EQUINE DISEASE QUARTERLY

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IN THIS ISSUE

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LLOYD'S

COMMENTARY

VACCINATION OF THE NEONATAL FOAL AGAINST *Rhodococcus equi (R. equi)* pneumonia presents significant challenges, not least of which is the foal's immunological immaturity and the inevitable lag in onset of its active immune response. The first weeks of life are a time when the foal is highly susceptible to uncontrolled replication of *R. equi* in its alveolar macrophages, with resultant abscess formation and onset of pneumonia.

Mortality associated with *R. equi* peaks in North America from June through July, reflecting the slow, relentless course of the disease. The ability of the foal to control *R. equi* replication and generate protective immune responses increases rapidly in the first months of life and depends on enhanced bactericidal ability of non-immune macrophages and immune activation of macrophage cells.

Experiments have demonstrated that clearance of *R. equi* is dependent on cell- mediated immune responses involving CD4 + Th1 lymphocytes and interferon γ (IFNγ) production. Although T cells in the neonatal foal are competent, the signaling pathways essential for IFNγ secretion do not function for some weeks. The IFNγ deficit is further deepened in infected older foals by products released by *R. equi*. The bias away from a protective Th1 toward an ineffective Th2-like response results in unrestrained replication of the pathogen and extension of primary lesions. This contrasts with the situation in older immunologically mature foals and adult animals in which clearance is mediated by mechanisms involving IFNγ producing CD4 + and CD8 + lymphocytes.

Humoral factors also contribute to acquired resistance to *R. equi* pneumonia. Dr. Nathan M. Slovis, in his article on *R. equi* pneumonia elsewhere in this issue, mentioned the value of hyperimmune plasma transfused after foaling and again three or four weeks later. IgGa specific for Vap protein of *R. equi* appears to be functionally protective, whereas IgGb and IgG(T) may actually enhance susceptibility. Interestingly, synthesis of IgGb in foals does not begin until two months after birth, whereas production of IgGa may begin in the last trimester *in utero* and continue actively during the first two months of life. Paradoxically, IgGb is the dominant isotype in hyperimmune plasma. Perhaps its value lies in neutralizing other virulence components of *R. equi*.

Although antibody transfused in hyperimmune plasma appears to contribute to protection, events in the broncho-alveolar macrophage are pivotal to the outcome of the host parasite interaction. Since control of replication requires activation of these cells by IFNγ, how might secretion of this cytokine be upregulated in the newborn foal? One possible solution is vaccination with DNA, encoding *vap* and *Il*12 genes. The latter is a pro-inflammatory cytokine that drives a Th1 response with associated IFNγ secretion. If effective, would such a strategy be prudent? The low level of IFNγ secretion typical of the neonatal human, foal, and other species must have survival value as yet unrecognized. The staged maturation of the immune system has evolved to ensure survival of the neonate exposed for the first time to a host of potentially lethal pathogens. Perhaps a wiser course will be to pursue reduction in exposure of neonatal foals to virulent *R. equi* and investigate how mucociliary clearance is circumvented or overwhelmed.

CONTACT: Dr. John Timoney, (859) 257-4757, jtimoney@uky.edu, Department of Veterinary Science, University of Kentucky, Lexington, Kentucky.

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Editors
Roberta Dwyer
David Powell
Neil Williams

Staff
Diane Furry

Correspondence should be addressed to the editors, Department of Veterinary Science, Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, Kentucky USA, 40546-0099
Telephone (859) 257-4757
Fax (859) 257-8542

Internet address:
http://www.uky.edu/Agriculture/VetScience/gluck1.htm

INTERNATIONAL

First Quarter 2004

THE INTERNATIONAL COLLATING CENTER, NEWmarket, and other sources reported the following disease outbreaks:

A case of Contagious Equine Metritis (CEM) in a Thoroughbred mare was reported from Japan. Respiratory disease attributable to equine herpes virus (EHV) was reported extensively from France among several breeds of horses. In the United Kingdom respiratory disease attributable to EHV was diagnosed on several equine premises, and EHV-1 was isolated at postmortem from a zebra, which died following respiratory distress.

Abortion caused by EHV-1 was reported from France in trotting and saddle mares; from Germany, in four Thoroughbred mares on four premises; from Ireland, in five mares on five premises; from Japan, in 11 mares on seven premises; and from Switzerland, three cases. The United Kingdom reported cases on six premises. On one farm there were 11 abortions among unvaccinated non-Thoroughbred mares. In three cases on other premises, EHV-1 was diagnosed by positive PCR of the placentae but not of the fetuses of vaccinated mares. EHV-1 was also diagnosed in a foal that died from a mare diagnosed with EHV-1 abortion the previous year. In Central Kentucky between August 2003 and the end of March 2004 there were 25 cases among Thoroughbred and five cases among non-Thoroughbred mares on 26 premises. The paralytic form of EHV-1 was reported on two premises in the United Kingdom.

Equine influenza was diagnosed at the San Isidro Training Center in Argentina; among several breeds at many different premises in France; at a trotting racetrack in Rome, Italy; on two premises in Ireland; among ponies on two premises in Sweden; and on three premises in the United Kingdom.

During the fall and winter months of 2003-4, 36 cases of Leptospira abortion were diagnosed on farms in Central Kentucky. Serological data confirmed Leptospira serovar kennewicki of the Pomona subgroup as responsible for the majority of cases. Most were single cases on individual farms except for six farms with two or three cases each. Rotavirus infection was diagnosed on four Thoroughbred farms in Ireland.

Strangles was reported from Australia, Ireland, Sweden, and Switzerland.

NATIONAL

Vesicular Stomatitis

VESICULAR STOMATITIS (VS) WAS CONFIRMED May 19 among horses on a premise in Reeves County, West Texas. The last reported outbreak of VS in the United States was in 1998. On June 4 a horse in Carlsbad, New Mexico, was diagnosed with VS, 100 miles northwest of the cases in Texas.

On May 27 the ban on livestock entering Kentucky from Texas, which had been imposed May 20, was amended. Only livestock from 60 West Texas counties surrounding the infected premise are presently prohibited from entering Kentucky. Livestock from the non-restricted areas of Texas are required to test VS-negative on the C-Elisa test. As of June 4 all livestock and wild and exotic animals from New Mexico are prohibited from entering Kentucky.

A negative C-Elisa test certificate for VS must accompany all equidae entering Kentucky from a state that has a common border with Texas and New Mexico, namely Arizona, Arkansas, Colorado, Louisiana, Oklahoma and Utah. The test must be performed within a 10-day period prior to the animal's entry into Kentucky.

Horses exported from the United States to the European Union currently require a negative virus neutralization test for VS.

USDA Tick Survey

BEFORE THE OLYMPICS GAMES IN ATLANTA, Georgia in 1996, the Federation Equestre Internationale (FEI) petitioned USDA to waive Equine Piroplasmosis (EP) testing requirements for foreign horses. Georgia officials were concerned that the entry of one or more EP-positive horses might create a risk for the United States. In response, USDA-APHIS assessed potential health risks associated with participation of EP-positive horses in the Olympics Games. This risk assessment showed that potential to infect local ticks increased in direct proportion to the amount of time EP-positive horses remained in the area. After a disease-prevention strategy was developed and several risk mitigating measures were drawn up and approved by FEI, the equestrian events proceeded as planned. During the risk assessment it became clear that our scientific knowledge of tick distributions was outdated. Therefore, a National Tick Survey was initiated by USDA-APHIS to assess the current distributions of tick species in the United States and disseminate this information to the public.

Worldwide, there are approximately 867 tick species. Of the 85 tick species found in the United States, only 34 tick species are known to be injurious to animals, and of these, approximately 16 species are harmful to equids. The distribution of each tick species is determined from records maintained by the Smithsonian's U.S. National Tick Collection (USNT) and the USDA's National Veterinary Services Laboratories (NVSL) tick identification program. Each dataset has 120,000 and 94,000 records, respectively. Using this information, we have recently completed a county-level distribution map for *Dermacentor andersoni* Stiles, the Rocky Mountain wood tick. A total of 5, 898 tick records were used to develop the distribution map. Populations of *D. andersoni* were identified in 267 counties and 14 states. The majority of the records were recorded from 1921 to 1940. Several preliminary county-level maps also have been produced for *Dermacentor variabilis* (Say)—American Dog Tick, *Amblyomma maculatum* (Koch)—Gulf Coast Tick, *Amblyomma americanum* (L.)—Lone Star Tick, and *Dermacentor nitens* (Neumann)—Tropical Horse Tick (Figure 1).

We are using Geographic Information System (GIS) and spatial analysis tools to model ecological factors influencing the distributions of the Rocky Mountain wood tick and the American dog tick in the United States. Initial spatial analyses of the distributions of *D. andersoni* and *D. variabilis* indicate that the Rocky Mountain wood tick appears to inhabit a domain that is semi-arid and mountainous; has cold, dry winters and warm, hot summers; and has short prairie grasses but few trees. The American dog tick may inhabit a more humid temperate domain with strong annual cycles of precipitation and temperature.

Lastly, we are establishing an interactive Web site to update and disseminate information on the distributions of tick species harmful to livestock, poultry, and wildlife. Distribution maps, life cycle information, host associations, methods of collecting and preserving ticks, and pictorial keys are included on the Web site. A tick map questionnaire was added to the Web site to supplement our current database as well as verify or change the present status of a particular tick species in the United States from reported to established.

Future efforts are aimed at using satellite imagery to generate models to predict the possible presence and distribution of ticks in areas where little information exists. Integrating temporal and spatial processes will provide novel methods to study the epidemiology of vector-borne diseases in horse populations. This methodology will result in better surveillance and control strategies to protect horses against tick-transmitted diseases.

We would like to thank James Keirans, Lance Durden, Jack Slater, and James Mertins for providing distribution records for the tropical horse tick and their invaluable support of the project.

CONTACT: Drs. Angela James and Jerome Freier (970) 494-7278 Angela.M.James@aphis.usda.gov, USDA, APHIS, VS, CEAH, Fort Collins, Colorado.

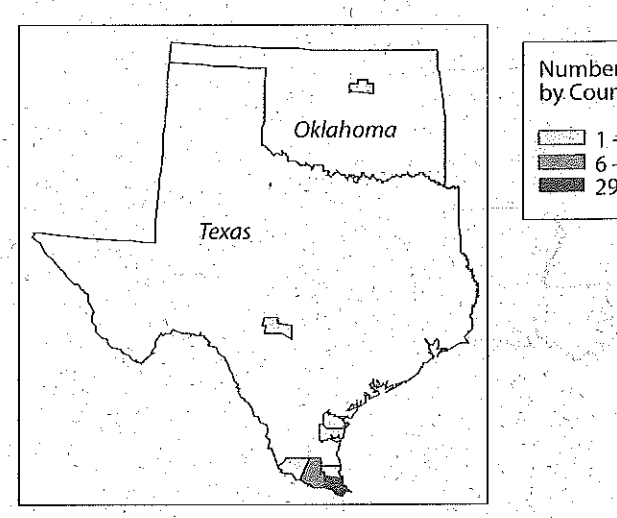

Figure 1. *Reported Distribution of Tick, in the United States, 1906-2*

Rhodococcus equi Pneumonia Update

PNEUMONIA IN FOALS, CAUSED BY *RHODOCOCcus equi (R. equi)* is a worldwide problem. Less common clinical manifestations of *R. equi* infections in foals include ulcerative enterocolitis, colonic/mesenteric lymphadenopathy, immune-mediated synovitis and uveitis, osteomyelitis, and septic arthritis. Inhalation of contaminated dust particles is an important route for pneumonic infection of foals. Ingestion is also a significant route of exposure and immunization but may not lead to pneumonia unless the foal has multiple exposures to a large number of bacteria. Recent epidemiologic evidence indicates foals that develop *R. equi* pneumonia are infected during the first few days of life, but clinical signs do not develop until they are 30 to 60 days of age.

The common manifestation of *R. equi* in foals is a suppurative bronchopneumonia with extensive abscessation and suppurative lymphadenitis. The slow spread of pneumonia coupled with the ability to compensate for progressive loss of functional lung makes diagnosis difficult. Clinical signs may include only a slight increase in respiratory rate and mild fever. These symptoms are often missed, allowing the disease to progress. Therefore, respiratory signs are often apparently acute in onset. A smaller percentage of foals may be found dead or in acute respiratory distress with high fevers (105-106° F) and no history of clinical respiratory disease. Approximately 50% of *R. equi* pneumonic foals presented at necropsy have intestinal manifestations characterized by granulomatous or suppurative inflammation of Peyer's patches and mesenteric and/or colonic lymph nodes. The majority of foals with *R. equi* pneumonia do not show clinical signs of intestinal disease. However, foals with subclinical intestinal manifestations may be slow to gain body weight. Immune-mediated polysynovitis, particularly the tibiotarsal and stifle joints, can be seen in 30% of cases with *R. equi* pneumonia.

Recognition of *R. equi* pneumonia prior to the development of clinical signs would reduce losses and limit costs associated with long-term treatment. Many diagnostic tests, including complete blood cell count, fibrinogen level, thoracic ultrasound, radiographs, and serology, have been used to distinguish *R. equi* pneumonia from other causes. However, bacteriologic culture or PCR amplification combined with cytological examination of a tracheobronchial aspirate (TBA) are still the gold standard for a diagnosis. A recent study suggested serological assays, on single or paired samples, cannot confirm or exclude a diagnosis of *R. equi* pneumonia. Serological tests are problematic because of the widespread exposure of foals to this organism at a young age. Measurements of white blood cell count (WBC) or fibrinogen concentrations are non-specific indicators of infection or inflammation. A recent study revealed that measurement of fibrinogen concentrations and WBC concentration were useful for early identification of *R. equi*-infected foals. WBC was significantly better than measurement of fibrinogen concentrations. On an endemic farm, a foal with a WBC of more than 13,000 cells/μL and fever should warrant careful veterinary examination. Foals with a WBC of more than 14,000 cells/μL, no clinical signs, and normal lung sounds should be considered for additional tests such as thoracic ultrasonography that might reveal abnormalities of the peripheral pulmonary parenchyma. If abnormalities are detected, a TBA and/or antibiotic treatment should be initiated. Farms with endemic *R. equi* that have suffered significant morbidity and/or mortality rates should monitor rectal temperatures of foals twice daily, with febrile foals selected for thoracic ultrasonography or treatment. Performing twice-monthly thoracic ultrasonography (starting at two weeks of age) has been effective for early recognition and reduction of mortality attributed to *R. equi* pneumonia on several endemic farms. The rationale is that earlier initiation of treatment will not only improve the prognosis but also reduce the antibiotic treatment period. Ultrasonography can be used to determine when antibiotic therapy should be discontinued.

Although controlled studies to evaluate treatment are lacking, erythromycin and rifampin are considered standard but are costly, labor intensive (three-times-a-day treatment), and can result in adverse reactions, including diarrhea and hyperthermia. Other macrolides, such as azithromycin (Zithromax®) and clarithromycin (Biaxin®), have also been used for treatment. The pharmacokinetics of azithromycin has shown that 10mg/kg per mouth every 24 hours for the first five days of treatment and then every other day is appropriate. Clarithromycin is recommended at a dose of 7.5 mg/kg per mouth every 12 hours. Azithromycin and rifampin can be

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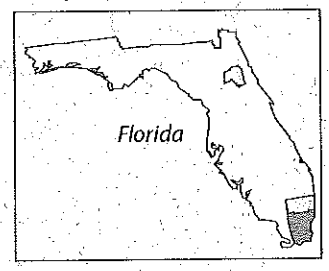

used in combination in cases that do not respond to azithromycin alone. Foals that recover from *R. equi* pneumonia have been shown to perform to expectation.

The only method proven to prevent *R. equi* pneumonia is transfusion of hyperimmune plasma. The amount that should be administered and the time(s) of administration for optimal protection are unknown. It is recommended that 1L of hyperimmune (HI) plasma should be administered during the first 24 hours of life and again 25 days later. Studies emphasize that the protection conferred by HI plasma is not complete, and control of the disease on endemic farms should be combined with other strategies.

DNA vaccines to promote mucosal immunity are being investigated. Other studies are seeking to identify if mares are a source of *R. equi* infection. If dams of affected foals shed more *R. equi* in their feces than dams of unaffected foals, it may be possible to screen mares to identify foals at risk. If mares are not an important reservoir of *R. equi*, other explanations would have to be sought for the source of infection and the tendency for some mares repeatedly to have affected foals. Further research is needed to identify methods for control and prevention of this important disease.

CONTACT: Dr. Nathan M. Slovis, 859-253-0002, nmslovis@yahoo.com, Hagyard–Davidson-McGee PLLC, Lexington, Kentucky.

Dissolving the Stain of Pain

THE PRESENCE AND DEGREE OF PAIN AN ANIMAL experiences is meant to be beneficial. Pain signals actual or impending body damage, and may help prevent further damage by initiating movement away from the cause or by limiting use of injured areas during healing. Pain associated with acute injury typically has an identifiable cause and can be relieved by resolving the cause. In the veterinary medical setting, acute pain associated with injury is chiefly managed pharmacologically through effective use of nonsteroidal anti-inflammatory drugs, opioids, and other analgesic agents. Moreover, the efficacy of a pain treatment plan may be enhanced by engaging the body's powerful pain-modulating systems through adjunctive pain-relieving modalities such as acupuncture, acupressure, chiropractic manipulation, therapeutic massage, therapeutic ultrasound, or numerous additional methods. With some exceptions, under-treatment of acute or subacute pain generally results from failure of assessment, not from lack of treatment modality.

In treating chronic pain, it is also important to identify the underlying cause(s), as an effective management plan cannot be formulated without a sound, working diagnosis. However, as persistent pain is often multi-factorial in origin, and specific diagnoses may be lacking, chronic pain management can be a very challenging and complex endeavor. Over time, initially untreated or improperly treated disease states or injuries can place undue stress on remote body regions, leading to deconditioned or over-use states. The long-standing stress of chronic painful conditions can overtax, or even exhaust, the hypothalamic-pituitary axis, leading to severe neuroendocrine or metabolic imbalance. Unremitting severe pain can lead to sensory hypersensitization secondary to functional and anatomical changes within pain processing pathways (Type III pain). The result can be a diffuse and complex array of pain sources and dysfunction. For veterinarians trained to seek a single diagnosis to explain all symptoms, this array can be a cause for extreme frustration. A good medical history (particularly with regard to previous treatments and responses), a thorough physical examination, and appropriate diagnostic testing comprise the foundation for developing a successful pain management plan. Additionally, it is essential that the practitioner determine that serious, treatable medical conditions are absent.

Before therapy is initiated, appropriate treatment goals should be determined. These goals will serve as outcome measures by which treatment efficacy is ascertained. Ideally, all symptoms are eliminated by treatment; however, this may not occur quickly. In fact, in the case of long-standing conditions, complete resolution of painful symptoms may not be feasible.

For chronic pain, treatment needs to address not only the physical pathology initiating the pain but also the sequellae arising from long-term adaptation. The goal of pain management is to shorten the duration of disability and to enhance the animal's ability to perform

at some reasonable level of activity. Chronic pain levels may not significantly improve until the patient has begun to recondition and increase the daily exercise level. Treatment, therefore, necessitates a comprehensive approach using both medical and functional rehabilitative modalities. Functional rehabilitation includes identification and management of contributing factors (whether independent of, or secondary to, a primary cause), retraining the animal to some level of work, and client education/training.

Effective control of pain depends on combining various therapeutic modalities, routinely evaluating efficacy of treatment, and changing therapeutic plans according to the needs of the patient.

Contact: Dr. Michael Tomasic, (505) 466-0151, drmtomasic@yahoo.com, Veterinary Pain Management, Santa Fe, New Mexico.

KENTUCKY

Equine Placenta Workshop Proceedings

THE PROCEEDINGS OF THE EQUINE PLACENTA Workshop held in December 2003 are now available in print. To obtain a copy contact: Gracie Hale, ghale@uky.edu, Telephone (859)-257-4757 ext. 81147, Morris Library, Maxwell H. Gluck Equine Research Center, University of Kentucky, Lexington, Kentucky 40546. Copies of proceedings of the workshop on Mare Reproductive Loss Syndrome also are available and may be obtained from the same address.

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Department of Veterinary Science
Maxwell H. Gluck Equine Research Center
University of Kentucky
Lexington, Kentucky 40546-0099

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