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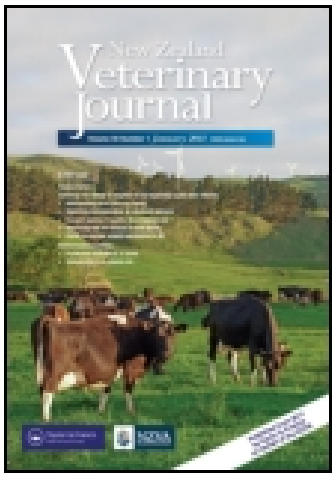

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A review of equid herpesvirus 1 for the veterinary practitioner. Part A: clinical presentation, diagnosis and treatment

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Review Article

A review of equid herpesvirus 1 for the veterinary practitioner. Part A: clinical presentation, diagnosis and treatment

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Abstract

Equid herpesvirus (EHV) type 1 is a common pathogen of horses with worldwide distribution. Although severe tracheobronchitis has been described in some field outbreaks of EHV-1 respiratory disease, many EHV-1 infections occur asymptomatically or are accompanied only by signs of mild respiratory disease. However, EHV-1 infection can also result in outcomes other than respiratory disease such as abortion, neonatal death or neurological disease. This review provides an overview of the diagnosis, treatment and prognosis for EHV-1-associated diseases, with an emphasis on neurological presentations of EHV-1 infection.

KEY WORDS: *Equine herpesvirus 1, equid herpesvirus, EHV-1, equine herpesvirus myeloencephalopathy, EHM, neurological disease*

Key points

- EHV-1 is a common infection worldwide, including New Zealand.
- Many EHV-1 infections are subclinical; others are associated with respiratory disease of varying severity. Occasionally, EHV-1 infection can result in abortion, neurological disease or neonatal foal death.
- EHV-1 abortions usually occur in late pregnancy. There are no long-term effects of EHV-1 abortion on reproductive performance of the mare in subsequent years.
- Diagnosis of EHV-1-associated disease is based on clinical history, presentation and pathological examination (when applicable). It can be confirmed by detection of the virus in appropriate samples.
- Ante-mortem diagnosis of EHV-1 neurological disease is challenging and not always conclusive.
- Serological confirmation of past infection or exposure to EHV-1 is complicated by close antigenic similarities between EHV-1 and EHV-4.
- Treatment of EHV-1 neurological disease is focused on reduction of inflammation associated with EHV-1-induced vasculitis. Prognosis for non-recumbent horses is good if appropriate supportive care is available. Prognosis for recumbent horses is poor.
- Vaccination alone is unlikely to control EHV-1-associated diseases. It should be used in conjunction with implementation of good management strategies to reduce stress, and appropriate infection control practices.

Introduction

Equid herpesvirus 1 (EHV-1) is a common pathogen of horses with a worldwide distribution (Slater 2007). It is one of the seven currently recognised herpesvirus types that can infect equids, five of which (EHV-1, EHV-2, EHV-3, EHV-4 and EHV-5) are natural pathogens of horses (Davison *et al.* 2009). Of these, infection with EHV-1 is considered to be the most important due to its diverse clinical presentations and the potential to cause high economic losses (Lunn *et al.* 2009a). Despite serological evidence that EHV-1 is a common infection among foals (Dunowska *et al.* 2002) and horses (Donald 1998) in New Zealand, EHV-1-induced abortion storms have rarely been documented in this country, and the first outbreak of EHV-1-induced neurological disease occurred only this year (Anonymous 2014). The virological and biological properties of EHV-1, and of the closely related EHV-4, have been previously reviewed by several authors (Allen *et al.* 2004; Patel and Heldens 2005; Slater 2007). The current review focuses on currently available information related to the diagnosis, treatment, management and prognosis for EHV-1-associated diseases, with an emphasis on the neurological presentations of infection. The aim of the paper is to raise the awareness and understanding of the neurological presentations of EHV-1 infection among New Zealand veterinarians, so that suspect cases of equine herpesvirus myeloencephalopathy (EHM) can more easily be recognised and investigated. Pathogenesis and epidemiology of EHV-1-associated diseases are described in a companion paper (Dunowska 2014).

Classification, structure and genome organisation

Equid herpesviruses types 1 and 4 are large, enveloped, DNA viruses that are classified within the family *Alphaherpesviridae* in the order *Herpesvirales* (Davison *et al.* 2009). The two viruses

CNS	Central nervous system
EHM	Equine herpesvirus myeloencephalopathy
EHV	Equid herpesvirus

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are closely related and were considered to be the same virus prior to 1981 (Studdert *et al.* 1981). The complete genomes of both EHV-1 and EHV-4 had been sequenced (Telford *et al.* 1992, 1998). The genome of EHV-1 is approximately 150 kbp in size and has been predicted to contain 76 unique genes, which code for an array of regulatory proteins, enzymes and structural proteins of the virus.

Clinical presentation and prognosis

Many infections with EHV-1 occur asymptomatically or are accompanied by respiratory disease of varying severity (Gilkerson *et al.* 1999). However, EHV-1 infection can also result in comparatively more serious clinical outcomes such as abortion (Carrigan *et al.* 1991), neonatal death (Frymus *et al.* 1986) or neurological disease (Henninger *et al.* 2007). The existence of EHV-1 viruses with different pathogenic potential has been described by several authors (Patel *et al.* 1982; Tearle *et al.* 2003); however, the virus, host and environmental factors that influence the clinical outcome of EHV-1 infection are poorly understood.

Respiratory disease

Experimental infection of presumed-naive horses with virulent strains of EHV-1 results in upper respiratory disease characterised by fever, depression, anorexia and progressive lymphadenopathy, as well as ocular and nasal discharges that often progress from serous to mucopurulent (Gibson *et al.* 1992a). Some animals may cough, although this is not a consistent clinical feature of EHV-1 infection. An initial leukopenia is followed by leukocytosis that develops approximately 1 week following EHV-1 infection, coinciding with the second peak of fever, and often with the change in character of the nasal discharge (Gibson *et al.* 1992a). The clinical signs of upper respiratory disease usually subside within approximately 2 weeks of EHV-1 infection, although it may take longer for the lymph nodes to return to normal size (Slater 2007).

Severe rhinitis and bronchopneumonia described in association with natural EHV-1 infections could rarely be reproduced experimentally. Isolates sourced from animals showing severe respiratory disease typically induced only mild respiratory disease in experimentally infected animals (Allen and Bryans 1986). The incubation period observed for natural infections was also longer (up to 10 days; Slater 2007) than that observed under experimental settings (1–3 days; Gibson *et al.* 1992a, b). This suggests that the severe respiratory disease observed in some field outbreaks may reflect secondary bacterial infections, with mild or asymptomatic primary viral infections acting as a predisposing factor.

Horses affected by respiratory disease usually recover uneventfully, although the time to recovery may be affected by the presence of concurrent or secondary infections. Some horses may show prolonged poor performance after apparent recovery from EHV-1 respiratory disease, which adds to the economical burden of disease (Slater 2007).

Abortion

Equid herpesvirus-1 is considered one of the common infectious causes of abortions in horses (Smith *et al.* 2003). Abortions due to EHV-1 infection usually occur in the third trimester. The mare often appears healthy, without evidence of any prior respiratory disease. Aborted fetuses are typically fresh, and may or may not show histopathological changes suggestive of EHV-1 infection. Most abortions occur as sporadic cases and are presumed to have resulted from re-activation of the latent virus, rather than from *de-novo* EHV-1 infection. Occasionally, EHV-1 abortion storms have been described with lateral transmission of the virus between horses (Mumford *et al.* 1987). There are no long-term effects of EHV-1 abortion on the reproductive performance of the affected mare. Mares can successfully conceive shortly after EHV-1 abortion and typically produce normal foals in subsequent pregnancies (Schulman *et al.* 2013).

Neonatal disease

EHV-1 infection of a mare around the time of parturition may result in the birth of a weak, severely leukopenic foal (Dixon *et al.* 1978). It is not clear whether foals become infected *in-utero*, during birth or shortly after birth. Affected foals typically die within the first few days of life; those that survive longer develop progressive pneumonia that is complicated by secondary bacterial infections, and die by approximately 2 weeks of age (Slater 2007).

Neurological disease

Neurological disease due to EHV-1 infection is often referred to as equine herpesvirus myeloencephalopathy or EHM. In a similar manner to cases of EHV-1 abortion, EHM can occur as a single sporadic case or as an outbreak, which is likely to represent endogenous (reactivation of a latent virus) and exogenous (lateral spread of EHV-1) sources of infection, respectively. The incubation period for EHM is hence difficult to define, because the primary EHV-1 infection might have occurred months before the reactivation event that led to the development of neurological disease.

Fever has been listed as one of the most consistent clinical signs of EHV-1 infection in several outbreaks of EHM. In these outbreaks, the interval between the first detection of fever and the development of neurological signs typically ranged from 4–9 days. Neurological deficits appeared after cessations of viraemia, typically 1–4 days after resolution of the second febrile period in the biphasic temperature profile displayed by EHV-1-infected horses (Henninger *et al.* 2007; Walter *et al.* 2013).

Some EHV-1 isolates appear to be more likely to induce EHM than others (Nugent *et al.* 2006; Goodman *et al.* 2007), although all EHV-1 should be considered to be potentially neuropathogenic (Lunn *et al.* 2009b; Pronost *et al.* 2010). Experimentally, however, it is difficult to consistently reproduce severe neurological disease similar to that usually observed in field outbreaks (Goehring *et al.* 2010b). This suggests that factors other than the genetic make-up of the virus are also important for the development of EHM following EHV-1 infection.

Clinical signs of EHM, in both experimental (Allen 2008; Goehring *et al.* 2010b) and field (Van Maanen *et al.* 2001; Henninger *et al.* 2007) infections, range from mild ataxia to severe neurological deficits in a recumbent horse. Neurological signs appear suddenly and are not usually accompanied by respiratory disease. The caudal spinal cord (thoracic, lumbar, sacral and coccygeal segments) is typically most severely affected. This results in clinical signs of weakness in the hind limbs, ataxia, sensory deficits in the perineal area and hind limbs, as well as bladder dysfunction characterised by atony, urine retention and incontinence. More severely affected horses cannot support their weight, due to paresis, complete paralysis of hind limbs, or even tetraplegia.

The prognosis for resolution of EHV-1 neurological disease depends upon the severity of the neurological impairment and the level of supportive care available. In general, the outlook is good for a non-recumbent horse that is provided with the appropriate care, but poor for one that has become recumbent (McCartan *et al.* 1995; van Maanen *et al.* 2001). In one study, within 1 year of an EHM outbreak, 26 of 32 neurologically affected horses had returned to an exercise level comparable to that seen before the outbreak (Henninger *et al.* 2007). The severity of neurological signs displayed by these horses during the outbreak ranged from grade 1 to 3 on a 1–5 scale; where 1 relates to very mild ataxia/weakness, 4 relates to severe ataxia with stumbling, and 5 is a horse that is unable to bear weight on one or more limbs.

Immune responses

This section provides an overview of those aspects of the immune response to EHV-1, which are, in the author's opinion, most relevant to the diagnosis and management of EHV-1 infection by veterinary practitioners. For more complete information related to EHV-1 immunology the readers are referred to other recent publications (Kydd *et al.* 2006; Slater 2007; Ma *et al.* 2013).

As with other viral infections, both humoral and cell-mediated immune responses are generated by infected or vaccinated horses (Soboll *et al.* 2006; Paillot *et al.* 2007). The duration of immunity following EHV-1 infection is thought to be short, and re-infection can occur every 3–6 months (Bryans 1969, 1980). However, mares that abort due to EHV-1 infection rarely abort again in the following year, suggesting that protection from EHV-1 disease is complex and possibly longer-lasting than protection from re-infection. The issue is further complicated by the fact that it is often impossible to differentiate between reactivated and exogenous EHV-1, and by the close antigenic similarities between EHV-1 and EHV-4.

Although an animal's EHV-1 antibody status provides information on past exposure to the virus, the strength of the humoral response does not seem to correlate with protection against disease. Clinical EHV-1 infections have been reported in horses with high titres of neutralising antibodies (Henninger *et al.* 2007). In addition, following experimental infection with EHV-1, no relationship was detected between pre-infection EHV-1 titres of neutralising antibody and the duration of cell-associated viraemia, or the outcome of pregnancy (Mumford *et al.* 1994). In another study, high neutralising antibody titres induced by vaccination failed to prevent challenge infection with heterologous strain of EHV-1, although the severity of clinical disease and the magnitude and duration of virus shedding from the nasopharynx were reduced (Hannant *et al.* 1993). It should be kept in mind that many cross-reactive epitopes exist between EHV-1 and EHV-4 (Hartley *et al.* 2005), so some of the EHV-1 titres reported in the above studies may reflect EHV-4-specific, rather than EHV-1-specific, responses. Furthermore, an additional complication in the interpretation of serological data is the potential for reactivation of latent EHV-4 following experimental infection with EHV-1. In such cases, development of both EHV-1 and EHV-4 humoral responses would be expected (Tewari *et al.* 1993).

Despite the confusion surrounding the level of cross-reactivity and cross-protection between antibodies raised to EHV-1 and EHV-4 antigens, there is a general agreement between researchers that cellular, and possibly mucosal, immunity is more important for protection against EHV-1-induced disease than humoral responses (Kydd *et al.* 2012). In support of this view, high pre-infection frequencies of EHV-1-specific cytotoxic T lymphocytes were correlated with protection from abortion following challenge with virulent EHV-1 (Kydd *et al.* 2003). Similarly, low pre-infection levels of EHV-1-specific leukocytes were associated with increased risk of abortion following EHV-1 challenge (Pachciarz and Bryans 1978).

Herpesviruses, including EHV-1, have evolved sophisticated mechanisms to avoid being eliminated by the host immune response (Van Der Meulen *et al.* 2006; Ma *et al.* 2013). One such mechanism is the ability of EHV-1 to down-regulate expression of the major histocompatibility complex-1 proteins on infected cells (Ma *et al.* 2012), which results in avoidance of natural killer cell-mediated lysis. Other evasion mechanisms include the development of latency (Edington *et al.* 1994), interference with antibody-dependent and cell-mediated cell lysis (Stokes and Wardley 1988), and suppression of lymphocyte activation through interactions with the host cytokine network (Coombs *et al.* 2006).

Diagnosis

It is recommended that the following samples are collected from cases of suspected EHV-1 infection: nasal swabs for detection/isolation of the virus, acute and convalescent coagulated blood (serum) for serology, and anticoagulated whole blood for detection of cell-associated viraemia. Signalment (age, gender, breed, use) and EHV-1 vaccination history should be noted (Kydd *et al.* 2012).

The ante-mortem diagnosis of EHV-1 infection poses a number of difficulties, which are intricately linked to the biological features of the virus. Ante-mortem detection of asymptomatic, latently infected animals may be difficult because there is no shedding of the infectious virus, and the number of latently infected cells may be low, or they may not be easily accessible for sampling (e.g. within the trigeminal ganglion). Although it is assumed that any unvaccinated seropositive horse must be latently infected, no data are available on the levels of EHV-1-specific antibody produced by latently infected horses. Hence, it is possible that EHV-1 titres in such horses may be below the detection limits of the diagnostic tests available. Subsequently, latent EHV-1 infection cannot be fully excluded in a horse with negative EHV-1 serology results.

Infection with exogenous virus initially leads to viral replication in the nasopharyngeal mucosa (Gryspeerdt *et al.* 2010). During this time, EHV-1 is excreted in respiratory tract fluids for a variable number of days, which can be detected using either PCR or virus isolation (McBrearty *et al.* 2013). The virus grows well in primary equine kidney cells, as well as in a variety of continuous cell lines including RK-13, Vero and equine skin fibroblast cells (Allen and Bryans 1986). A number of PCR assays have been described in the literature, in both traditional (e.g. Lawrence *et al.* 1994) and real-time (e.g. Hussey *et al.* 2006) formats. Some of the assays have the additional capability of distinguishing between the mutant neuropathogenic (D_{752}) and wildtype, often referred to as non-neuropathogenic (N_{752}), genotypes (e.g. Smith *et al.* 2012).

Serological diagnosis of recent EHV-1 infection requires demonstration of at least a four-fold rise in titres between acute and convalescent samples. The testing is complicated by the routine use of EHV-1 vaccination and by extensive cross-reactivity between EHV-1 and EHV-4. The amount of sequence identity between EHV-1 and EHV-4, at the amino acid level, ranges from 55% to 96% across the genome (Telford *et al.* 1998). This means that the two viruses cannot be distinguished antigenically using polyclonal antisera. However, a type-specific ELISA has been developed (Hartley *et al.* 2005), although is not currently offered by any of the New Zealand diagnostic laboratories.

Respiratory disease

Diagnosis of EHV-1 respiratory infection is reasonably straightforward and can be accomplished by detection of the virus in nasopharyngeal secretions using either PCR or virus isolation (McBrearty *et al.* 2013). It should be kept in mind that several respiratory viruses and bacteria can be aetiologically involved in equine respiratory disease and it is possible to detect subclinical EHV-1 infection in a horse concurrently infected with other pathogens. Therefore, the detection of EHV-1 in a nasal or nasopharyngeal swab from a single diseased horse, although suggestive, does not necessarily imply aetiological involvement of the virus.

Abortion and neonatal disease

Diagnosis of EHV-1 abortion and neonatal disease is based on clinical history, presentation, and detection of EHV-1 in fetal or neonatal tissues. However, virologically negative fetuses aborted following experimental EHV-1 infection of pregnant mares, presumably due to EHV-1-induced placental dysfunction, have also been described (Smith *et al.* 1992). Therefore, it is recommended that both the fetus and the placenta are submitted for the diagnosis of EHV-1 abortion. The highest concentrations of virus are usually found in the fetal lung, liver and spleen, and these are recommended as the samples of choice, if submission of the entire fetus is not feasible (Gardiner *et al.* 2012). Fetal post-mortem findings vary, but often include subcutaneous oedema, presence of straw-coloured fluid in plural and abdominal cavities, and pulmonary oedema. Other lesions include variable icterus, splenomegaly, hepatomegaly with necrotic foci, as well as petechiation in the lungs and of serosal and mucosal surfaces in other tissues (Prickett 1970). Histopathological changes suggestive of EHV-1 infection include necrotising bronchiolitis, pneumonitis and lymphoid depletion and necrosis in the spleen, liver, lymph nodes, thymus and adrenal glands. The presence of eosinophylic intranuclear inclusion bodies in necrotic cells is highly suggestive of EHV-1 infection (Allen *et al.* 2004).

Neurological disease

The ante-mortem diagnosis of EHM is difficult (Pusterla *et al.* 2009). There is no single test that can be used to definitively rule in or rule out EHV-1 involvement. Detection of EHV-1 in the cerebrospinal fluid in a febrile horse with neurological deficits would provide laboratory confirmation of the EHM diagnosis. However, this is rarely achieved, even if attempted (Pusterla *et al.* 2009). In order to maximise the likelihood of EHV-1 detection in nasal secretions or in leukocytes, the samples should be collected early in infection, ideally within the first week. However, neurological signs often develop 4–9 days after the initial EHV-1 infection (as determined by the first detection of fever), which is often after the cessation of EHV-1 viraemia (Henninger *et al.* 2007; Walter *et al.* 2013). Therefore, both nasal swabs and blood samples may be EHV-1 negative by the time they are collected from clinical cases of EHM. To illustrate this, Burgess *et al.* (2012) estimated that 1 day after the onset of neurological signs the average expected probability of EHV-1 nasal shedding was 66.7%, but this had dropped to 4.8% 9 days later. Another impediment to the diagnosis of EHM in an individual horse is the fact that the disease could presumably be induced by local reactivation of EHV-1 within endothelial cells of the central nervous system (CNS); in such cases, nasal shedding of EHV-1 would not occur.

Thus, ante-mortem diagnosis of EHM is often presumptive and based on information from clinical, epidemiological, and laboratory data, combined with the exclusion of other causes of neurological disease in the horse. The schematic algorithms for the establishment of EHV-1 diagnosis in a horse with neurological deficits are presented in Figure 1.

While detection of EHV-1 in individual cases may be difficult, it is often possible to demonstrate circulation of EHV-1 among horses in an outbreak (Walter *et al.* 2013). Both clinically affected and healthy in-contact horses should be sampled. As fever is the most consistent initial clinical indication of recent EHV-1 infection, in order to maximise detection of EHV-1, nasal swabs and blood samples should ideally be collected at the time of first detection of fever. Convalescent serum samples for serology should be collected from all horses 2–4 weeks after the collection of acute samples. It would be of value to determine the serological status of all horses, including those that remained healthy throughout the outbreak.

Outside an outbreak, it is generally not recommended to collect random samples for EHV-1 PCR testing from afebrile, clinically normal horses (Pusterla *et al.* 2009). This is because horses may periodically shed the virus without any clinical signs of disease. Thus, interpretation of the positive test result is not straightforward and requires thorough understanding of the complexities of EHV-1 infection in any given equine population.

At post-mortem examination, horses affected by EHM show vasculitis in the CNS, which is associated with vascular damage, thrombosis and haemorrhage (Platt *et al.* 1980; Studdert *et al.* 2003). The pathological changes may be localised and serial transverse cuts of the spinal cord may need to be thoroughly examined in order to detect the affected areas (Edington *et al.* 1986). Vasculitis and haemorrhages may also be present in other tissues.

Control and treatment of EHV-1 diseases

A detailed overview of EHV-1 control strategies has been presented by several authors (Slater 2007; Pusterla *et al.* 2009; Kydd *et al.* 2012). The ability of EHV-1 to infect young foals in the presence of maternal antibody (Gilkerson *et al.* 1999), combined with the development of latency following primary infection (Allen 2006), makes it unrealistic to fully eliminate EHV-1 from any equine establishment. Inevitably, some horses are likely to reactivate latent EHV-1 and become the source of infection for others. This circulation of EHV-1 may be silent, accompanied only by mild respiratory disease in some horses, or it may result in cases of abortions or neurological disease. Consequently, EHV-1-associated disease can occur even in a closed herd without any immediate prior exposure to an external source of the infectious virus.

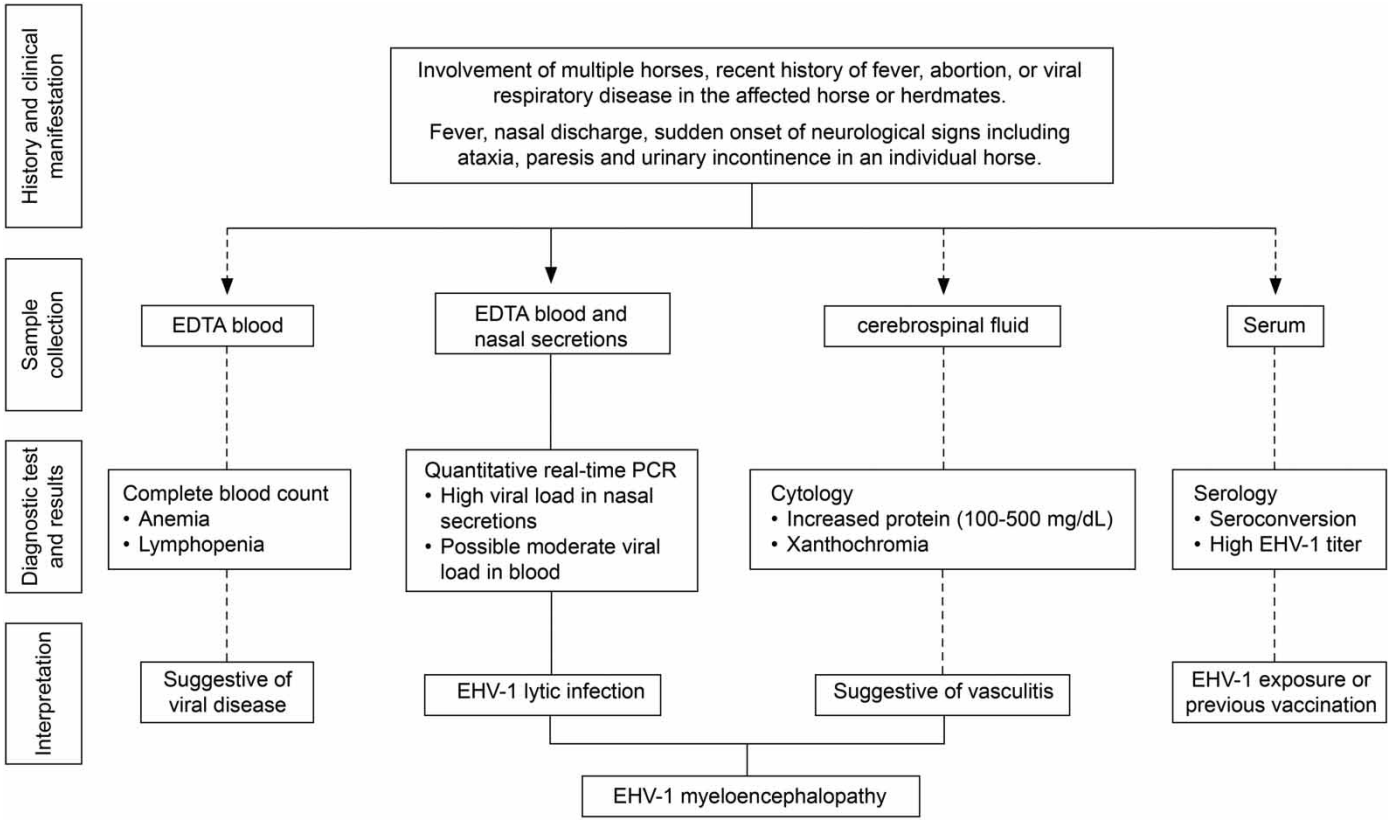

Figure 1. Algorithm to establish a rapid ante-mortem laboratory diagnosis of equid herpesvirus 1 (EHV-1) infection in a horse with neurological deficits. Dashed arrows represent a presumptive pathway, and solid arrows a diagnostic pathway. Reproduced from Pusterla *et al.* (2009), with permission from the publisher (Elsevier)

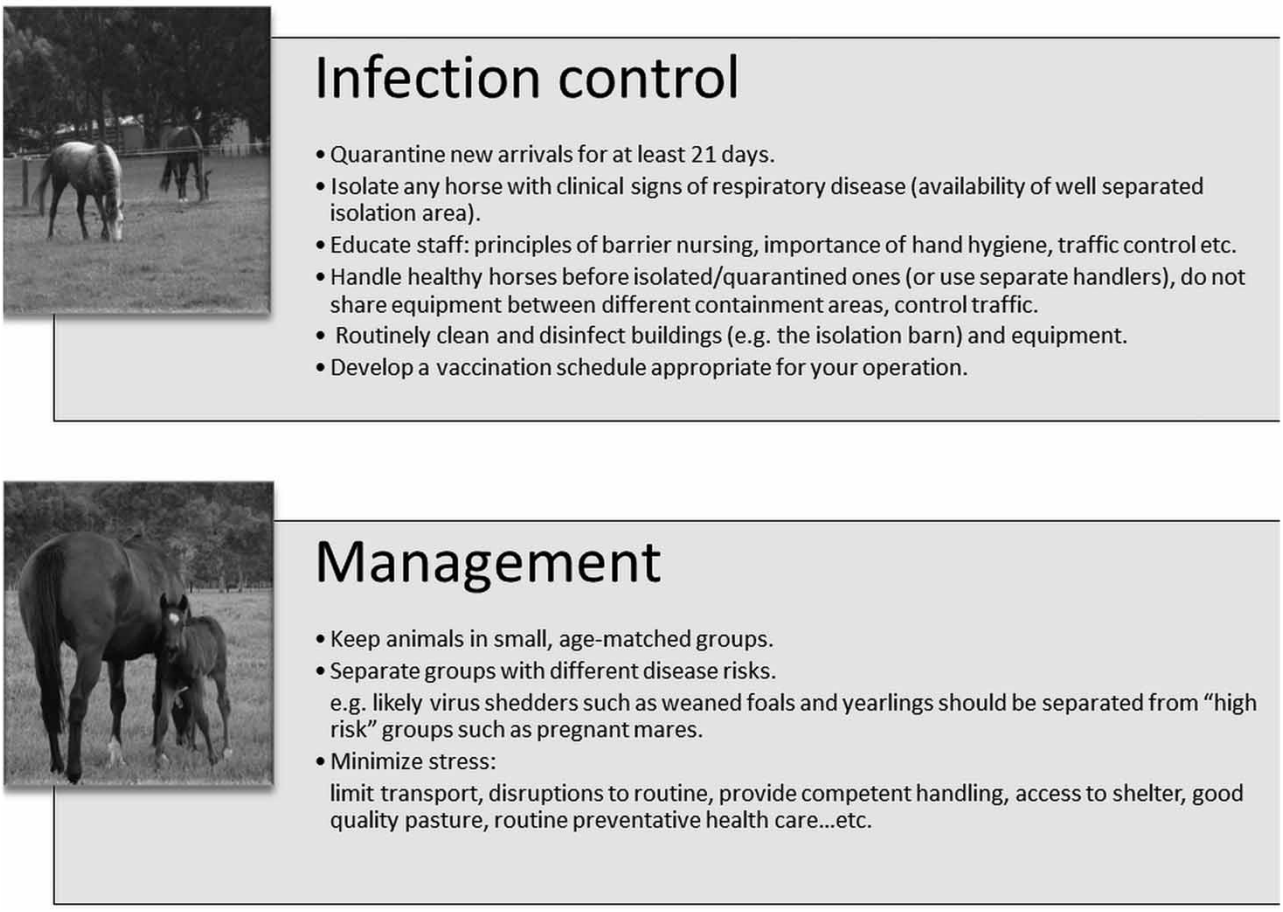

Figure 2. Examples of infection control and management practices useful in control of equid herpesvirus 1 associated diseases. For details see Slater (2007), Kydd *et al.* (2012) and Pusterla *et al.* (2009)

Management strategies that minimise stress may affect the frequency of EHV-1 recrudescence and thus limit the sources of infectious EHV-1 on the premises. In addition to good management, routine infection control strategies are useful, both for minimising the probability of introducing external sources of EHV-1 and for limiting spread of the endemic viruses between different groups of horses on a property (Figure 2).

In an outbreak, body temperature should be monitored in all affected and in-contact horses following identification of an index case, ideally twice daily. If febrile horses are identified, they should be considered infectious and kept under conditions that minimise the spread of the virus to other animals. The exact measures implemented would depend on the type of establishment affected (e.g. a stud farm vs a veterinary hospital), but should include physical separation of identified cases, control of traffic (both in-and-out and within the establishment), and use of barrier precautions when handling infected animals. The latter include wearing gloves and dedicated protective clothing, frequent hand washing, as well as cleaning and disinfection of any equipment shared between different animals (Goehring *et al.* 2010a; Kydd *et al.* 2012).

Globally, there are at least 12 commercially available EHV-1/4 vaccines (Slater 2007), three of which are currently available in New Zealand. Most are marketed for help in the prevention of EHV-1/4 respiratory disease, with some having an additional claim for helping to prevent EHV-1 abortions. Therefore, vaccination can be effectively used as an aid to control EHV-1 infections on any establishment by minimising the levels of virus shed by infected animals, the severity of EHV-1 respiratory disease and the number of EHV-1 abortions. None of the available vaccines, however, are currently marketed for prevention of EHV-1 neurological disease. In addition, none claim to prevent establishment of latency following EHV-1 infection. Hence, even regularly vaccinated horses can still be latently infected with EHV-1, and the virus may reactivate if appropriate conditions, such as high levels of stress or immunosuppression, are encountered. In summary, vaccination alone is unlikely to provide an effective measure for prevention of EHV-1-associated diseases in the absence of good infection control and management practices, which remain the hallmark of control of EHV-1 infections on any premises (Figure 2).

Treatment of EHV-1-associated disease has been attempted most often for cases of EHM, with the focus on reducing the inflammation associated with EHV-1-induced vasculitis (Pusterla *et al.* 2009). Most clinicians used a combination of anti-inflammatory drugs (e.g. flunixin meglumine, dexamethasone, prednisolone) and free-radical scavengers (e.g. dimethyl sulphoxide; Table 1). The use of acetylsalicylic acid (aspirin) in suspect EHM cases at the time of fever detection (6 mg/kg per os once daily), and vitamin E supplementation (500–1000 IU per os once daily) for its presumed beneficial effect of free radical scavenging within the CNS, has been proposed by Goehring *et al.* (2005). In horses that require urinary catheterisation, the administration of antimicrobials (e.g. trimethoprim-sulfamethoxazole, ceftiofur) is recommended in order to reduce the risk of bacterial cystitis (Pusterla *et al.* 2009). Other supportive treatments (e.g. polyionic fluid, tranquilisers, parenteral nutrition) can be implemented as dictated by the condition of an individual horse (Pusterla *et al.* 2009).

In addition to non-specific supportive treatment, the use of specific anti-herpesvirus drugs has also been reported (Henninger *et al.* 2007). The efficacy of acyclovir for the resolution of EHM is difficult to assess because of the many confounding factors typically present in an outbreak situation. Nevertheless, in one EHM outbreak, the administration of acyclovir appeared to be associated with decreased severity of disease and increased survival (Henninger *et al.* 2007). However, other researchers have reported poor bioavailability of acyclovir in the horse and variable serum time profiles of the drug (Wilkins *et al.* 2005). Another nucleoside analogue, valacyclovir, has recently been shown to have better pharmacokinetics in the horse than acyclovir, and may provide an antiviral treatment option for EHM affected horses in the future (Garre *et al.* 2009).

Table 1. Examples of protocols used for the treatment of cases of equine herpesvirus myeloencephalopathy (EHM). The protocols below reflect empirical treatments used in the face of EHM outbreaks. The success of these treatments varied in individual cases. In general, the prognosis was good for non-recumbent horses, but poor for recumbent ones. For details, the readers are referred to the references cited

Treatment Details	Reference
Flunixin meglumine (1.1 mg/kg I/V sid) Dexamethasone (0.2 mg/kg I/V, sid for 3 days, then 0.1 mg/kg I/V, sid for 3 days) ±acyclovir (20 mg/kg *per os,* tid for 5 days) 10% DMSO (1 g/kg I/V sid for 3 days) for horse with grade >2/5 Nursing care and supportive treatment as required (I/V polyionic fluids, repositioning, tranquilisation, bladder catheterisation)	(Henninger *et al*. 2007)
Flunixin meglumine (1.1 mg/kg I/V sid for 5 days) DMSO (0.25 g/kg in LRS I/V sid for 5 days) ±acyclovir (20 mg/kg *per os,* tid for 5 days) ±dexamethasone (0.3 mg/kg I/V sid for 3 days, then 0.1 mg/kg I/V sid for 3 days) Supportive care as required (bladder catheterisation, antibiotics, polyionic fluids, nitroglycerin patches)	(Friday *et al.* 2000)
Fluids (20 mL/kg Hartmann's solution) Flunixin meglumine (1 mg/kg, unspecified frequency) 10% DMSO (1 g/kg, unspecified frequency) ±phenylbutazone (4 mg/kg *per os*, sid), slinging as required	(Studdert *et al*. 2003)

DMSO=dimethyl sulphoxide; LRS=lactated ringers solution; sid=once daily; tid=three times daily

Concluding remarks

Despite the fact that EHV-1 is a common infection among horses worldwide, the diagnosis, treatment and prevention of EHV-1-associated diseases remain challenging. This partly reflects the complexity of the virus-host interactions, and our limited understanding of the factors that are important for expression of clinically different forms of disease following EHV-1 infection or recrudescence. Prevention and control efforts are also hampered by the fact that many EHV-1 infections occur early in life, and are presumably followed by a life-long latency. Understanding these limitations is important for the development of rational disease control programmes.

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