Review of Controversial Issues (Nomenclature, Case Definition, Diagnostic Testing, and Management Practices) in Equine Herpes Myelitis (EHM)

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Equine Herpesvirus Type 1 infection with or without the highly neuropathogenic strain (D752 and N752, respectively) can cause neurologic disease in horses. Success in minimizing economic losses and protecting the health and welfare of horses requires the equine veterinary profession and regulatory officials to agree on nomenclature, case definition, interpretation of molecular diagnostic tests, and appropriate biosecurity responses. Authors’ addresses: Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Skip Bertman Drive @ River Road, Baton Rouge, Louisiana 70803 (McConnico); and Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 1601 Campus Drive, Fort Collins, Colorado 80523 (Lunn); e-mail: mcconnico@vetmed.lsu.edu. © 2010 AAEP.

1. Introduction
Equine Herpesvirus Type 1 (EHV-1) is highly contagious in horses and transmitted by direct contact or inhalation of respiratory secretions. Clinical signs can include rhinopneumonitis, abortion, or myeloencephalopathy. After a horse is infected, it may typically take anywhere from 24 h to 14 days for a horse to become ill, with fever often the only sign in most cases and equine herpes myelitis (EHM) sometimes developing without the prior observation of fever. In many cases, infected horses show no signs of illness but can shed the virus and spread virus to other horses through nasal secretions. Shedding in clinical and non-clinical cases can continue for 14 days or longer, although it typically lasts for 7 days or less. Although current American Association of Equine Practitioners (AAEP) recommendations are for a 28-day quarantine period, it is unusual for a period of longer than 14–21 days to be acceptable to owners and veterinarians. Sometimes, retesting for EHV-1 shedding is used to end the quarantine after these shorter periods, but this is expensive and its value is uncertain. Neurologic disease caused by EHV-1 is often treatable, and common differential diagnoses include equine protozoal myeloencephalitis (EPM), cervical vertebral malformation (Wobbler disease), West Nile Virus encephalitis, and others.

Recent devastating outbreaks of neurologic EHV-1 (EHM) disease have been reported at racetracks, horse shows, and veterinary hospitals in the United States and worldwide, prompting EHM’s re-
cent designation as a potentially emerging disease by the United States Department of Agriculture (USDA).\(^2\) This development prompted some state regulatory officials to designate EHM cases as a reportable disease, leading to mandatory quarantine for affected and exposed horses when EHV-1 is detected. The availability and increasingly widespread use of sensitive molecular-testing techniques for EHV-1,\(^3\)\(^-\)\(^5\) coupled with the difficulty in confirming an ante-mortem diagnosis of EHM and the impact of lengthy and extensive quarantine of potentially affected horses, has caused a serious clinical conundrum for our profession. Although recommended best-practice protocols are evidence-based,\(^6\) the chain of events triggered after an EHV-1 positive test in a neurologically abnormal horse can be complex, and it is often met with resistance to compliance with quarantine measures and misunderstanding of the implications of the test result. Success in minimizing economic losses and protecting the health and welfare of our horses requires the equine veterinary profession and regulatory officials to agree on nomenclature, case definition, interpretation of molecular diagnostic tests, and appropriate biosecurity responses.

2. Methods

Difficulties in diagnosing and managing EHM stem in part from a lack of understanding of several different aspects of the disease and limitations of our current knowledge. The purpose of this review is to evaluate our current understanding of the implication of EHV-1 strain identification, define diagnostic criteria for EHM, review interpretation of available molecular diagnostic tests, and make recommendations for the best biosecurity management practices possible. Consistent use of evidence-based science in interpretation and application of this information will be important in maintaining public trust in our ability to successfully manage EHM.

3. Results and Discussion

1. What Are the “Neuropathogenic” and “Non-Neuropathogenic” Strains, and What Do They Mean in a Clinical Setting?

Recent research has shown that EHV-1 with a single nucleotide polymorphism in the DNA polymerase gene (D\(_{752}\)) is more commonly isolated from horses suffering from EHM than is the alternate strain (N\(_{752}\)).\(^7\) This strain is commonly referred to as the neuropathogenic strain because of this association. In contrast, the non-neuropathogenic N\(_{752}\) strain is much more commonly isolated from cases of EHV-1 infection in which signs of neurological disease are absent. This original observation was made using archived samples from outbreaks of EHM or EHV-1 infection without neurological signs, and it has been confirmed by at least one similar study.\(^8\) Importantly, in a series of experimental challenges using D\(_{752}\) and N\(_{752}\) strains, it has been shown that the D\(_{752}\) strain challenges infection results in higher levels of viremia\(^9\) and more commonly, causes neurological disease,\(^10\) although this is an inconsistent outcome of experimental challenges. Although this information powerfully suggests that infection with the neuropathogenic D\(_{752}\) strain carries a higher risk of the development of EHM, the same studies cited above also clearly showed that 15–25% of EHM cases are caused by infections with the N\(_{752}\) strain. Therefore, the terms “neuropathogenic” and “non-neuropathogenic” are, to some extent, misnomers, because the association of strain type, as defined by this genetic polymorphism, with EHM is not absolute. Therefore, the best that science can tell us today is that retrospective analysis of EHM outbreaks and experimental challenge studies indicates that EHM is more likely to be associated with infection with the D\(_{752}\) strain. It is vital for the clinician to recognize that N\(_{752}\) strains can also cause EHM. The key points about EHV-1 neuropathogenic and non-neuropathogenic strains are as follows:

- EHV-1 strains expressing the D\(_{752}\) polymorphism in the DNA polymerase gene are more commonly identified in EHM cases and outbreaks than N\(_{752}\) strains.
- In a clinical scenario, when the diagnostic criteria for EHM are met (see below), you need to respond in the same way, independent of whether a D\(_{752}\) or N\(_{752}\) strain is identified.
- As our knowledge and experience of EHM cases and outbreaks associated with these two strains grows, we may determine that the risks and appropriate control practices are different for each strain and change our practices, but at this time, there is no evidence for this change.
- This issue provides a compelling argument for careful investigation of all EHM outbreaks and documentation of the EHV-1 strain involved, because this will inform our clinical practice in the future.

2. What Is the “Wild-Type” Strain, and Are the Strains Changing?

The non-neuropathogenic N\(_{752}\) strain has sometimes been termed the “wild-type” strain, implying that the neuropathogenic D\(_{752}\) strain is a mutation or relatively recent origin that can explain the perceived increase in EHM outbreaks in recent years. There is little evidence for this theory. When archived samples of clinical EHV-1 isolates from as long as 50 yr ago are examined, both D\(_{752}\) and N\(_{752}\) strains are identified. In fact, the oldest and best characterized EHV-1 strains are D\(_{752}\) strains. There is, therefore, no evidence that D\(_{752}\) strains emerged recently, and they may be as ancient as EHV-1 itself. It is intriguing to note that other closely related alphaherpesviruses, including EHV-4, are all D\(_{752}\) viruses. One recently reported piece of information showed that the prevalence of
EHV-1. The key points are as follows:

- The term “wild-type” is meaningless and should be discarded, because it is misleading. As far as we know at this time, the D752 neuropathogenic strain is as old as EHV-1 based on the available evidence. There is no evidence at this time that it represents a mutation, and it might, in fact, be the most ancient form of EHV-1.
- There may be changes in the prevalence of the D752 strain in the EHV-1 gene pool, because there is evidence for this in isolates from abortion cases in Kentucky between the 1960s and 1990s.

3. How Do You Diagnose EHM?
The criteria for diagnosing EHM have recently been reviewed, and a useful algorithm has been defined.\(^4\) History taking and physical examination are critical in determining the designation of a neurologic case as possible EHM. This becomes more problematic when the history is not available or handlers, trainers, or managers are unwilling to provide complete details. Typical cases of EHM often include an initial fever followed by weakness and ataxia, dysuria, fecal retention, tail- and anal-tone deficits, and dog-sitting. Cranial nerve deficits and primary brain dysfunction can be present. Unless there is known trauma or another well-defined cause for the neurologic disease, any case of acutely progressive myelopathy and encephalomyelopathy plus or minus cranial nerve deficits should include EHM. Although initial clinical signs include fever of 102°F or greater, fever occurrence may have been missed. In most cases, it is impossible to rule out EHM, and thus, testing for this disease must be included in the work-up. The key diagnostic criteria for EHM are as follows:\(^4\):

1. Acute onset of neurological signs, usually including ataxia, paresis, and urinary incontinence.
2. A history of fever and sometimes, abortion or respiratory signs.
3. Multiple horses involved.
4. Cerebrospinal fluid (CSF) changes including xanthochromia and elevated protein concentration (but they may be normal).
5. Identification of EHV-1 (independent of strain) from nasal swabs or blood samples by viral isolation or polymerase chain reaction (PCR).
6. Post-mortem confirmation by histology or immunohistology.

A tentative diagnosis of EHM can be supported by a combination of all of the first four signs, and an ante-mortem diagnosis is typically made when the fifth criteria is met. A final confirmation of the diagnosis is only possible for EHM after meeting the sixth criteria.

4. How Do You Use PCR to Test for EHV-1?
If EHM is on your differential diagnosis list, then you should test for the presence of EHV-1 so that appropriate treatment, prognosis, and herd-management response can be based on the best diagnostic testing information. Nasal swab/nasopharyngeal wash and whole-blood buffy-coat samples should be submitted to an approved laboratory for EHV-1 testing, as previously reviewed.\(^1,12\) Although it is always highly advisable to attempt viral isolation, we are increasingly dependent on PCR-based testing because of its sensitivity and speed. These molecular testing techniques can include conventional PCR or increasingly common, real-time PCR. Many commercial laboratories running real-time PCR test for EHV-1 use a test that discriminates between the D752 and N752 (neuropathogenic and non-neuropathogenic, respectively) strains. Some laboratories use real-time PCR tests that target another gene (typically, the gB gene) and do not discriminate between neuropathogenic and non-neuropathogenic strains, but they may be more sensitive in detecting EHV-1.\(^9\) Interpretation of these test results needs to be driven by our understanding of the roles of EHV-1 strains and the associated risk factors, as reviewed in detail above and elsewhere.\(^4,6\) The key points are as follows:

- PCR testing is the preferred technique; it is generally the fastest and most sensitive test available.
- Whenever possible, attempt viral isolation as well. It is not as sensitive or fast as PCR, but it can add substantially to our ability to understand an outbreak and learn more about EHM.
- Real-time PCR has advantages over conventional PCR. It is typically more sensitive and can distinguish between neuropathogenic and non-neuropathogenic strains.

5. Biosecurity: How and When Do You Lift Quarantine After an EHM Outbreak?
The biosecurity measures for preventing and managing EHV-1 outbreaks have been extensively and recently reviewed.\(^1,6\) One question that is particularly challenging is when to lift quarantine after an EHM outbreak. The current AAEP Outbreak Control guidelines\(^1\) specify a period of 28 days. In many situations, veterinarians are finding this lengthy quarantine period to be impractical and are adopting shorter quarantines of 21 or even 14 days. This decision needs to be based on how “risk-averse” you are in any given situation. After 28 days, the likelihood of further shedding of infectious EHV-1 virus is judged by expert opinion to be low, although
the stresses of transportation may again increase this risk. For this reason, whenever quarantine is lifted, it is important to consider horses leaving the quarantined area as carrying increased potential risk for shedding and treat them accordingly. What about shorter quarantine periods? Based on what we know about viral shedding, 7 days is simply too short, but 14 days may be considered a minimal quarantine period if you are willing to accept some level of risk. For this reason, some authorities use a 14-day quarantine period followed by testing of all horses on 1 or more days to show a lack of shedding. Given the cost of this testing, it may be cheaper to wait another week and use a 21-day quarantine period. The time and money invested in board instead of testing will also lead to a further reduction in the risk of spread of EHV-1.

6. Concluding Remarks

Recently, owners and trainers in many jurisdictions are learning that if their horse tests positive for EHV-1 after a clinical diagnosis of neurologic disease, then there is a strong possibility of a state or other mandated quarantine. These quarantine periods may last anywhere from 14 to 28 days, depending on the situation and subsequent disease occurrence. There is the potential for owners to exert pressure on their veterinarians to not perform EHV-1 testing in their horses. This risk is compounded if the veterinarian shows a lack of confidence in the testing methods and interpretation. The problems can be greater where the neurologic case is positive for the non-neuropathogenic N752 strain of EHV-1, because we do not know at this time whether this changes the risk of spread of EHM. Another concern is that owners may elect for euthanasia and necropsy rather than treatment in an effort to find a diagnosis that can rule out EHM. This is unfortunate, because many times, EHM is successfully treated with appropriate medical care. In many states, equine veterinarians can pass the responsibility for the management of EHV-1-positive neurologic cases to regulatory officials. However, this can just shift the responsibility for difficult decisions, and we all need to share the responsibility for doing the best for these horses. There is growing concern among state regulatory officials and veterinarians that some cases of neurologic disease in horses may go unreported by veterinarians because of increasing pressure from owners and other people involved.

The bottom line is that, in the presence of neurologic signs and a positive test for EHV-1, EHM must remain high on the list of possible diagnoses. These neurologic patients must be isolated, and exposed horses should be quarantined and monitored for fevers every 12 h for at least 2 wk. EHV-1 testing of EHM-exposed horses showing clinical signs must be included in a diagnostic work-up. Quarantine periods may need to be extended and additional isolation areas may need to be identified if additional cases of EHM are confirmed.

References and Footnote


*Pusterla N. Davis, CA (personal communication).