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COMMENTARY

IN THIS ISSUE

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College of Agriculture, Food and Environment
Department of Veterinary Science

LLOYD'S

Immunotherapies on the Horizon for Insect Bite Hypersensitivity?

The season is upon us when approximately 10 percent of horses worldwide are faced with one of the most frustrating skin diseases in the equine industry, insect bite hypersensitivity (IBH), more commonly known as "sweet itch" or "summer eczema." IBH is an allergic, recurrent, seasonal dermatitis caused when the immune system overacts or becomes "hypersensitive" to allergens in the saliva primarily of biting midges (*Culicoides*) and other biting insects.

Dr. Susan White in her article provides an overview of current diagnostic and management practices to combat signs of IBH. Although there is no cure for IBH, there is ongoing research to assess immunotherapies as future treatment options for horses suffering with IBH.

While IBH has a multifactorial cause, it is acknowledged that the immune system plays a role in its development. Hypersensitivity reactions are classified into four types, and IBH is a combination of Type I and Type IV. Type I hypersensitivity reactions develop when antigen specific allergens bind to IgE and cross-link receptors on mast cells, basophils and also involve eosinophils. These cells release vasoactive amines, such as histamine, that affect blood vessel size and leakage and produce inflammatory cytokines and other mediators, which result in inflammation and pruritus. Type IV reactions, often referred to as delayed-type hypersensitivity reactions, involve cell-mediated responses particularly of activated Th-2 lymphocytes which produce IL-5 cytokine and large numbers of eosinophils, both contribute to the clinical manifestations of IBH. Immunotherapy treatment is based on a century-old concept that the immune system can be desensitized to specific allergens that trigger hypersensitivity reactions. Allergen immunotherapy (AIT) involves inoculation with gradually increasing doses of an allergen to which the individual is allergic. The incremental increases in exposure to the allergen cause the immune system to become less sensitive to the substance, which reduces the allergy signs when the substance is encountered in the future. Data are conflicting as to whether or not traditional AIT therapies are successful in treating IBH. Research is now exploring whether IBH can be prevented by vaccination with recombinant *Culicoides* antigens versus whole antigen preparations to more successfully modulate the immune response, in particular, IgE response. Another interesting area under current investigation is oral immunotherapy, whereby transgenic barely expressing allergens are administered orally to prevent hypersensitivity to *Culicoides.*

Finally, given the important role of eosinophils in the pathology of IBH and the fact that IL-5 drives eosinophil activity, a novel and allergen-independent vaccine has been evaluated that targets IL-5 and limits eosinophil recruitment to the affected skin. This is one of the few equine studies to investigate whether a vaccine can induce autoantibodies to cytokine IL-5 and result in clinical efficacy for IBH. This immunotherapeutic approach may be the new generation for treating chronic immune diseases, and may signal that new therapies are on the horizon for horses suffering from IBH.

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INTERNATIONAL

First Quarter, 2018

The International Collating Centre, Newmarket, United Kingdom, and other sources reported the following equine disease outbreaks.

The Republic of South Africa (RSA) reported an expected seasonal increase in cases of African Horse Sickness. A total of 88 cases were recorded in eight of the nine provinces. No cases occurred in the Western Cape Province, including the Disease Controlled Area.

The UK and the USA reported outbreaks of equine influenza. Two cases in recently imported non-vaccinated horses were recorded in the UK. The disease can be considered endemic in the USA in which it was confirmed in three states, with multiple outbreaks in one of the states.

France, Germany, Ireland, and the USA reported multiple outbreaks of strangles. The number of outbreaks included 21 in France, two in Germany, numerous cases in Ireland, and 65 outbreaks in 22 states in the USA, 10 involving multiple cases of the disease.

Equine herpesvirus 1 (EHV-1) infection was recorded in France, Germany, Ireland, Japan, RSA, Switzerland, the UK, and the USA. Infection associated with fever was reported by France (two outbreaks), Ireland (seven outbreaks), and Switzerland (one outbreak of combined EHV-1 and equine herpesvirus 4 infection). Respiratory disease was diagnosed in Germany (25 cases), the UK (eight outbreaks, majority in non-vaccinated, non-Thoroughbred horses), and the USA (widespread in various states). Cases of EHV-1 abortion were recorded in France (eight outbreaks, three involving multiple cases), Germany (four cases), Japan (single cases on 13 premises, all but four in vaccinated mares), the UK (five outbreaks involving vaccinated or non-vaccinated Thoroughbred and non-Thoroughbred mares), and the USA (two cases).

EHV-1 associated neurologic disease was reported from France (one case), RSA (two cases on same premises), Switzerland (one case), the UK (a single case on two premises), and the USA (23 outbreaks involving 27 horses and multiple states).

EHV-4 infection was recorded by France (four outbreaks) and Switzerland (two cases). France (10 outbreaks) and Germany (four cases) reported occurrences of EHV-4 related respiratory disease. Also, France confirmed one case of EHV-4 abortion.

The USA recorded multiple cases of EHV-2/5 infection in several states, some associated with clinical evidence of respiratory disease.

Equine infectious anemia was confirmed by Canada (three cases, one of which was clinical and died), France (one clinical case), and the USA (one case).

France reported equine piroplasmosis was endemic in the country. The RSA recorded several cases of the disease in four provinces.

Taylorella equigenitalis, the causal agent of contagious equine metritis was detected in an aged stallion in France, and in six stallions and one mare on a total of six premises in Germany.

A single case of equine coital exanthema caused by EHV-3 was diagnosed in a mare in Kentucky.

A number of cases of nocardioform placentitis were reported by the USA, several involving infection with *Amycolatopsis* spp and an additional group associated with *Crossiella equi* infection, all but one in Kentucky.

The USA confirmed 11 cases of salmonellosis during the review period, all isolates belonging to serogroup B.

Three cases of *Clostridium perfringens* Type A toxin genotype were diagnosed in foals in Kentucky.

Germany confirmed rotavirus infection in two foals on the same premises.

A case of *Lawsonia intracellularis* infection was diagnosed in a foal in Kentucky.

The USA recorded four cases of Eastern Equine Encephalomyelitis (EEE) in the first quarter of 2018, all in Florida.

Equine encephalosis was reported by the RSA, with numerous cases in one province and isolated cases in three other provinces.

Rhodococcus equi infection is endemic in the USA, with many cases going unreported.

Equine Disease Quarterly

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Insect Bite Hypersensitivity in Horses

A large percentage of horses affected with seasonal pruritic dermatitis are hypersensitive (allergic) to the bites of insects. *Culicoides* spp (gnats), black flies, stable flies, and horn flies are the most commonly implicated insects although any biting insect may contribute to insect bite-induced hypersensitivity (IBH). IBH is characterized by intense pruritus (itching) that often leads to excoriation (abrasive skin damage), extensive hair loss, secondary infections, and chronically to hyperkeratosis and lichenification (thickened skin). Many horses develop IBH in middle age or later, although horses with atopy may exhibit clinical signs as early as 1 year of age. Clinical signs often progress in each subsequent year.

Diagnosis is made from the signalment, history, clinical signs, and ruling out of other possible diagnoses. The distribution of lesions on an affected horse with IBH is dependent on the biting characteristics of the insect(s) responsible. Since there is still much to be learned about the identification and feeding habits of many insects implicated in allergic dermatoses, it may not be possible to identify the exact etiological agent(s). IBH typically improves and exacerbates seasonally, whereas clinical expression of allergies in atopic horses may occur at any time of the year. Urticaria (hives), commonly found in atopy, is not a diagnosis but a cutaneous reaction pattern that may be induced by a wide variety of causes, both immunologic and non-immunologic. Rule outs for urticaria include drug and vaccine reactions; stinging and biting insects (such as wasps) and arachnids; infections; contact irritation; vasculitis; and cold, stress, or exercise-induced lesions. Other diseases that exhibit pruritus are *Oxyuris* (pin worm) infestation, onchocerciasis, and mite (*Chorioptes*) and tick infestations. Diseases that occasionally are associated with pruritus include ringworm and pemphigus, an autoimmune disease.

In all cases of pruritic dermatitis, managerial procedures to decrease exposure to exciting agents as well as symptomatic therapy to reduce pruritus is warranted. In IBH procedures to decrease exposure to insects should be fully implemented. Farm sanitation to compost manure properly, eliminate wet areas with decomposing vegetation, and the use of fly predators or feed through fly inhibitors can greatly reduce fly populations. Heat, humidity, and solar radiation exacerbate pruritus, thus the provision of shade and wind currents by fans provide relief. Stabling to avoid the most significant insects (Table 1) and the use of fly sheets and face masks are helpful. Because some horses develop contact allergies to topical products, judicious and cautious use of fly repellants is advisable. Simple feeds and whole grains are better than mixed, multiple-grain sweet feeds. Cool-water rinses and shampoos can rehydrate and sooth dry skin as well as reduce the amount of allergens on the skin. Colloidal oatmeal, pramoxine, and 1 percent hydrocortisone shampoos or leave-on hydrocortisone rinses may reduce pruritus and minimize or reduce the amount of systemic antipruritic medication needed. Systemic medications (steroids and antihistamines) may help interrupt the itch-scratch cycle, however long term use, particularly of steroids, should be avoided. A complete and detailed investigation into the etiology of the disease should occur simultaneously with general symptomatic care. Intradermal skin testing to determine antigens for allergen specific immunotherapy may be helpful, particularly in young animals with atopy. Clients should understand that hypersensitivities and atopy are lifelong. Affected horses will need continuous management and/or therapy. Often a patient may be symptom-free with low exposure to inciting antigens and symptomatic as the antigen load increases. Antigen exposure is additive, thus comprehensive management is needed to best control clinical disease.

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Theiler's Disease

Theiler's disease, or equine serum hepatitis, is an infrequent but sometimes life-threatening liver disease of adult horses. Sir Arnold Theiler first described the disease in the early 1900s as a form of highly fatal acute liver failure that occurred 4-12 weeks after administration of equine antiserum, which was used as part of a vaccination strategy for African Horse Sickness. Since then, many additional cases of serum hepatitis have been reported, and a variety of blood products of equine origin have been associated with the disease. In North America, the majority of recent

Insect Bite Hypersensitivity in Horses (le

Table 1. Breeding location and time
with IBH.

Insect	Breedi
Stable flies	Manure a vege
Horn flies	Cattle
Horse and deer flies	Vegetation
Culicoides spp	Standing ma
Simulium (black) flies	Runnin

Rabies in the Horse and Beyond in Kent

Table 2. Rabies virus test results brok
species (excluding horses), and horse

Results	Wildlife	Dom Sp (excl ho
Negative	12,378	16
Positive	680	
Unsatisfactory specimen	823	6
TOTAL	13,881	17

Figure 1. Geographic location of the 25 horses testing positive for rabies virus in Kentucky from 1989 to 2017.

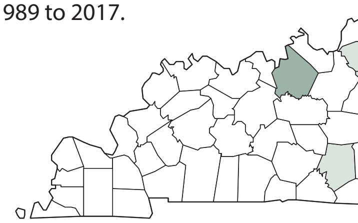
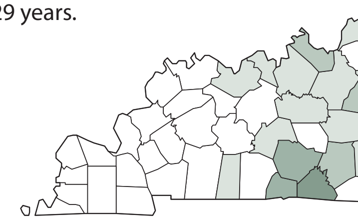


Figure 2. Geographic location of skunks in Kentucky testing positive for rabies virus in the last 29 years.



Insect Bite Hypersensitivity in Horses (left):

Table 1. Breeding location and time of feeding for insects associated with IBH.

Insect	Breeding Area	Feeding Times
Stable flies	Manure and rotting vegetation	Daytime
Horn flies	Cattle manure	Daytime
Horse and deer flies	Vegetation and water	Daytime
Culicoides spp	Standing water and manure	Twilight to dawn
Simulium (black) flies	Running water	Morning and evening

Rabies in the Horse and Beyond in Kentucky (page 5):

Table 2. Rabies virus test results broken down by wildlife, domestic species (excluding horses), and horses.

Results	Wildlife	Domestic Species (excluding horses)	Horses	TOTAL
Negative	12,378	16,733	1,034	30,145
Positive	680	28	25	733
Unsatisfactory specimen	823	675	11	1,509
TOTAL	13,881	17,436	1,070	32,387

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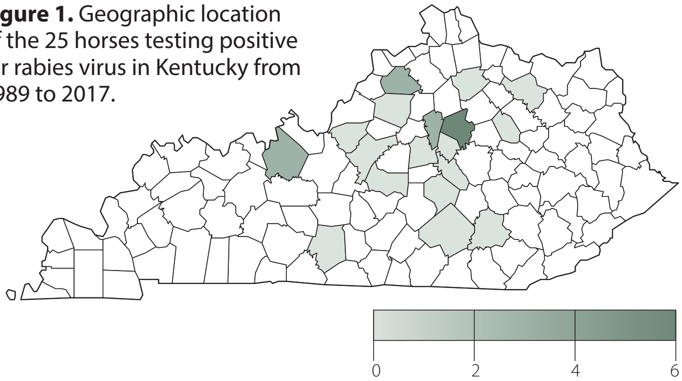

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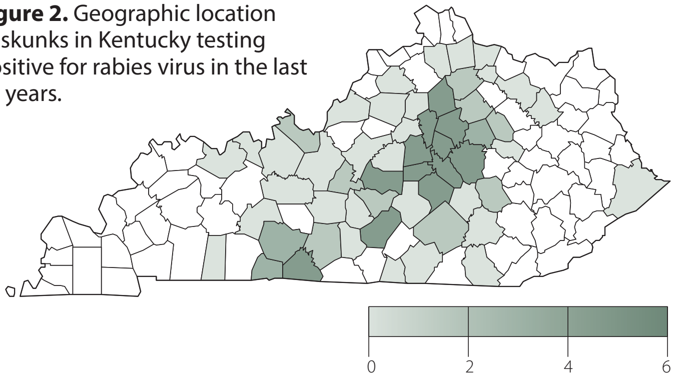

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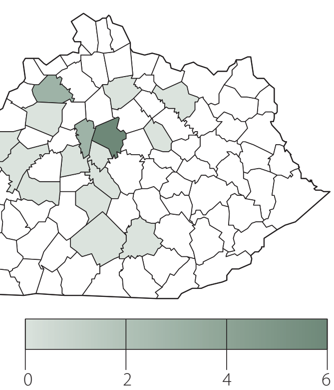

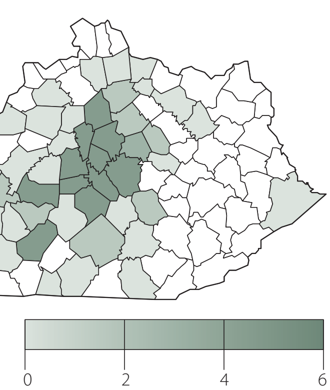

cases have been associated with the administration of tetanus antitoxin, although commercial plasma products also have been incriminated. The number of horses that become ill following administration of a specific lot of incriminated blood product is estimated at 1 to 2 percent, although more horses might have sub-clinical disease. An infectious agent, such as a virus, has long been suspected to cause this condition, and a new equine parvovirus was recently discovered in a horse with a fatal case of serum hepatitis. The parvovirus was present in the diseased horse and in the biologic product that it had received nine weeks earlier. Inoculation of experimental horses with the commercial product resulted in transmission of this newly discovered virus and in liver disease. Variation in individual immune responses to the virus could explain the low percentage of clinically affected horses.

An identical disease, both in terms of clinical signs and pathologic findings, is sporadically seen in adult horses without recent administration of an equine origin biologic. These "non-biologic" cases tend to mostly occur between June and November and can occur in small outbreaks that span a few weeks. Non-biologic cases seem to occur most commonly on broodmare farms. The seasonal incidence of the non-biologic cases suggests the possibility of insect transmission of parvovirus in these "non-biologic" cases.

Clinically affected horses with Theiler's disease frequently have both neurologic signs (hepatic encephalopathy: head pressing, stumbling, blindness) and jaundice (yellow gums and eyes). Once the neurologic signs are noted, there is a rapid progression to death in approximately 70 percent of the cases. Horses that receive supportive therapy and survive for five days after the onset of fulminant disease generally recover and have no long-term effects.

Another recently discovered virus that causes liver disease in horses is non-primate hepacivirus (NPHV). NPHV is genetically the closest homolog of human hepatitis C virus (HCV) discovered to date. Experimental horse infections consistently result in biochemical and histopathologic evidence of hepatitis, but the disease is mild and clinical signs are either absent or very mild in recently infected horses. NPHV and equine parvovirus are present in some healthy horses, indicating that horses can become healthy carriers of these viruses.

The USDA Center for Veterinary Biologics has issued a notice that all licensed equine blood products have to test free of equine parvovirus and NPHV. This should improve horse health by eliminating most of the blood product-associated cases of hepatitis. Non-biologic associated cases will likely continue to occur until natural means of virus transmission are determined and necessary control methods implemented.

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NATIONAL

Importance of Protecting your Horse against Eastern Equine Encephalomyelitis and West Nile Encephalitis

The two most frequently encountered causes of equine encephalitis or equine encephalomyelitis in North America are Eastern Equine Encephalomyelitis (EEE) and West Nile Encephalitis (WNE) viruses. Both are mosquito-borne and neurotropic. The respective viruses are not restricted to equids in terms of their host range; each can be transmitted to humans and certain other mammalian and avian species. Both diseases are a source of concern for the equine industry not only from the potentially life-threatening consequences of either infection, but also from the economic losses involved.

Eastern equine encephalomyelitis poses an annual threat to equids in the Gulf and Atlantic coastal states and the Great Lakes region, extending in certain years as far north as eastern Canada. It is occasionally recorded in some inland states such as Arkansas, Oklahoma, Tennessee, Kentucky, and Iowa. Evidence of EEE activity is most often reported in Florida, in which it has been confirmed as early as January, as recorded in 2018. Over the past 15 years, the yearly incidence of EEE cases in equids has ranged from 60 (2011) to 712 (2003), with an annual average of 206 cases. In 2017, 86 cases of the disease were reported in 13 states.

In temperate regions, transmission of EEE virus is seasonal, occurring in the summer and the fall. In sub-tropical regions such as Florida, there is a year-round risk of EEE, with virus transmission peaking in the summer months.

Equids and humans are tangential or dead-end hosts of EEE virus and neither plays a role in the natural life-cycle of the virus. Infections in horses, mules, and donkeys are frequently life-threatening; case fatality rates can be as high as 90 percent.

West Nile encephalitis (WNE) is also a cause of significant concern to veterinary practitioners and members of the equine industry. Within four years following initial introduction of the causal virus in New York State in 1999, the virus had spread to 48 states and several provinces in Canada. Since 1999, the yearly incidence of WNE cases in equids has ranged from 60 (2000) to 15,257 (2002). The annual average number of cases over the past 10 years was 272. In 2017, 307 equine cases were reported in 39 states.

Similar to EEE, transmission of WNE virus is seasonal, occurring in the summer and extending well into the fall. Neither equids nor humans serve as amplifying hosts for WNE virus insofar as viremias are insufficient in magnitude and duration to infect mosquitoes. Unlike EEE, only about 10% of WNE virus-exposed horses will develop clinical infections. Reported case-fatality rates in affected horses can reach 30-40 percent, less than half that encountered in cases of EEE.

The American Association of Equine Practitioners (AAEP), in accordance with criteria defined by the American Veterinary Medical Association with respect to "core vaccines"–namely those that protect against diseases that are endemic, of potential public health significance, and represent a risk of causing severe disease—strongly recommends that horses be immunized against EEE and WNE. Available inactivated whole-virus vaccines against EEE (including Western Equine Encephalomyelitis) have been shown to be safe and effective in protecting against this disease. Two inactivated whole-virus vaccines, a live canary pox vector vaccine and an inactivated flavivirus chimera vaccine are available against WNE. All have been confirmed safe and effective in preventing the disease.

Despite the AAEP recommendations to horse owners to vaccinate their horses against EEE and WNE, regrettably many fail to do so. The vast majority of equine cases of EEE and WNE either have no history of vaccination against the particular virus or else the vaccination history is incomplete. There is need for an ongoing concerted effort, utilizing all avenues of communication including social media, to alert horse owners of the dangers of these two vector-borne diseases and of the importance of vaccination as an effective means of prevention and averting the losses that continue to occur every year in unprotected horses.

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KENTUCKY

Rabies in the Horse and Beyond in Kentucky: A Look at the Last 29 Years

Rabies virus exposure typically occurs following the bite of an infected animal. Depending on the anatomic site of exposure, an incubation period of variable duration follows as the virus evades the immune response by hiding in the central nervous system. Amplification of the virus occurs in the dorsal root ganglion after which it travels towards the brain via the spinal cord. At this point, clinical signs of rabies become manifest and therapy is almost invariably futile. Without early treatment, rabies is nearly 100 percent fatal. Rabies is a zoonotic (capable of being transmitted from animals to humans) disease that is distributed nearly worldwide. Attention to the disease is primarily focused on preventive and control strategies. Many countries are considered rabies-free for the purposes of importing dogs into the United States (https://www.cdc.gov/importation/rabies-free-countries.html).

Rabies can be prevented by pre-exposure vaccination of humans and animals. A human diploid cell vaccine and a purified chick embryo vaccine are available for humans (the latter is mainly used outside of the USA) for pre- and post-exposure to rabies, with rabies immune globulin available only for post-exposure treatment in exposed humans.

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Pre-exposure vaccination involves administration of three doses of vaccine given over a one month period. In unvaccinated humans, post-exposure treatment consists of the administration of five doses of vaccine. Vaccines for multiple species of domestic animals are available to licensed veterinarians. Wildlife vaccines may be available from veterinarians, but are typically used in targeted locations by the Kentucky Department of Fish and Wildlife and the United States Department of Agriculture.

From January 1989 through December 2017, Kentucky tested 32,387 animals for rabies virus. Of this total, 2.3 percent (733 animals) tested positive, 93.1 percent (30,145 animals) tested negative, and 4.6 percent (1509 animals) were unsatisfactory for testing (i.e. the sample was untestable due to maceration, degradation, or insufficient material). Of note: Animals suspected of having rabies should not be euthanized by traumatic insult (e.g. gunshot) to the brain, because trauma frequently renders the sample unsatisfactory for testing. Of the 733 positive animals, only 7.2 percent (53 animals) were from domestic species (i.e. pets and farm animals), and the other 92.8 percent (680 animals) were wildlife. Twenty-five of the positive domestic animals were horses (Table 2), which means that horses accounted for less than 1 percent of the total positive rabies cases in Kentucky over the last 29 years. Rabies-positive horses were primarily located in Central Kentucky (Figure 1). The terrestrial reservoir for rabies in the state is the striped skunk, and skunks positive for rabies virus have been located in all counties where infected horses have resided (Figure 2).

As a closing comment, a robust surveillance program involving the UK Veterinary Diagnostic Lab, Breathitt Veterinary Center, the Kentucky Cabinet for Health, Kentucky Fish and Wildlife, and USDA is in place to thoroughly monitor rabies in Kentucky. The vast majority of animals testing positive for rabies are wildlife, with little or no exposure to humans, pets and domestic animals. More importantly for horse enthusiasts within the state, the number of horses testing positive for rabies is extremely low.

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