FEATURE

Horse Care

# Equine Herpes Viruses: A Challenging Foe

by HEATHER SMITH THOMAS

To date, at least nine different herpes viruses are known to infect horses, according to Dr. Frank Cook, Research Assistant Professor at the Maxwell Gluck Equine Research Center, University of Kentucky. "Although some of these viruses, such as the gamma herpes viruses—equine herpesvirus two and five (EHV-2 and EHV-5)—have been associated with eye infection and respiratory disease, these associations are not proven," he says.

"In view of the fact that EHA-2 can be isolated from almost all horses, it is likely that in most cases infection with these gamma herpes viruses produces very few disease problems. In contrast, EHV-4 and particularly EHV-1 (two members of the alpha-herpes group) pose a substantial threat to equine health and well being."

Cook says the unfortunate thing about herpes viruses is that they are probably transmitted at a very early age. "EHV-1 and EHV-4 tend to be transmitted from mare to foal or from animal to animal within the same group of horses," he says. By two years of age, almost all horses have antibodies to EHV-1 and EHV-4, demonstrating that they have been exposed to these viruses.

"As a result of this almost ubiquitous infection rate, these viruses are difficult to control by good management practices, compared to viruses that have a much lower incidence of infection, such as Equine Infectious Anemia. Once a horse has been infected, it tends to remain infected because equine herpes viruses (in common with many other types of herpes viruses) use stealth tactics including a dormant state to avoid being eliminated by the powerful immune responses unleashed by the body," says Cook.

*Horse with EHV-1*

These viruses can then be reactivated at some future time, such as when the horse undergoes stress. "Unfortunately, effective immune responses to EHV-1 are relatively short-lived. Once they have declined, the horse is susceptible to re-infection with different strains of the virus," he says.

Viruses have evolved many strategies to survive within the host. These strategies vary, depending on the type of virus. The lentiviruses (such as the one that causes Equine Infectious Anemia in horses, or HIV in humans) have developed numerous mechanisms to persist in the body by resisting the effects of the immune system.

"For example, the host produces neutralizing antibodies that block viral infections by binding to those areas on the viral surface proteins responsible for attachment to the host cell. In lentiviruses, these sensitive areas are for a majority of the time buried deep within the structure of the surface protein, making them inaccessible to most neutralizing antibodies," explains Cook.

By contrast, the herpes viruses can avoid immune response by becoming latent. "Equine herpes viruses such as EHV-1 can enter white blood cells or nerve cells and hide by becoming almost completely inactive," he says.

In this latent stage, they are not making viral structural components and the immune system cannot detect them. "As a by-product of replication, small fragments of viral proteins are transported to the host cell membrane and presented to the outside world by MHC-1 molecules. When foreign protein fragments are bound toMHC-1 molecules, they serve as a distress signal that prompts the immune system to initiate an attack to destroy what in effect is a virus production factory." If an equine herpesvirus is shut down within the cell, however, there is nothing there to alert the immune system to its existence.

"Herpes viruses are big, complicated viruses and encode a large number of proteins. Some of those proteins have the effect of interfering with immune responses. This is an intensive area of research, right now, trying to find out how the different herpes viruses fool the immune system," says Cook.

"The immune system has two components—an initial non-specific or innate response involving the production of antimicrobial molecules, some of which are responsible for symptoms of disease (fever, inflammation), and a highly specific or adaptive response. EHV-1 appears to interfere with both responses by producing proteins that slow pro-

duction of certain antimicrobial molecules and other proteins that partially inhibit the binding of viral protein fragments to MHC-1," he explains.

"The immune system is extremely powerful and capable of causing tremendous damage to the body, as evidenced by diseases such as lupus (in humans) when it is not tightly controlled. A persistence strategy employed EHV-2 (a gamma-herpesvirus related to Epstein Barre virus in humans) is that it encodes a protein closely resembling one of the major host proteins (interleukin 10) involved in limiting or controlling immune responses once a pathogen has been eliminated."

Fortunately, the strategies employed by an equine herpesvirus to undermine immune responses are not 100 percent effective. "The immune systems of most EHV-1 infected horses eventually bring viral replication under control. The only viruses that survive are the ones that achieve latency.

Unfortunately, the latent herpes viruses can come out of hiding and cause disease. "We don't know exactly know what enables them to do this, but the common things seem to be stress, transport, racing, etc. Then we see a recrudescence of disease—at which point the horse becomes sick and can infect other horses via nasal secretions," says Cook. When the virus is hiding, the risk for transmission is much lower.

"An analogy would be Herpes Simplex Virus-1 (HSV-1) that causes cold sores in humans. If a mother with an active infection on her lip kisses a child, the virus can be transmitted to the child, causing a localized skin lesion on the child. Although the child's immune system will respond, some viruses escape—entering nearby nerves and migrating to a group of nerve cells (neuroganglion) at the base of the skull, where they become inactive and hide. If something activates them, the virus travels back down the nerve and can cause disease again," says Cook.

Another example occurs with Varicella-Zoster Virus (VZV). "This virus causes chicken pox (varicella) and later in life can reactivate to induce bouts of shingles (herpes zoster). However, while many people have had chicken pox, not all of them get shingles," he says.

"It's the same with horses; disease can crop up again later. The two herpes viruses that have the most impact on performance in horses are EHV-1 and EHV-4. Although both infect the respiratory tract, EHV-1 is probably the most dangerous in that it can cause a high incidence of abortion—a phenomenon that rarely occurs with EHV-4. This is why most horse breeders vaccinate their mares against EHV-1."

Some variants of EHV-1 can also cause severe neurological paralysis. "The paralysis can be anything from mild ataxia in the hind legs to total recumbency—with the horse unable to get up—depending on the severity of the lesion and where it is in the central nervous system," says Cook.

"We think EHV-1 is mainly a respiratory infection. In some cases, however, it can get from the lungs into the blood stream. When it does this, it infects the cells lining

**Continued on next page**

## Horse Care Cont'd.

the blood vessels, including capillaries in the spinal cord. It infects those tiny capillaries and closes them down because of all the dead cells and inflammation. This starves the neural tissue for oxygen."

EHV-1 does not actually infect neural cells of the horse, but has this indirect effect by shutting down the tiny capillaries. "This is what causes damage to the spinal cord, or sometimes the brain," explains Cook. The outcome can be quite variable when a horse becomes infected with an equine herpesvirus.

"The strain of virus makes a difference, as does the individual horse's response. Some horses seem much more susceptible. The risk factors are also variable. One of the main risk factors for developing neurologic disease is old age. The older horse is more at risk than a horse in the prime of life," he says. The older horse seems to lose some ability to fight off disease; there's a reduction in effectiveness of immune responses.

*A horse with nasal discharge*

*An aborted foal*

The use of steroids may also create risk. "Steroids are often utilized to treat an inflammatory problem, but they are also knock down the immune system. They hinder all the immune responses and not just the ones you don't want (fever, swelling and inflammation). Steroids reduce the body's responses to viruses like herpes or EIA." Steroids can be used short term, but if a person is treating a chronic pulmonary disease, they can have the side effect of allowing some of these viruses to escape control.

"This applies to all types of infection. If the animal is on an immunosuppressant like steroids, there is always a chance this will make that animal susceptible to other diseases—whether bacterial, viral or fungal. Ordinarily the veterinarian will try to give a compromise dose, just enough to limit the clinical signs but still allow the immune system enough force to function. It's wise to not use steroids for very long," says Cook.

### The Disease

EHV-1 and EHV-4 are part of a large group of viruses (the alpha herpes viruses) that cause potentially serious disease in horses and other species, including humans. "EHV-1 and EHV-4 both induce similar respiratory diseases (cough, clear nasal discharge and fever) that usually permits secondary bacterial infections to occur—with characteristic thick nasal discharge (containing mucus and pus). However, EHV-4 is not as efficient at getting into the bloodstream and infecting other cell types. Therefore, it is less likely to cause abortion," he says.

EHV-1, often called "rhinovirus," is probably the most important for horse owners to know about. Like EHV-4, this virus causes respiratory disease (rhinopneumonitis), but has a higher propensity to infect white blood cells—enabling it to be transported around the body to the uterus and capillaries supplying the central nervous system.

"Although almost all EHV-1 strains are capable of inducing abortion, only some variants can produce neurologic problems. Recent outbreaks that have caused concern involve the respiratory/neurologic form. Epidemics of all three clinical entities (respiratory, abortion, neurologic) may occur separately or at the same time within any horse population.

"We think that whatever may be associated with the neurovirulant type seems to increasing in recent years. The USDA, in 2007, classified herpesvirus myeloencephalopathy (neurologic disease) as a potentially emerging disease of the horse," says Cook.

There's a lot of research in progress, looking at herpesvirus in cattle, chickens and humans. "There is also research being done to learn more about what constitutes a neuropathogenic virus—why some strains are neuropathogenic while others are not. There have been mutations identified in at least one herpes virus gene that seems to be associated with that neurovirulent type," he says.

Viruses, and the immune system, are tremendously complex. "They have co-existed for a long time, each one trying to out-do the other," says Cook. The herpes virus has evolved to where it can live within horses for the lifetime of an animal by using the strategy of latency. Up to half of any horse population may serve as a reservoir for EHV-1, with certain horses latently infected and intermittently shedding the virus.

One of the challenges of doing research on EHV-1 is that it is virtually impossible to find seronegative horses. Almost all horses have been exposed to EHV-1 and EHV-4 by the

time they are two-years-old. Almost all horses are latently infected, perhaps by multiple strains of EHV-1 and EHV-4.

The virus also has the potential to increase its virulence. "Viruses can increase in virulence, however we and other labs have shown that horses can be simultaneously latently infected with 'neurovirulent' and 'non-neurovirulent' forms of EHV-1. Not all viral isolates containing the mutation are associated with neurologic diseases, however, and some viruses lacking the mutation have been isolated from cases of paralysis," explains Cook. It's a very complex and challenging disease.

Historically the neurologic form of the disease has been rare. But in recent years we've seen significant increase in outbreaks in North America, Europe and other parts of the world. A few years ago there were several outbreaks at racetracks in Kentucky, followed by cases in New Jersey, Florida and California, and the disease drew a lot of attention.

"We have recently completed analysis of EHV-1 strains from Kentucky, isolated over a period of almost 60 years. Strains containing the mutation were present as early as the 1950s, so they are not new. However, the incidence at which they occur increased from 3.6 percent in the 1960s to 13.3 percent in the 1990s. The incidence from 2000 to 2006 was 19 percent, suggesting that viruses with that mutation are still increasing in prevalence," says Cook.

The herpes virus is spread primarily through direct contact between horses (nose to nose), and by humans carrying the virus from one horse to another on hands and equipment or by using the same equipment for more than one horse (water and feed tubs, bits and tack, clippers, grooming cloths, "snot rags," etc.). Practicing good hygiene can often help prevent transmission.

This virus can also be spread if a susceptible horse comes into contact with an aborted fetus or placental tissues; these can contain high levels of virus. "If another mare comes in contact with this material, she should be placed under strict quarantine. I was involved in an investigation of an EHV-1 outbreak on a large stud farm in England where mares were moved after coming into contact with an aborted fetus. As a result of this contact, there were 22 abortions or infected foals that did not survive," says Cook.

Some researchers think that for a short time after the horse develops fever he can also spread the virus through aerosolization when coughing. You may be able to reduce the risks for transmission of EHV-1 by keeping horses separated.

This virus is primarily transmitted by direct contact, nose to nose, however. If your horse is in a stall next to another horse or standing in line by another horse, close contact could put your horse at risk. The incubation period once a horse is exposed can vary, depending on the clinical form of disease. Signs of respiratory disease usually appear between three and six days following exposure to the virus. Abortion, however, may take place seven days to several months later. The long time periods between exposure and abortion are usually due to reactivation of the virus following latency.

The neurologic form of the disease may appear within two weeks following respiratory tract exposure to the virus. Horses that have experienced prior infection may be at greater risk for developing neurological manifestations, since they are likely to harbor latent viruses. "However, immune responses generated by a recent infection tend to have a protective effect—at least for several months. For example, research has shown that horses are more resistant to the development of neurologic disease following exposure to a neurovirulent strain if they have experienced a recent EHV-1 outbreak," explains Cook.

After first signs of illness (fever) the sick horse may shed the virus for seven to 10 days, sometimes up to 28 days. Some horses that have no symptoms (clinically normal) can shed the virus. Horses with the neurological form shed much higher numbers of the virus than aborting mares or horses with respiratory illness.

## Vaccination

There are several vaccines for immunizing horses against EHV-1 and these are generally recommended for horses who might be at risk. "We are concerned about the effectiveness of vaccines, however. They are not 100 percent effective," says Cook.

"The herpes viruses are difficult to vaccinate fully against. A great deal of research is currently being done, to see if we can develop more effective vaccines. We are beginning to understand more about how herpes viruses work. Some of them have ways of inhibiting immune responses. We must develop vaccines that can overcome some of the ways these viruses reduce the effectiveness of the immune response," he says.

Some veterinarians recommend that horses exposed to a sick one should *not* be vaccinated, due to possibility of immunization-induced exacerbation of neurological symptoms, but this worry is controversial. "There is no conclusive evidence suggesting vaccine-enhancement of disease. However, the commercial vaccines are ineffective in preventing development of neurologic disease," he says.

"The concensus about currently available inactivated and modified live vaccines is that they can reduce severity of respiratory disease and may decrease the period of viral shedding. In addition, appropriate vaccination of pregnant mares can decrease the incidence of abortion. However, to quote one researcher, Dr. N. Osterrieder, the incidence of neurologic disease is "mockingly unmitigated by vaccination'," says Cook.