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Equine Viral Arteritis (2-Apr-2002)

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Introduction

Equine viral arteritis (EVA) is a contagious respiratory disease of equids, so named for the characteristic inflammatory lesions induced by the causal virus in the smaller blood vessels, especially the arterioles of the acutely infected animal [1,2]. Identified with the "equine influenza-abortion" complex for many years, EVA was finally determined to be an etiologically separate disease following a major outbreak of respiratory illness and abortion on a Standardbred breeding farm near Bucyrus, Ohio in 1953 [3]. Based on reports in the veterinary literature of the late nineteenth century, there is little doubt that a clinically identical or very similar disease referred to by various names, epizootic cellulitis - pinkeye, pferdestaube, etc., was prevalent in Europe at least a century earlier [4-7].

For more than 30 years after it was first recognized and characterized, EVA aroused little interest as a viral disease of the horse, much less as a cause for concern in relation to international movement [8]. That changed dramatically, however, following a widespread occurrence on a significant number of Thoroughbred breeding farms in Kentucky in 1984 [9]. Fears that a highly pathogenic strain of the causal virus had emerged, fueled by the belief that most equine populations were susceptible to the virus, resulted in a major reassessment of the significance of the disease by many horse industries worldwide [10]. Severe restrictions were imposed on the movement of horses with positive antibody titers to the virus. In the ensuing years, these measures have largely been eased, with greatest emphasis currently placed on controlling the international trade in carrier stallions and infective semen which have frequently been implicated in spread of the virus both within and between countries [11-14].

Some contend that the level of notoriety afforded EVA since 1984 is unwarranted, [15-17]. maintaining, not without justification, that there are other equine infectious diseases of greater veterinary medical importance which are not as rigorously regulated internationally [17]. Regardless of how valid this contention may be, however, there are horse owners, veterinarians and health officials who still perceive EVA as a significant disease threat for equine populations worldwide.

Etiology

Equine viral arteritis is caused by a small, enveloped RNA virus, equine arteritis virus (EAV), which is the prototype virus of the genus *Arterivirus*, family *Arteriviridae*, order *Nidovirales* [1,18,19]. Based on genomic structure and replication strategies, three other viruses have been classified in the same genus and family, lactic dehydrogenase elevating virus of mice, simian hemorrhagic fever virus and most importantly, porcine reproductive and respiratory syndrome virus; [20] the latter is a source of significant economic loss in swine populations in North America, Europe and elsewhere [21].

All the evidence to date would indicate that natural infection with EAV is restricted to members of the family *Equidae* [8]. The virus is non-transmissible to humans.

Based on extensive antigenic and genomic cross-comparison studies, only one major serotype of EAV, namely the Bucyrus strain, has so far been recorded [8,22]. Nonetheless, considerable diversity has been demonstrated between geographically and temporally disparate isolates of the virus [23-27]. Similarly, there is variability in pathogenicity among strains of EAV, [8] with some strains capable of causing the range of clinical signs collectively referred to as EVA, [1,28,29] and others eliciting nothing other than a low to moderate febrile response [29,30].

Of major importance when considering the pathogenic properties of strains of EAV, is the fact that historically, the virus has been recognized as a cause of contagious abortion in pregnant mares [3,28,31]. While there is no dispute that certain strains

of EAV have been responsible for widespread outbreaks of abortion in susceptible mares, [32,33] there is also evidence which would suggest that not all strains of the virus are abortigenic [8]. The latter elicit little, if any, clinical response and are considered by some, candidate vaccine strains of the virus. From a practical viewpoint, however, the distinction between strains of EAV that are capable of causing abortion and those that are not, is a mute one. Currently there is no highly reliable and rapid means of categorizing strains based on their abortifacient properties. Hence, from a clinician's viewpoint, all strains of the virus must be considered potentially abortigenic unless shown otherwise.

For many years, there was a widely held misconception that EAV is a highly virulent equine pathogen, with an attendant case-fatality rate of 50 to 60 percent [8,17]. This misconception most likely originated from descriptions of EVA in veterinary texts of the time which were based on the findings of experimental studies with a laboratory-derived velogenic variant of the original Bucyrus strain of EAV [34]. It should be emphasized that these early descriptions of the experimental disease caused by this particular strain of the virus contrast markedly with the nature and severity of clinical signs and case-fatality rate described in field outbreaks of EVA [8,33,35]. To this point, no naturally occurring strain of EAV has been isolated with virulence properties akin to or even approaching those of the experimentally derived velogenic variant of the Bucyrus virus [8].

Equine arteritis virus is not a particularly resistant virus outside the body and is readily inactivated under a range of physico-chemical conditions [8,34]. It is sensitive to sunlight, high temperatures and low humidity and various disinfectant and lipid solvents. However, viability of the virus is preserved at refrigeration or freezing temperatures. Equine arteritis virus can remain infective in frozen semen for very lengthy periods of time, extending to many years [13].

Distribution

Based on recorded outbreaks of EVA and the results of serological surveys, EAV is known to be present in many horse populations throughout the world; Japan and Iceland are notable exceptions [8,36-43]. There are a considerable number of countries, however, whose status for this infection remains in question because of an absence of reliable surveillance data.

Surveys of different equine populations have shown that the prevalence of EAV infection can vary widely among breeds of horses both between countries and in the same country [8,36,44-46]. This is exemplified by the significantly higher seropositivity rate frequently found in Standardbreds and some Warmblood breeds compared to that found in Thoroughbreds and certain other breeds, e.g., Quarter Horses. While it is tempting to speculate that this may reflect an inherent predisposition to infection with EAV among particular breeds, viz. Standardbreds, experimental evidence in support of such a hypothesis is lacking (McCullum & Timoney, unpublished data). From limited available data, EAV does not appear to have spread to any significant extent to populations of feral equids in countries in which it has been studied (Timoney & McCullum, unpublished data) [47].

Clinical Response

A degree of confusion still persists among some over the actual clinical significance of EAV. This stems largely from the misconception that EVA is a serious disease with a case-fatality rate of 40 to 60 percent [8,17]. The fact of the matter is that the majority of natural cases of EAV infection are subclinical [8,9,48]. Exposure to the virus may result in clinical or inapparent infection depending on the virus strain involved, virus dose, age and physical condition of the animal(s) infected and various environmental factors [8]. The morbidity rate can differ significantly between outbreaks of EVA, with highest rates most often reported among large groups of horses closely congregated together, for example, at racetracks [49,50]. Horses kept under such circumstances are frequently stressed from the demands of training and racing. Onset of clinical signs is preceded by an incubation period of 3 to 14 days which varies with the route of infection [1,3,8,51]. It is shorter in the case of aerosol exposure and longer where transmission occurs by the venereal route.

Typical cases of the disease can present with all or any combination of the following signs:

- Fever up to 41°C that can last for 2 to 9 days;
- A variable degree of anorexia and depression (Fig. 1);
- Leukopenia;
- Limb edema which is most pronounced in the lower hind limbs but may involve all four limbs (Fig. 2);
- A serous to mucoid nasal discharge associated with a variable degree of rhinitis;
- Supraorbital or periorbital edema (Fig. 3);
- Conjunctivitis of varying severity commonly referred to as "pink-eye";

- Epiphora that may be unilateral or bilateral (Fig. 4);
- Photophobia, most frequently observed in cases with severe conjunctivitis;
- Edema involving the scrotum and prepuce of the colt/stallion and the mammary glands of the mare (Fig. 5 and Fig.6);
- Urticarial rash which may be localized and occur as small, discrete lesions, usually on the cheeks, sides of the neck or pectoral region, or it may be generalized and present as a maculo-papular rash over most of the body; [8,9].(Fig. 7)
- Abortion in the mare;
- A fatal interstitial pneumonia or pneumoenteritis in young foals [52,53].



Figure 1. Depression in an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 2. Severe lower hind limb edema in an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 3. Periorbital edema and conjunctivitis or "pink-eye" in an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 4. Epiphora in an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 5. Scrotal and preputial edema in an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 6. Edema of the mammary glands in an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 7. Urticarial rash over the neck and shoulder of an experimental case of EVA. - To view this image in full size go to the IVIS website at www.ivis.org . -

Other clinical signs that may be observed less frequently include:

- Adventitious edematous swellings in the intermandibular space, beneath the sternum, the shoulder region or other

parts of the body;

- Respiratory distress, including polypnea and dyspnea, especially in young foals;
- Coughing,
- Diarrhea;
- Posterior paresis and ataxia;
- Submaxillary lymphadenopathy;
- Papular eruptions on the mucous membrane inside the upper lip; these are usually found in association with a skin rash; [9].
- Gingival and buccal erosions [54].

In general, the severity of EVA tends to be greater in very young or aged horses, in debilitated individuals, and in horses that are being physically stressed [8,49]. It is important to emphasize that with very few exceptions, horses affected with this disease invariably make complete clinical recoveries, even in the absence of any symptomatic treatment. Horses in training may experience a period of impaired performance during the acute and early convalescent phases of the infection [49,50]. Mortality in natural cases of EAV infection occurs infrequently in neonatal foals that are usually congenitally infected with the virus; these succumb from a fulminating interstitial pneumonia within 48 to 96 hours of birth [31,53,55,56]. Deaths have also been reported in foals a few weeks to months of age that develop a rapidly progressive pneumo-enteritis [35,52].

Pregnant mares exposed to EAV may abort late in the acute phase or early in the convalescent phase of the infection and not months after viral exposure, as some might believe [1,17,28,31]. Abortion may or may not be preceded by clinical signs of EVA in the infected mare [8]. Natural or experimental cases of EAV-related abortion have been recorded from 3 to over 10 months of gestation [1,28,33]. Abortion rates in susceptible mares can vary widely from less than 10 percent to between 50 and 60 percent and even as high as 71 percent in one experimental study involving the Kentucky 1984 strain of the virus [32]. Exposure of pregnant mares to EAV late in pregnancy may not result in abortion but rather the birth of a foal that is congenitally infected with the virus [31,56]. Such foals invariably succumb from a rapidly progressive interstitial pneumonia within the first 3 to 4 days of life. Mares that have aborted due to EAV do not appear to suffer any resultant adverse effects on fertility.

In contrast, stallions affected with EVA may undergo a period of short-term subfertility [57]. This is believed to result from increased testicular temperature which in turn, is caused by the pyrexia and severe scrotal edema that can be experienced by an acutely infected stallion. It is not considered to be due to the direct effects of EAV. Equine viral arteritis affected stallions frequently exhibit reduced libido which is associated with decreased sperm motility, concentration and percentage of morphologically normal sperm. Such changes have been shown to persist for up to 16 to 17 weeks in experimentally infected stallions. While the severity of these changes in semen quality is sufficient to cause temporary impairment of fertility in some stallions, this effect is not long-term. Persistence of EAV in the reproductive tract of chronically infected stallions does not appear to have any discernible adverse effect on fertility [8]. Such animals are asymptomatic carriers of the virus. Mares that become infected from breeding to a carrier stallion also do not experience any apparent short or long-term virus-related fertility problems.

Epidemiology

In spite of the distribution of EAV in many equine populations around the world, few confirmed outbreaks of EVA were recorded prior to 1984 when the disease occurred on a significant number of Thoroughbred breeding farms in Kentucky [9]. The last 10 to 15 years, however, have seen an increase in reported outbreaks of EVA in North America and Europe [8,10,11]. While this may reflect a greater awareness of the disease among horse owners, breeders and veterinarians and enhanced diagnostic laboratory capability, many believe that there has been a bona fide increase in the incidence of EVA. This has largely been due to changing trends in the equine industry, especially the continued increase in international trade in horses and semen [11]. On numerous occasions, outbreaks of EVA have been traced back to the movement of horses, for example, carrier stallions, or the use of virus infective, fresh-cooled or frozen semen [12-14].

It is important to appreciate that widespread dissemination of EAV can occur at racetracks and on breeding farms [49,50,58]. Since many cases of primary infection with EAV are asymptomatic, the absence of clinical evidence of EVA is no guarantee of absence of the virus in any given equine population.

Virus-, host- and environment-related factors are involved in the epidemiology of EVA [8,58]. Among those identified of importance are: variation in pathogenicity among naturally occurring strains of EAV, routes of transmission during acute and

chronic phases of the infection, persistence of the virus in the stallion and the nature of acquired immunity to infection.

Viral Characteristics - It has been recognized for a long time that naturally occurring strains of EAV vary in pathogenicity [8]. Experimental infectivity studies have demonstrated that strains may be of low, moderate or high virulence for the horse [29,30]. There is evidence to indicate that some, but not all, strains of the virus are abortigenic. While many carrier stallions shed strains of EAV that appear to be of low inherent pathogenicity, on occasion, such animals have served as the source of infection for outbreaks of EVA [13,59].

Modes of Transmission - Acutely infected horses shed EAV for a limited period of time in various body secretions and excretions [60-62]. The greatest concentration of virus is usually shed via the respiratory tract; shedding can last for up to 16 days [60]. Aerosol transmission is the most significant means of spread of EAV either on breeding farms or wherever horses come into close contact with one another, for example, at racetracks, shows, sales or veterinary clinics [8,60]. An additional important means of dissemination of the virus on breeding farms is venereally by the acutely infected stallion [58]. Transmission of EAV may also occur by the congenital route, resulting either in abortion or in the birth of a congenitally infected live but diseased foal [1,31,56]. In such instances, the placenta, placental fluids and the fetus are plentiful sources of virus. In the case of the carrier stallion, transmission of EAV occurs only by the venereal route [63].

Aside from virus spread by direct contact, EAV can also, though infrequently, be transmitted indirectly by means of shanks, halters, apparel, breeding shed equipment, etc., contaminated with infective secretions/excretions [8,58].

Viral Reservoir - The natural reservoir of EAV that ensures its persistence in various horse populations throughout the world, is the carrier stallion [8,63]. The carrier state has only been identified in the stallion and not in the mare, gelding or sexually immature colt. The virus may persist in the stallion for weeks, months or many years, perhaps even for the lifetime of certain individuals. Frequency of the carrier rate in any given population of stallions can vary from less than 10 percent to greater than 70 percent [64]. Equine arteritis virus is localized in certain of the accessory sex glands in the chronically infected stallion [61,65]. Establishment and persistence of the carrier state has been shown to be testosterone dependent [65]. Carrier stallions shed the virus constantly in the semen and consequently, only pose a risk of transmission of infection at time of breeding [8,63]. Transmission rates can be as high as 85 to 100 percent, irrespective of whether breeding takes place by natural service or artificial insemination. Stallions that are carriers of EAV are clinically healthy and exhibit no apparent decrease in fertility. A variable percentage of long-term carrier stallions spontaneously eliminate EAV from their reproductive tracts and no longer pose any risk of transmission of infection [8,64].

Donkeys and other non-horse equids have been investigated as alternative reservoirs of EAV in countries with significant populations of feral equids [40,47,66,67]. The evidence to date would indicate that they do not play any appreciable role in the epidemiology of this virus.

Immunity - A strong and durable immunity is stimulated in horses following natural infection with EAV [68,69]. A protective level of immunity is known to last for a least several years and probably, longer. Foals born of seropositive dams are passively protected against clinical disease for the first 2 to 5 months of age [70]. Immunization through vaccination has been employed successfully in certain countries to prevent EVA and also, to protect stallions against establishment of the carrier state [8]. A high level of immunity has been obtained after repeat vaccination, especially where the modified live virus vaccine against EVA (Arvac®, Ft. Dodge Animal Health) has been used (McCollum & Timoney, unpublished data).

Laboratory Diagnosis

In view of its clinical similarity to several other infectious and non-infectious equine diseases, a provisional diagnosis of EVA should always be confirmed by the submission of appropriate specimens for laboratory examination [71]. Where acute EAV infection is suspected, confirmation of a diagnosis is based on virus isolation or detection of viral nucleic acid or antigen and/or demonstration of a specific antibody response by testing paired (acute and convalescent) sera collected 3 to 4 weeks apart [8].

Appropriate specimens to test from acutely infected horses include nasopharyngeal and conjunctival swabs and citrated or EDTA blood samples. To optimize the chances of detection of virus, samples should be obtained as soon as possible after the onset of fever or suspected signs of EAV infection. Swabs should be transferred to a suitable viral transport medium and shipped either refrigerated or frozen in an insulated container to a suitably qualified laboratory, preferably using an overnight delivery service. Unclotted blood samples should be shipped refrigerated, but not frozen.

In suspect cases of EAV-related abortion, virus isolation/detection should be attempted from placental tissue and fluids, and fetal lung, liver and lymphoreticular tissues [8,72]. Where EVA is suspected in the death of young foals or older horses, a wide range of tissues including, but not exclusive of the lymphatic glands associated with the respiratory and alimentary tracts, should be collected for laboratory examination [53]. Specimens should be submitted for virus isolation/detection, immunohistochemical and histopathologic examination for the vascular lesions characteristic of this infection.

Equine arteritis virus infection is frequently confirmed serologically by demonstration of seroconversion or a significant (four-fold or greater) rise in antibody titer to the virus [73]. While a number of serological procedures have been employed in the past for antibody detection, the complement enhanced microneutralization test has been used successfully for many years for the diagnosis of acute EAV infection, for import-export testing, and in seroprevalence studies [74]. Several ELISA tests have been developed, some of which offer significant promise as alternative serodiagnostic assays with comparable sensitivity and specificity to the neutralization test [75-77].

When investigating the possible carrier status of a stallion, it is important first of all, to establish whether the individual is serologically negative or positive for antibodies to EAV [78]. Since the carrier state has never been confirmed in a seronegative stallion, only stallions with a titer of 1:4 or greater to the virus without an appropriately certified history of vaccination against EVA, need be considered putative carriers [64]. The carrier state can be confirmed either by virus isolation or detection of viral nucleic acid in a sample of semen containing the sperm-rich fraction of the ejaculate [63,78,79]. A slower, more expensive but very reliable alternative is to test breed a suspect carrier stallion to two mares which are monitored clinically and serologically for up to 28 days for evidence of transmission of infection [63].

Serological differentiation of carrier stallions from those whose seropositivity is the result of vaccination, though desirable, is not yet possible. Even if it were, through the use of a marker vaccine and companion diagnostic test, it would not differentiate a non-carrier stallion that had been vaccinated and subsequently naturally exposed to infection from one that was a carrier and subsequently vaccinated with a marker vaccine. In light of the longevity of the species and the frequency with which horses move both within and between countries, there is ample opportunity for them to be exposed to EAV on at least one occasion during their lives. What is more important to emphasize is that stallions can be successfully protected against establishment of the carrier state through vaccination, and that currently available diagnostic tests on semen can detect the carrier state in a stallion with a very high degree of accuracy.

Differential Diagnosis

A number of infectious and non-infectious, respiratory and systemic diseases of equids can be confused on clinical grounds with EVA [8]. Among the more significant are equine herpesvirus 1 and 4 infections, equine influenza, equine infectious anemia, purpura hemorrhagica, urticaria and toxicosis due to hoary alyssum (*Berteroa incana*). Additional diseases that EVA needs to be differentiated from and which are exotic to many countries are African horsesickness, dourine and Getah virus infection.

Abortion or death in neonatal foals due to EAV bears close resemblance to that caused by EHV-1 and less frequently, EHV-4. Accordingly, it is always advisable to submit appropriate specimens for laboratory examination to determine which viral infection is involved.

Treatment

In the absence of a specific anti-viral drug against EAV, treatment of cases of EVA is symptomatic, with emphasis on controlling the fever and amount of dependent edema, especially in affected stallions [8,72]. Adequate rest should be provided, particularly to breeding stallions and to horses in training, if adverse effects on performance are to be minimized or avoided. At the present time, there is no successful treatment for young foals with EAV-related interstitial pneumonia or pneumo-enteritis. Prophylactic administration of antibiotics is indicated in older foals acutely infected with EAV to counter possible secondary bacterial infection. Efforts are continuing into devising a safe and effective therapeutic means of eliminating the carrier state in the stallion.

Prevention and Control

The prevention and control of EVA can be successfully achieved based on what is known about the biology and epidemiology of EVA. Of added advantage in certain countries is the availability of safe and effective vaccines with which to immunize against the disease [8,68,69,80].

Most control programs are directed at preventing or restricting the spread of EAV in breeding horse populations to minimize or eliminate the risk of virus-related abortion or death in young foals, and establishment of the carrier state in stallions [8,72]. Such programs are predicated on the observance of sound breeding management practices, identification of any carrier stallions and immunization of the non-carrier breeding stallion population.

Two vaccines have been developed against EVA, a modified live virus product (Arvac®, Ft. Dodge Animal Health) and an inactivated adjuvanted virus product (Artervac®, Ft. Dodge Animal Health) [8,73]. Extensive use of the modified live virus vaccine since 1985 has confirmed its safety and immunogenicity for stallions, non-pregnant mares, fillies and colts. The vaccine manufacturers advise against its use in pregnant mares and foals less than 6 weeks of age, unless under conditions of significant risk of natural exposure to EAV. The inactivated vaccine, though safe for use in pregnant mares, is not as strongly immunogenic as the modified live virus vaccine. Two or more vaccinations are frequently required to stimulate a detectable neutralizing antibody response. The durability of immunity produced by this vaccine has yet to be established.

An important component of current EVA control programs is the identification of any carrier stallion [8,14,58]. These should be managed separately to ensure that there is no risk of the inadvertent spread of EAV to previously uninfected or unvaccinated horses on the premises, especially pregnant mares. Under appropriate conditions of management, carrier stallions can continue to be used for breeding. It is recommended they only be bred to naturally seropositive mares or mares adequately vaccinated against EVA.

Aside from immunization of non-carrier breeding stallions against EVA, it is highly advisable to implement a program of prophylactic vaccination of all colt foals between 6 and 12 months before they run the risk of being naturally infected with EAV [8,81]. In time, this measure would significantly reduce the natural reservoir of the virus, especially in breeds in which the infection is endemic.

As previously alluded to, there is a significant risk of the introduction of EAV into a susceptible equine breeding population through the use of infective fresh-cooled or frozen semen [12-14]. Accordingly, it is important to determine the infectivity status of semen used for artificial insemination, especially if imported from abroad. Appropriate precautions should be taken when breeding mares with EAV-infective semen to avoid the risk of spread of the virus to other susceptible horses on the premises.

In view of the sporadic and infrequent occurrence of outbreaks of EVA at racetracks, shows, sales, veterinary clinics, etc., it is questionable whether the equine population at large should be vaccinated against the disease [16]. Many would consider the risk not great enough to justify adopting such a precautionary measure. Such a strategy would have the disadvantage of debarring the export of seropositive horses to certain countries at the present time.

Economic Significance

Equine viral arteritis can have a significant economic effect on both breeding and performance sectors of the horse industry [8,10]. Sources of economic losses attributable to this infection are as follows:

- Outbreaks of abortion and/or deaths in young foals;
- Decreased commercial value of carrier stallions and the demand to breed to these animals;
- Denied export markets for carrier stallions, virus infective semen and in the case of some countries, any horse seropositive for antibodies to EAV;
- Disruption of training schedules and reduced race entries or race cancellations in racetrack outbreaks of EVA.

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