrophoretic profiles of the DNA fragments generated by BAMHI digestion of the genomic DNA of EHV-1 and EHV-4. - To view this image in full size go to the IVIS website at www.ivis.org . -

Antigenic diversity is also limited [6]. Each virus exists as a single neutralizing serotype. The viruses are antigenically stable and do not exhibit the gradual, continuous changes in epitope structure of their surface glycoproteins that is characteristic of equine influenza virus. Because the permanent biological reservoir of latent herpesvirus is excluded from recognition by the host immune system, immune-mediated selection of spontaneously occurring antigenic variants is not a significant biological activity. Virologic surveillance of new isolates for antigenic variants is therefore not relevant to the overall control procedures for equine herpesvirus UR TD. Induction of protective immunity against the herpesviruses is associated with strong humoral and cellular immune responses in both the systemic and respiratory mucosal compartments.

The four critical priorities facing veterinary personnel engaged in the management and control of equine herpesvirus UR TD are

1. Effective prevention measures,
2. Rapid establishment of diagnosis in the face of an epizootic,
3. Therapeutic intervention in individual clinical cases, and
4. Control of the spread of infection during outbreaks of disease.

Respiratory Disease Prevalence

Only a few investigations have systematically addressed the quantitative significance of equine UR TD attributable to EHV-1 or EHV-4 (equine rhinopneumonitis) (Powell DG. Personal communication) [1,11-17]. From that handful of available studies, the following conclusions can be drawn about the importance of EHV-1 and EHV-4 as causes of clinically overt UR TD in the horse:

1. The relative importance of the various etiologic agents responsible for equine viral UR TD (herpesviruses, influenza virus, rhinoviruses, equine arteritis virus, etc.) fluctuates greatly from year to year and is, likewise, dependent upon

geographical location and specific characteristics of the target population of horses (e.g., age, population size and density, environment, performance category, vaccination and exposure history, and management practices).

- Neither the precise annual incidence (number of cases/1000 horses) for EHV-1 and EHV-4 URTD nor the exact proportion of total clinical cases of viral URTD attributable to the two herpesviruses have, at this time, been determined for any defined study group of horses.
- The occurrence of overt EHV-1 or EHV-4 respiratory tract disease in foals younger than three months of age is uncommon (particularly in foals from vaccinated dams), presumably because of maternally derived passive antibody.
- The greatest burden of URTD caused by EHV-4 is borne by foals during their first year of life; i.e., as sucklings and weanlings between 4 and 12 months of age. EHV-4 is thus a major etiologic agent for the commonly observed but ordinarily mild upper respiratory disease in foals often described by practitioners as "foal snots".
- In locales supporting large broodmare farm operations, the relative importance of EHV-4 as a cause of URTD is also significant in yearling horses assembled for activities associated with annual yearling sales events. Horses escaping exposure to EHV-4 infection until yearlings can be expected to experience clinically more severe episodes of respiratory disease.
- In two- and three-year-old horses in training or on the racing circuit, in which horses from diverse origins are kept together in enclosed, confined spaces such as race or show barns, outbreaks of viral respiratory disease are common. Epizootics of EHV-1 or EHV-4 upper respiratory tract disease have been described in such settings with some outbreaks resulting in neurological sequelae. Quantitatively, herpesvirus outbreaks generally take second place to equine influenza virus as a significant threat for acute URTD in two- and three-year-olds.
- Previously exposed horses older than 3 years of age continue to show serological evidence of periodic re-infection by the EHV-1 and EHV-4 throughout their lifetimes with only minimal and transient clinical signs of respiratory tract infection. In such animals, however, the risks for the more serious sequelae of abortion and/or neurological disease following subclinical respiratory infection by EHV-1 are not eliminated.

Epizootiology

Both EHV-1 and EHV-4 are enzootic in most domestic horse populations. Widespread exposure of adult horses to EHV-4 demonstrable by high rates of seropositivity has been documented [6]. By 2 years of age, most horses have seroconverted to EHV-4 [18]. Seroprevalence is less for EHV-1. The two herpesviruses have evolved to occupy a unique ecological niche within the horse that allows postinfection viral persistence (latency) over the lifetime of the individual animal. The epizootiological reservoir for EHV-1 and EHV-4 is the large and globally distributed pool of latently infected, intermittently-shedding carrier horses, which may comprise up to half of a given horse population [19].

The epizootiological life style of the two equine herpesviruses is one of continuously repetitive cycles of three consecutive events that amplify and maintain the virus reservoir:

- Inter-generational (vertical) transmission of the viruses from latently infected dam to foal;
- Postinfection establishment of viral latency in affected foals; and,
- Periodic reactivation and shedding of latent herpesvirus to result in homo-generational (horizontal) horse-to-horse virus transmission (Fig. 4).

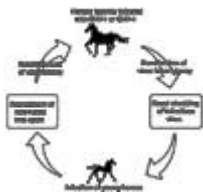


Figure 4. Biological life cycle of EHV-1 and EHV-4, illustrating the central role of latently infected carrier horses as reservoirs from which the herpesviruses are perpetually transmitted to new generations of equine hosts. - To view this image in full size go to the IVIS website at www.ivis.org . -

Within each individual horse, the biological life cycle of EHV-1 and EHV-4 can be described as a quiescent intra-host reservoir of replicatively-inactive (latent) virus punctuated by episodes of reactivation from the quiescent state during which infectious virus is released from the latent reservoir into the nasal secretions with the opportunity for transmission to susceptible equine hosts. In this evolutionarily ancient, cyclical pattern of equine herpesvirus (1) infection, (2) establishment of latency, (3) periodic reactivation from latency, and (4) respiratory shedding with transmission to new hosts, the majority of horses are recruited early in their lives into the epizootiological reservoir for EHV-1 and EHV-4. This epizootiologic cycle of EHV-1 and EHV-4 transmission is principally a silent one, with the majority of transmission events resulting in inapparent respiratory tract infections or signs so mild as to cause little alarm [18,20-22]. As such, the seroconversion rate for the two herpesviruses exceeds the incidence of clinically recognizable URTD associated with viral infection. It is only the occasional case (or outbreak) of respiratory tract infection by the two equine herpesviruses that rises above the usually silent

transmission activity to produce a level of tissue damage within the respiratory tract severe enough to result in clinically overt URTD.

Respiratory disease caused by EHV-1 or EHV-4 is typically more widespread among young horses, with disease outbreaks most likely in the period between weaning and 2 - 3 years of age [4] (Powell DG. Personal communication). Risk factors for such outbreaks of herpesvirus URTD include overcrowding, heavy parasite burden, poor nutritional state, climatic extremes, concurrent disease, and the intermingling of animals from different social groups. Transmission of EHV-1 and EHV-4 infection between horses is efficient, and outbreaks of respiratory disease can spread rapidly in susceptible horse populations. In some outbreaks of herpesvirus respiratory disease occurring in densely populated clusters of susceptible horses, morbidity can approach 100%. A more common scenario for equine rhinopneumonitis is low clinical morbidity with a higher rate of subclinical infection demonstrable by seroconversion.

Latency

The latently infected, chronic carrier horse is one in which EHV-1 or EHV-4 (or both) persists, subsequent to exposure, in a noninfectious form beyond the usual recovery period for the acute respiratory tract infection. The asymptomatic carriage rate is high with as many as 60% of horses recovering from primary respiratory infection with the two herpesviruses becoming latently infected, lifelong carriers capable of serving as a source of infection for susceptible horses [19,23]. The cellular reservoirs for latent EHV-1 and EHV-4 are sensory neurons of the trigeminal ganglia and T lymphocytes within lymphoid tissue draining the equine upper respiratory tract (e.g., submandibular, retropharyngeal and bronchial lymph nodes) [24,25]. In such resident cells, the viral genome is present without production of infectious virus particles. The latent herpesvirus genome persists in a non-integrated, transcriptionally restricted state. While infectious EHV-1 or EHV-4 is exposed to the full force of the horse's immune control, the latent herpesvirus is protected from recognition and destruction by the immune system and can remain with the horse for life in the presence of strong acquired immunity.

The latent carrier state is critically important to the maintenance and spread of EHV-1 and EHV-4 and to their success as widespread, deeply entrenched pathogens of the horse. Because herpesvirus latency is a reversible state, the latent virus genome may become reactivated to regain its full transcriptional activity with a consequent production of infectious virus. Periodic reactivation of latent EHV-1 and EHV-4 is associated with episodes of stress or corticosteroid administration [26,27]. The stimuli for herpesvirus reactivation are diverse and include surgery, boarding, parturition, prolonged transport, weaning, lactation, inclement weather, and social disruption. Reactivation of the latent herpesviruses may occur in the absence of concurrent clinical signs. Respiratory tract shedding from carrier horses in which latent virus has been reactivated has been documented, and shedding of reactivated virus into the respiratory mucus is often not accompanied by clinical signs [24].

Pathogenesis

The respiratory tract is the natural portal of entry for EHV-1 and EHV-4, and the respiratory mucosal epithelium is the primary target tissue for infection [2,28,29]. Respiratory infection is acquired by close physical contact with another horse that is actively shedding infectious virus into its respiratory secretions. Virus-laden droplets generated by forced, high-velocity expirations through the airways (snorting) can produce infective aerosols capable of traveling over short distances (between box stalls, fenced paddocks, etc). The efficiency of aerosol transmission and the consequent capacity for rapid spread of herpesvirus infections are generally less than those exhibited by equine influenza virus. Indirect virus transmission through contamination of human hands, feed and water utensils, endoscopes, and other fomites is also possible.

The incubation period for signs of respiratory infection after natural exposure to the herpesviruses ranges from 2 to 5 days. Horses infected for the first time may shed the viruses for prolonged periods (up to 14 days). Peak virus shedding occurs during the first few days after the onset of nasal discharge and coincides with the febrile phase of the infection. Disease severity is influenced by prior infection history, state of health, concurrent infections, stress, and variation in virulence level of the infecting herpesvirus strain.

The pathology of herpesvirus URTD is characterized by focal, cytolytic destruction and exfoliation of the nasopharyngeal respiratory epithelium (down to the basal layer), an outpouring of respiratory glandular secretions, and a concomitant vigorous inflammatory response that includes infiltration of mononuclear cells into the lamina propria underlying the destroyed epithelium (Fig. 5) [28-30]. Respiratory signs of EHV-1 or EHV-4 infection (nasal discharge and fever) are initiated by the direct viral cytopathic destruction of airway epithelium. Mild pulmonary lesions develop in some foals [31]. Quickly following replication in the upper respiratory tract epithelium, the virus is carried by migratory dendritic cells and macrophages into the draining lymph nodes (Fig. 6) [32].

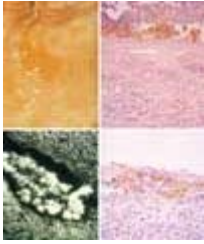


Figure 5. Equine respiratory disease caused by EHV-1 or EHV-4 demonstrating herpetic vesicular lesions in the nasal mucosa (top left), focal destruction of ciliated respiratory epithelial cells (bottom left), and the presence of viral antigens (brown stain) in nasal epithelial cells (right). Reproduced from: Allen GP, Kydd JH, Slater JD, et al. Equid herpesvirus-1 (EHV-1) and equid herpesvirus-4 (EHV-4) infections. With permission of the publisher: Coetzer JAW, Thomson GR, Tustin, eds. Infectious diseases of livestock. Capetown: Oxford University Press, 2002. [6]. - To view this image in full size go to the IVIS website at www.ivis.org . -

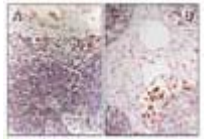


Figure 6. Immunoperoxidase staining of EHV-1 antigen in mononuclear leucocytes within submandibular lymph node of an infected horse. Virus antigen-expressing leucocytes are present in the subcapsular sinus (A), medullary sinus (B), and within the cortex parenchyma (A) of the lymph node. With permission of the publisher, reproduced from: Allen GP, Kydd JK, Slater JD, et al. Advances in understanding of the epidemiology, pathogenesis and immunological control of equid herpesvirus-1 abortion. In: Wernery U, Wade J, Mumford J, et al, eds. Equine infectious diseases VIII. Newmarket: R & W Publications 1999; 129–146. [29]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Infection of mononuclear leukocytes within draining lymph nodes results in a leukocyte-associated viremia, which may persist for several days. With EHV-1 in particular, viremic viral spread to other viscera is common and often results in widespread infection of vascular endothelial cells. Such an EHV-1 vasculitis in blood vessels of the central nervous system or gravid uterus forms the pathogenetic basis for the post-respiratory sequelae of EHV-1 abortion or neurological disease [6,28].

Clinical Presentation

Uncomplicated URTD occurring in horses as a result of infection by EHV-1 or EHV-4 presents as an acute rhinitis and pharyngitis with the potential for extension into the more distal airways to cause tracheobronchitis, bronchiolitis and/or pneumonitis [2,3,6,30]. Its clinical presentation is highly variable among individual horses and can range from inapparent illness to a life-threatening, primary viral pneumonia.

The clinical hallmark and most constant clinical manifestation of EHV URTD is bilateral nasal discharge (Fig. 7) [6]. In the early stages of infection, the nasal discharge is watery, free-trickling, inconspicuous and frequently goes unnoticed by attending personnel.



Figure 7. Nasal discharge in weanling horses with EHV-1 or EHV-4 respiratory tract infections. - To view this image in full size go to the IVIS website at www.ivis.org . -

The clear (serous) secretions are laden with high titers of infectious virus. As infection progresses, the character of the discharge changes rapidly (by the second or third day) from watery to that of a thicker, mucilaginous state, whitish in color, with the addition of inflammatory leukocytes and desquamated respiratory epithelial cells. The viscous (mucoïd) nasal secretions often dry to form more easily recognizable encrustations in and around the nostrils of the affected horse. As secondary bacterial infection ensues by 4 - 5 days after clinical onset, the character of the nasal efflux advances further to become thicker, more opaque and yellowish (mucopurulent).

Other clinical manifestations, variably associated with EHV respiratory infection, include pyrexia, submandibular lymphadenopathy, conjunctivitis manifested by a mild ocular discharge, lethargy, or anorexia. Fever may range from slight to as high as 106°F. In all but the severest of cases, a normal appetite is maintained during the infection. Occasionally, signs of lower respiratory tract involvement, from either viral or bacterial infection (or both), may also be present (e.g., cough, abnormal auscultatory sounds, increased respiratory effort, etc.).

The respiratory disease associated with infection by EHV-1 or EHV-4 is abrupt in onset and follows an acute course. Clinical signs are most intense and virus shedding most abundant during the first few days of infection. In uncomplicated cases of EHV URTD, the prognosis for full recovery is good, spontaneous resolution of clinical signs is complete by the end of the second week, and the mortality rate is low. Severe secondary bacterial infections can protract the illness and compromise the prognostic outlook for survival.

Hematologic analysis of horses with herpesvirus URTD usually reveals a mixed leukopenia (neutropenia and lymphopenia) during the first several days following the onset of clinical signs. In cases complicated by significant bacterial superinfection, neutrophilic leukocytosis and hyperfibrinogenemia may follow the initial, virus-associated leukopenia [33,34].

Horses severely affected with herpesvirus respiratory disease tend to be seen in outbreaks involving previously unexposed weanlings and yearlings whose maternally derived immunity to the viruses has declined to undetectable levels. Subsequent infections with the herpesviruses are generally more transient and clinically less severe. After multiple infections of a horse with EHV-1 or EHV-4, re-exposure predictably results only in clinically undetectable infections of the respiratory tract.

Overt respiratory disease due to EHV-1 or EHV-4 is therefore rare in fully mature, adult horses.

Respiratory disease caused by EHV-1 or EHV-4 is not altogether clinically distinct from that associated with infections by other viral respiratory pathogens of the horse (e.g., influenza virus, adenovirus, rhinovirus, equine arteritis virus). Likewise, cases of URTD caused by EHV-1 and EHV-4 are clinically and pathologically indistinguishable, requiring ancillary laboratory procedures for diagnostic differentiation.

Complications and Sequelae

Herpesvirus-inflicted damage to the protective respiratory mucosal barrier predisposes affected horses to opportunistic bacterial infections. As a result, secondary bacterial rhinopharyngitis (primarily by *Streptococcus equi zooepidemicus*) commonly accompanies EHV URTD and contributes to the overall severity of the illness. In the absence of appropriate antibiotic therapy, involvement of the lower airways - with the consequent development of bacterial tracheobronchitis, bronchiolitis, or pneumonia - can further complicate URTD initiated by EHV-1 or EHV-4. Secondary invasion by clonally-derived *S. equi zooepidemicus* strains with enhanced virulence can dramatically influence the severity and duration of the disease episode and may be associated with increased levels of morbidity and greater risks for mortality (Timoney JF. Personal communication).

While EHV-4 is a respiratory tract pathogen whose replication is ordinarily restricted to the URT mucosal epithelium and regional lymphoid tissue, the potential health consequences of EHV-1 infection extend beyond the respiratory tract. EHV-1 has the potential for causing more serious, invasive diseases involving other organ systems. Even in the absence of signs of overt respiratory disease, infection by EHV-1 (and rarely also by EHV-4) carries the attendant risk for five highly significant, clinical sequelae (abortion, neonatal foal death, myeloencephalopathy, pulmonary vasculotropic infection, and ocular disease). Highly pathogenic (hypervirulent) strains of EHV-1 exist that possess the capacity for causing high-attack rates of these clinical sequelae [29,35].

Abortion (Fig. 8) - Late-term abortion resulting from viral spread to the fetus that follows respiratory infection of pregnant mares with EHV-1 has been recognized for many years as a prominent cause of equine fetal wastage [3]. Most abortion occurrences associated with EHV-1 infection involve only one or two mares in a group. However, epidemic abortigenic disease claiming high percentages of the potential foal crop also occurs. The EHV-1 respiratory tract infection of the mare that precedes herpesvirus abortion is usually asymptomatic. Mares carrying EHV-1 infected fetuses abort precipitously without impending signs and, other than the abortion event, are clinically normal. Their subsequent reproductive efficiency is not compromised. The aborted fetus, which presents without postmortem decomposition, dies from anoxia during a rapidly progressive placenta-endometrium separation that immediately precedes the event of expulsion. The abortus possesses high levels of virus and extensive histopathological evidence of multi-organ infection. Abortions caused by EHV-4 also occur but at a frequency much less than that associated with EHV-1 infection [2].



Figure 8. Gross pathology of equine abortion caused by EHV-1 infection. (A) aborted fetus, (B) pleural effusion, (C) meconium staining of perineal region, (D) foci of necrosis on surface of liver. With permission of the publisher, reproduced from: Allen GP, Kydd JH, Slater JD, et al. Equid herpesvirus-1 (EHV-1) and equid herpesvirus-4 (EHV-4) infections. In: Coetzer JAW, Thomson GR, Tustin, eds.

Infectious diseases of livestock. Capetown: Oxford University Press, 2002. [6]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Neonatal Foal Death (Fig. 9) - Fetuses infected with EHV-1 during late gestation may be born alive at term but sick either at birth or within one to two days of parturition [36-39]. The foals are weak, fail to nurse, become lethargic, pyrexic, lymphopenic, hypoxemic, and exhibit severe respiratory distress. Clinical deterioration in such foals infected in utero with EHV-1 occurs rapidly, and the prognosis is always grave. Mortality in congenitally infected foals approaches 100%, as a viral pneumonia leads to respiratory failure within a few days. The foals are highly susceptible to secondary bacterial disease. Progression and outcome of the disease are unaffected by intensive, supportive nursing care, and successful antiviral therapy with acyclic nucleoside analogs has only rarely been reported. Congenital EHV-1 infection can be epizootic and may occur in

association with an outbreak of EHV-1 abortion. Rarely, EHV-4 may also cause neonatal foal disease resembling that caused by EHV-1 [40].

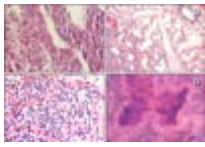


Figure 9. Histopathological examination of full term newborn foals dying of EHV-1 infection acquired in utero. (A) viral bronchiolitis with intraluminal cellular debris, subepithelial infiltrate of inflammatory cells, and intranuclear inclusion bodies in respiratory epithelium, (B) interstitial pneumonia with thickening and hypercellularity of alveolar walls, (C) bronchopneumonia with intra-alveolar inflammatory cell exudates, (D) lymphocyte depopulation in thymus. - To view this image in full size go

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Myeloencephalopathy (Fig. 10) - Long recognized as a potential clinical sequela to EHV-1 respiratory tract infection, equine herpesvirus myeloencephalopathy is an uncommon but potentially devastating disease [41,42]. Isolated cases of EHV-4 neurological disease have also been identified [43,44]. The interval between initial herpesvirus infection of the respiratory tract and the subsequent onset of neurological signs is 6 to 10 days. Although the neurological signs are variable, the most common clinical manifestation of the disease is hind limb ataxia, which may progress to recumbency. The neurological deficits result from a thrombotic, ischemic vasculitis within small blood vessels of the central nervous system. The neurological signs appear suddenly, reach their peak intensity within 2 - 3 days of onset and are generally not progressive. The prognosis for non-recumbent horses is favorable, but is poor for animals that remain recumbent for longer than 2 days.



Figure 10. Neurological manifestations of EHV-1 infection. (A) ataxic mare supported in sling as part of nursing care, (B) macroscopic hemorrhagic lesions in spinal cord, (C) microscopic hemorrhage and axonal swelling in spinal cord, (D) thrombo-occlusive vasculitis with immunoperoxidase-positive endothelial cells in the spinal cord. With permission of the publisher, reproduced from: Allen GP, Kydd JH, Slater JD, et al. Equid herpesvirus-1 (EHV-1) and equid herpesvirus-4 (EHV-4) infections. In:

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Pulmonary Vasculotropic Infection - Several cases of generalized, peracute disease following EHV-1 respiratory infections have recently been reported in young adult horses [45]. The new syndrome, termed "pulmonary vasculotropic EHV-1 infection", is characterized by high fever, anorexia, severe depression, respiratory distress and high mortality. Neurological signs have been absent. Affected horses may be found dead. Onset of the condition is sudden, and its course of progression to death is rapid. The dominant necropsy finding is a multisystemic vasculitis, particularly prominent in the small blood vessels of the lungs.

Ocular Disease - Respiratory tract infections in foals associated with hypervirulent strains of EHV-1 may be accompanied by serious ocular disease, which manifests as uveitis and/or chorioretinitis [46]. In the severest of cases, extensive retinal destruction and blindness have been observed. Suckling foals running with mares involved in high case-rate outbreaks of EHV-1 neurological disease appear to be at particular risk for this sequela of EHV-1 respiratory infection [39].

Treatment

Specific strategies for therapeutic management of equine herpesvirus UR TD must be individually tailored to each patient and guided by the severity and range of clinical signs as well as the expectations of the horse owner. The goals of therapy are to (1) ameliorate clinical signs of viral infection, (2) maintain hydration and meet the daily caloric needs of affected horses, and (3) minimize the complications arising from the effects of bacterial superinfection and/or systemic spread of viral infection beyond the respiratory tract [47-50]. Such treatment strategies for herpesvirus UR TD are usually rewarded with quicker recoveries, fewer complications and increased survival rates. In performing or working horses, an important adjunct of active treatment is resting from work.

The two therapeutic mainstays for uncomplicated equine rhinopneumonitis are (1) antipyretics for fever reduction and (2) non-steroidal anti-inflammatory agents for reduction of respiratory tract inflammation. These two requirements can be conveniently provided by administration of a single medication possessing both pharmacologic properties (e.g., phenylbutazone at 3 mg/kg, PO, q 12 h to 24 h or flunixin meglumine at 1.1 mg/kg, IM, q 12 h to 24 h). Bacterial rhinopharyngitis commonly occurs when the equine respiratory epithelium is injured by replicating EHV-1 or EHV-4 and, consequently, often becomes the eventual focus of the treatment strategy for herpesvirus UR TD. A preparation of trimethoprim/sulfadiazine (30 mg/kg, PO, q 24 h) administered for 7 - 10 days is an excellent and popular first choice for

broad-spectrum antibacterial therapy because of its capacity for once-a-day, oral administration. In congenitally infected neonatal foals or in young horses in which clinical signs of bacterial infection are severe, progressive or involve the lower airways, optional antimicrobials for treatment include amikacin (20 mg/kg, IM, q 24 h), procaine penicillin G (20,000 U/kg, IM, q 12 h), ceftiofur (2.2 mg/kg, IM, q 12 h), ticarcillin (44 mg/kg, IV, q 8 h), and ceftazidime (25 mg/kg, IV, q 8 h).

Extrapulmonary manifestations of herpesvirus respiratory infections present greater challenges for therapeutic management. Horses unwilling to eat or drink may require fluid-electrolyte replacement therapy with isotonic, dextrose-containing solutions administered intravenously. In EHV-1 infected newborn foals with respiratory distress and hypoxemia, intranasal therapy with humidified oxygen is indicated. The administration via nasogastric entubation of dimethyl sulphoxide (3 ml/kg, q 24 h) along with a parenteral corticosteroid (dexamethasone, 0.1 mg/kg, IV, q 24 h) are standard treatments for horses with EHV-1 associated paralysis. Horses with bladder wall or sphincter paralysis associated with EHV-1 myeloencephalopathy may require frequent urinary catheterization, post-catheter flushing of the bladder with povidone-iodine solution, and antibiotic treatment for cystitis. Horses exhibiting recumbency from EHV-1 neurological disease require intensive, round-the-clock nursing care [51]. Light tranquilization, thick bedding with frequent repositioning of the recumbent horse, daily cleansing and topical care of decubital ulcers and urine scalding, and the use of mechanical slings for limited periods of assisted support are often indicated. Euthanasia should be considered in laterally recumbent horses or sling-supported animals failing to show improvement after a few days or in animals developing severe, systemic complications from recumbency.

In certain clinical settings (e.g., EHV-1 neonatal foal infection; early stages of an outbreak of EHV-1 abortion or myeloencephalitis, etc.), antiviral drugs (e.g. acyclic nucleoside analogs; 10 - 15 mg/kg, PO, q 8h) offer a new and relatively unexplored, but potentially promising, mode of treatment for individual cases or for limiting the spread of epizootic EHV-1 infection [52].

Prevention

Herd elimination of equine herpesviruses is virtually impossible because of the pervasiveness of the carrier state. Disease prevention, rather than treatment or attempts at eradication, offers the most effective means for controlling herpesvirus URTD and its potential sequelae. Strategies aimed at reducing the economic and welfare impact associated with EHV-1 and EHV-4 respiratory infections include (1) prophylactic immunization and (2) the implementation of preventive herd-management practices.

Vaccination - Vaccination against EHV-1 and EHV-4 respiratory disease is recommended as part of the preventive, herd-health program for all horses at risk for acquiring infection [53,54]. Virtually all foals have measurable antibody specific for EHV-1 and EHV-4 after ingestion of the dam's colostrum. Maternally derived antibodies to EHV-1 and EHV-4 decay exponentially with a half-life of 26 days. Foals become seronegative and therefore maximally susceptible to infection by 5 - 6 months of age. Vaccinations and subsequent boosters should therefore be timed to provide the young horse with a maximal level of immune protection in preparation for the stresses associated with weaning, transport, relocation, introduction into new social groups, yearling sales, training and performance events. A reasonable course of vaccination for herpesvirus URTD is two intramuscular doses spaced at 3-week intervals just prior to weaning, with single booster doses every 3 to 6 months (depending on the level of risk) thereafter while the horse is engaged in training, racing, or attending show events. Higher titers of antibody are elicited when the primary dose of vaccine is delayed until the foals are five months of age [55]. In large animal groups, achievement of a high vaccination coverage rate can help reduce the spread of infection because of the added benefits of herd immunity. Pregnant mares should be immunized, according to the label instructions, with a product demonstrated by vaccination-challenge studies to be effective in preventing EHV-1 abortion [56,57]. No current vaccine has been demonstrated to protect against the central nervous system manifestation of equine herpesvirus infection. Both inactivated- and attenuated live-herpesvirus vaccines are available (Table 1). All commercial vaccines presently marketed for equine rhinopneumonitis are formulated for intramuscular administration. Combination vaccines containing both influenza virus and the two herpesviruses are available for convenience of use. To avoid any effects of the uncommon occurrence of a local vaccine reaction (swelling, muscle soreness and lethargy) on athletic performance, vaccinations should not be given within 7 to 10 days of a performance event. Vaccination of young horses does not prevent respiratory infection, but diminishes the intensity of clinical signs and both the magnitude and duration of shedding of infectious virus. Development of the latent carrier state is, likewise, not prevented by vaccination. Therefore, the current goal of vaccination for herpesvirus URTD is the lessening of respiratory disease severity and reduction in the spread of infection within the target population. Because immunity to EHV-1 and EHV-4 generated by vaccination is of short duration, frequent booster doses are necessary for maximal effectiveness. The development of a more efficacious vaccine for herpesvirus respiratory disease in young horse stock is clearly a priority.

Table 1. Vaccines Currently Marketed for Use in Horses for Control of Disease Caused by EHV-1 or EHV-4				
Vaccine	Manufacturer (country)	Vaccine Type	Virus Components	Manufacturer's Recommendations for
Duvaxyn EHV-1,4	Fort Dodge (Belgium)	Inactivated	EHV-1 & EHV-4	Abortion & respiratory disease
Equiffa	Merial (Europe)	Inactivated	EHV-1; EIV-1 & EIV-2	Respiratory disease
EquiGuard	Boehringer Ingelheim (USA)	Inactivated	EHV-1 & EHV-4	Respiratory disease
EquiVac EHV-1/4	Fort Dodge (USA)	Inactivated	EHV-1 & EHV-4	Respiratory disease
Fluvac EHV-4/1 Plus	Fort Dodge (USA)	Inactivated	EHV-4 & EHV-1; EIV-1 & EIV-2	Respiratory disease
Pneumabort K + 1B	Fort Dodge (USA)	Inactivated	EHV-1 (1P & 1B strains)	Abortion & respiratory disease
Prestige	Intervet (USA)	Inactivated	EHV-1 & EHV-4	Respiratory disease
Prestige II	Intervet (USA)	Inactivated	EHV-1 & EHV-4; EIV-1 & EIV-2	Respiratory disease
Prestige V	Intervet (USA)	Inactivated	EHV-1 & EHV-4; EIV-1 & EIV-2; EEE & WEE; Tet	Respiratory disease plus
Equigard-Flu	Boehringer Ingelheim (USA)	Inactivated	EHV-1 & EHV-4; EIV-1 & EIV-2	Respiratory disease
Double-E FT EHV	Fort Dodge (USA)	Inactivated	EHV-1 & EHV-4; EIV-1 & EIV-2; EEE & WEE; Tet	Respiratory disease plus
Prodigy	Intervet (USA)	Inactivated	EHV-1	Abortion
Resequin	Intervet (Europe)	Inactivated	EHV-1 & EHV-4	Respiratory disease
Resequin Plus	Intervet (Europe)	Inactivated	EHV-1 & EHV-4; EIV-1 & EIV-2	Respiratory disease
Rhinomune	Pfizer (USA)	Modified live	EHV-1	Respiratory disease
Rhino-Flu	Pfizer (USA)	Modified live & Inactivated	EHV-1; EIV-1 & EIV-2	Respiratory disease

EHV = equid herpesvirus; EIV-1 and EIV-2 = equine influenza virus A-1 or A-2, respectively; EEE & WEE = eastern & western encephalomyelitis viruses; T = tetanus toxoid

Preventive Management Strategies - Management recommendations described here are based on the practices of (1) segregation of horses on the premises into small groups, (2) the maintenance of each horse group as an isolated unit, and (3) stress reduction [59-61]. An effective strategy for reducing the risk for large-scale, farm-wide outbreaks of EHV-1 or EHV-4 URTD is subdivision of the at-risk population of horses on the premises into smaller groups and the maintenance of those groups as closed, physically separated units. For maximal effectiveness, group size should be as small as the physical facilities will reasonably allow, with each group kept under conditions that limit the transmission of virus between established groups. Horses should be segregated into groups that are similar in age, gestation status, use, and frequency of removal of individual animals. Restrictions should be placed on movement of horses into and out of each established group, and contact with transient horses in particular should be avoided. The greatest danger for exogenous herpesvirus infection lies in the introduction of new horses into established groups, especially those with recent opportunities for exposure to large, intermingled assemblages of horses from diverse sources (sales, shows, boarding stables, racetracks, competitions, training centers, etc.). The addition of any new horse into a closed group should be preceded by a 21-day period of isolation. A horse

temporarily removed from a group for purposes that may involve prolonged transport or its contact with other horses (e.g., breeding, showing, training, veterinary care, sales, etc.) should also undergo a 21-day period in isolation and evaluation for signs of infection before returning to its resident group. Another important management step in the prevention of herpesvirus respiratory disease is lessening of stress-induced reactivation and shedding of virus from latently infected carrier horses resident within the herd. Measures to control the frequency of reactivation of latent herpesvirus are aimed at minimizing stress caused to horses by crowding, poor nutritional state, heavy parasite infestation, lengthy transport, disruption of established social groups, inclement weather, *en masse* weaning, other disease states, etc.

Outbreak Control

In an outbreak of herpesvirus UR TD within a susceptible horse population, infection often spreads rapidly, the attack rate can be high, and significant economic and equine welfare consequences may ensue. Immediate intervention with infectious disease control measures is required for successful containment of the infection to its original focus and reduction of the negative impact of the epizootic. The priority for management of an active outbreak of equine rhinopneumonitis is prevention of further spread of the virus from initially infected horses to other members of the group and beyond the affected group to surrounding horses both on and off the premises. Implementation of the practices of isolation, quarantine and disinfection is the crux of outbreak management [50,56-62].

Clinically ill horses should be removed from their resident group and kept in physical isolation away from the remainder of the horse population until all danger of conveying the infection has passed. A zone of empty space sufficient to serve as a barrier to the airborne transmission of virus should surround the isolation area. Unnecessary human and horse traffic through the isolation area should be restricted. Personnel caring for horses placed in isolation should be instructed about the specific procedures to be used for controlling the further spread of infection. Such individuals should wear protective outer clothing, disposable latex gloves, and disinfectant-immersible footwear, all of which should be removed upon leaving the isolation area. Frequent hand washing and the use of disinfecting footbaths are beneficial in curtailing indirect spread of herpesviruses by way of contaminated fomites. Ideally, staff handling horses in isolation would be assigned to that group only. Indirect spread of virus from the focus of infection by inanimate objects can be prevented by thorough cleaning with detergent and water followed by vigorous disinfection with phenolic- or iodophor-type compounds to inactivate virus encountered on contaminated surfaces (hands, shoes or clothing of animal care personnel; lead ropes; tack; feed or water buckets; bedding; grooming utensils; stall-cleaning and mucking utensils; treatment instruments; etc.). A booster dose of vaccine given to non-exposed, susceptible horses to build an immune barrier around the focus of infection may also help to reduce spread of the outbreak.

All horses in physical contact or sharing facilities with clinically affected animals (including those in adjacent paddocks, stalls, treatment areas, etc.) should be considered as having been exposed to the virus, remained confined to their respective stalls or paddocks, and placed under a movement-restricted quarantine. The relocation and intermingling of in-contact horses during an active outbreak of herpesvirus UR TD creates the greatest risk possible for transmitting infectious virus into additional groups of horses. Movement of horses both onto and off the affected premises should be restricted until the outbreak has ended. An outbreak of herpesvirus UR TD may be considered as being over when 21 days have elapsed without the occurrence of any further cases of disease. Following the outbreak, the area used as isolation facilities should be thoroughly cleaned and disinfected. Viability of the herpesviruses outside the body of the horse is transient enough that, after a period of 21 days without the presence of horses, an area may be considered safe for reuse by horses without risk of infection.

Diagnosis

Rapid, unambiguous identification of the etiology of an outbreak of UR TD within a group of horses is essential for assisting veterinary personnel in making treatment decisions and in planning strategies for controlling epizootic spread of the infection. Key differential diagnoses for viral UR TD in the horse include, in addition to EHV-1 and EHV-4, influenza virus, adenovirus, rhinovirus and equine arteritis virus. Because presenting clinical signs alone are not sufficient to differentiate herpesviruses from these other common causes of equine UR TD, laboratory testing is necessary. Diagnostic confirmation of herpesvirus UR TD is predicated on demonstrating the presence of EHV-1 or EHV-4 in either nasopharyngeal secretions or venous blood leukocytes from affected horses.

Laboratory diagnostic success with EHV-1 and EHV-4 is influenced by the techniques used for collection, handling, transport, storage and processing of the clinical specimens. Success is greatest when the nasal mucus specimens for laboratory testing are taken within 48 hours of the onset of illness when the horse is still pyrexia and the nasal discharge still serous in nature. Respiratory secretions are collected with a cotton swab (e.g., guarded uterine swab) inserted through the

ventral nasal meatus and advanced into the nasopharynx (Fig. 11). The swabs must be placed in a fluid transport medium containing antibiotics and placed on ice to preserve the viability of the virus for tissue culture inoculation. At least 20 ml of venous blood should be collected for attempted virus isolation and transported chilled, but not frozen, to the laboratory. The period for greatest success in virus isolation from the blood is 4 - 10 days after onset of respiratory disease. Rapid transport to the laboratory and immediate processing are also important for successful laboratory diagnosis of EHV-1 and EHV-4 infections.



Figure 11. Illustration of the individual components and their assembly to construct a device for collecting nasopharyngeal secretions from horses with upper respiratory tract disease. - To view this image in full size go to the IVIS website at www.ivis.org . -

Methods available for the laboratory diagnosis of equine herpesvirus respiratory infections include virus isolation, polymerase chain reaction (PCR), immunofluorescent detection of viral antigens, and serologic testing [63]. The laboratory test for EHV-1 or EHV-4 that yields the most reliable results is virus isolation from nasopharyngeal secretions or blood leukocytes after inoculation of susceptible tissue culture monolayers. The cytopathic effect of EHV-1 and EHV-4 is characteristic, and seroidentification of the two herpesviruses can be made with type-specific monoclonal antibodies [64]. Standard virus isolation procedures have the disadvantage of requiring several days to obtain results, thereby making them less useful to the clinician.

Amplification of viral DNA using PCR is a rapid, sensitive and increasing utilized assay for detection of EHV-1 or EHV-4 respiratory tract infection [65-68]. Portions of the same clinical specimens used for virus isolation can be processed for herpesvirus detection by type-specific PCR.

Antigen detection methods also exist for the rapid diagnosis of EHV-1 and EHV-4 UR TD directly from clinical material. Cells from nasopharyngeal secretions can be stained using immunofluorescent antibodies that reveal the presence of the herpesviral antigens. When direct antigen detection methods are used for a rapid laboratory diagnosis of EHV-1 or EHV-4, it is important to confirm the direct test results by virus isolation.

Paired serum samples are required for reliable serologic diagnosis of equine herpesvirus infection [69]. The acute serum sample should be collected within 2 - 3 days of the onset of illness, and the convalescent sample approximately 3 weeks later. A positive result is a four-fold or greater rise in virus-specific antibody titer between the acute- and convalescent-phase serum samples. Because antibody induced by vaccination can confound interpretation of serologic results, the vaccination history of the horse must be taken into account to assure that detected rises in antibody titer reflect infection rather than a recent herpesvirus vaccination. On a single collection of serum, the complement-fixation test or IgM-ELISA may be beneficial in providing evidence for recent infection with EHV-1 or EHV-4 [39]. Antemortem identification of chronic carrier horses latently infected with EHV-1 or EHV-4 is difficult; neither infectious virus nor viral antigens are detectable, and clinical signs are not present.

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