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Leptospirosis in horses

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ABSTRACT

Leptospirosis in horses has been considered a relatively uncommon infection. However, recent data suggest that the infection is widespread, with the incidence and infecting serovars varying considerably in different geographical regions. The majority of infections remain asymptomatic. Clinical signs in equine leptospirosis resemble those seen in other animal species. However, leptospirosis as a cause of acute respiratory distress is becoming more frequently recognised. A particular feature of equine leptospirosis is post infection recurrent uveitis (moon blindness or periodic ophthalmia), which appears to be mediated by autoimmune mechanisms involving cross reactivity between ocular tissues and leptospiral membrane proteins. There are no leptospiral vaccines licensed for use in horses, with no prospect for any becoming available in the foreseeable future. Accordingly, prevention of equine leptospirosis must rely on good hygiene practices, minimisation of rodent contact, and vaccination of other species of production and companion animals.

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1. Introduction – *Leptospira*

Leptospirosis is a global veterinary and public health problem. It is caused by infection with one of more than 12 pathogenic species of *Leptospira* (Fig. 1), although *L. interrogans* and *L. borgpetersenii* are responsible for the majority of infections (Adler and de la Peña Moctezuma, 2010). The disease is endemic to many parts of the world, and is increasingly being recognized in both urban and rural areas of industrialized countries (Bharti et al., 2003; Vinetz, 1997). The prevalence of leptospirosis in many parts of the world is due to chronic kidney infection of a wide variety of domestic, peridomestic and wild reservoir mammals. Colonization of the renal proximal tubules of carrier animals results in shedding of virulent leptospires in the urine. The bacteria can persist for prolonged periods in aqueous environments and infection of a new host

usually occurs through contact with contaminated water, when the highly motile leptospires invade breaks in the skin or intact conjunctiva or mucous membranes. *Leptospira* spp. can also be transmitted from mother to foetus (Adler and de la Peña Moctezuma, 2010; Bharti et al., 2003; Vinetz, 1997).

The outcome of leptospiral infection in non-human animals varies according to animal and bacterial species. Animals that are natural reservoirs of *Leptospira*, such as rats and other rodents, do not exhibit any overt signs, and clear infections from their bodies except the kidney tubules. In contrast, some non-carrier animals are less able to control infection, which may have mild consequences or lead to tissue damage, pulmonary haemorrhage and death. The ability of leptospires to cross the placenta may lead to spontaneous abortion (Bharti et al., 2003; Coghlan and Bain, 1969; Faine et al., 1999, 1984).

As a consequence of animal carriage and urine transmission, humans who work with animals or waste water are often at high risk for leptospirosis (Campagnolo et al., 2000). *Leptospira* spp. are highly endemic in moist

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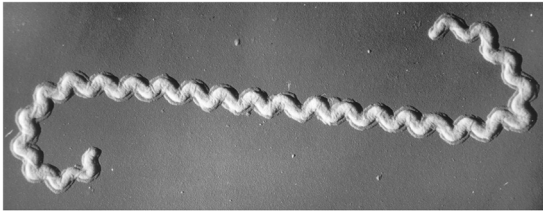


Fig. 1. Shadowed electron micrograph of *Leptospira*.

tropical and subtropical areas of the world, presenting important threats to the health of residents, military personnel, aid workers and tourists (Bharti et al., 2003; Ko et al., 1999). Even in temperate countries, leptospirosis poses a health threat to humans in many environments. Domestic and wild animals serve as reservoirs in rural areas, with rats and dogs as important reservoirs in cities (Levett, 2001; Meites et al., 2004; Vinetz et al., 1996). Natural disasters, such as floods and hurricanes, may be accompanied by leptospirosis outbreaks from contaminated water (Fuortes and Nettleman, 1994). The relationship between warfare and leptospirosis has long been appreciated, to the extent that leptospirosis has been described as “an occupational disease of soldiers” (Johnston et al., 1983).

Symptoms of human leptospirosis may differ widely from patient to patient, but commonly include fever, headache, myalgia, vomiting, conjunctivitis, uveitis, meningitis, and jaundice. Between 5 and 10% of patients progress to the more dangerous, icteric phase of leptospirosis. Fatality rates at this stage vary depending upon bacterial strain characteristics, geographic region, patient age, and levels of support given to patients, but may be upwards of 20%. Deaths have been attributed to acute renal failure, pulmonary haemorrhage, intracerebral haemorrhage, and multisystem organ failure (Bharti et al., 2003; Faine et al., 1999; Ko et al., 1999; Levett, 2001; Vinetz, 1997).

2. Equine leptospirosis

2.1. Incidence

The incidence and importance of leptospirosis in horses remain uncertain. Almost all epidemiological studies have relied solely on serology, with the reported incidence varying enormously depending on the geographical region investigated. There is likewise some variability in the deduced infecting serovar. For example, a recent survey in central Italy found only a 1.5% seroprevalence, with reactivity against serovars Icterohaemorrhagiae, Bratislava or Pomona (Ebani et al., 2012); the very small sample size precludes any meaningful conclusions about possible infecting serovars. In stark contrast, a Brazilian study of 119 racehorses claimed a seropositivity rate of 71% against serovar Copenhageni (Hamond et al., 2012b), a finding attributed to the endemicity of leptospirosis amongst rodents in the region. Somewhat strangely, there was no clinical evidence of leptospirosis in any of the horses. However, another study by the same group showed a

seropositivity rate of 48%, with 35% of urines positive by PCR, but none by culture (Hamond et al., 2013). Additional studies showing seroprevalence rates of 25% in Korea (mainly serovars Sejroe and Bratislava) (Jung et al., 2010), 79% in The Netherlands (Copenhageni and Bratislava) (Houwens et al., 2011), and 25% (Bratislava and Icterohaemorrhagiae) in Sweden (Båverud et al., 2009) suggest substantial differences in incidence and serovar prevalence according to geographical region and also indicate that the majority of equine infections are asymptomatic. An important proviso that must be noted is that the identity of infecting serovars cannot be determined by serosurveys. An analysis of isolates from aborting mares in North America found that 20 out of 21 were serovar Pomona subtype Kennewicki (Timoney et al., 2011), again consistent with the widespread presence of this serovar and subtype in the local wildlife population, especially racoons. In an earlier study (Ellis et al., 1983), serovar Bratislava was implicated as common in horses in Northern Ireland, based upon both serology and isolation. The suggestion of host adaptation by Bratislava to horses is not supported by subsequent studies elsewhere, but is consistent with the variability of infecting serovars reported in different geographical regions. However, there have been very few recent studies on equine leptospirosis in which leptospires were cultured.

2.2. Clinical features

The clinical features of equine leptospirosis are essentially similar to those observed in other animals, such as cattle, with low-grade fever, listlessness and anorexia the most common presentation in milder disease. In more severe forms of disease a range of typical signs may occur, including conjunctival suffusion, jaundice, anaemia, petechial haemorrhages on the mucosa and general depression. Renal failure may also occur, especially in foals. As a general rule, classic icteric leptospirosis occurs mainly in foals and is comparatively rare in adult horses. As with all mammals, infection of pregnant mares can result in placentitis, abortion or stillbirths (Timoney et al., 2011), in which case leptospires may be readily demonstrated in foetal and maternal tissues (Poonacha et al., 1993). Leptospiral abortions occur late in the gestation, typically without any prior clinical signs. In a small number of cases, premature or full-term emaciated and icteric foals are born (Donahue et al., 1995, 1991). Infected mares shed leptospires in the urine for up to 14 weeks and can potentially transmit the disease to in-contact animals (Donahue and Williams, 2000; Newman and Donahue, 2007).

A large number of leptospires can be demonstrated in the stroma and villi of the placenta. Grossly, the placenta is oedematous with nodular cystic allantoic masses and necrosis of the chorion. Microscopic placental lesions consist of vasculitis, thrombosis, inflammatory cells in the stroma and villi, cystic adenomatous hyperplasia of allantoic epithelium, and necrosis and calcification of villi. While both foetal liver and kidney are enlarged, the former is mottled and pale to yellow, and the latter shows pale white radiating streaks in cortex and medulla. Microscopic

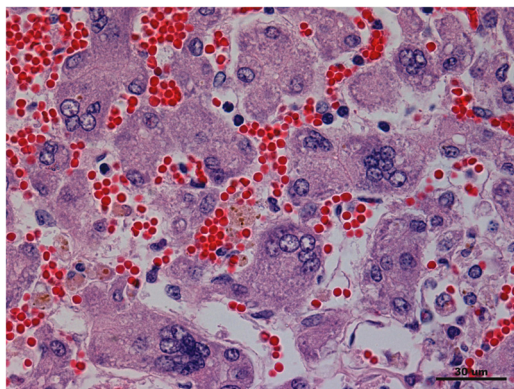


Fig. 2. Haematoxylin and eosin stained liver section of an aborted equine foetus showing giant cell hepatitis and loss of structure. Courtesy Dr. Murray Hazlett, University of Guelph.

foetal lesions include suppurative and nonsuppurative nephritis, hepatocellular dissociation, leukocytic infiltration of the portal triads, giant cell hepatopathy (Fig. 2), pulmonary haemorrhages, pneumonia, and myocarditis (Wilkie et al., 1988; Poonacha et al., 1993). Histopathological findings in young horses are likewise similar and may include petechiae and lymphocytic infiltration in renal proximal tubules and glomeruli (Bernard, 1993; Faine et al., 1999).

The pulmonary haemorrhage seen in severe leptospirosis in humans (Bharti et al., 2003), experimental animals and in some livestock species has commonly been considered to not be a common feature of equine leptospirosis. However, recent evidence suggests that this syndrome may be more common than thought previously, with acute respiratory failure described in foals (Broux et al., 2012) and endoscopy revealing pulmonary haemorrhage in 35% of seropositive adult horses (Hamond et al., 2012a). Although it has been generally considered that leptospirosis in adult horses is subclinical, recent studies suggest that it should be considered in the differential diagnosis of acute respiratory distress in adult horses and in foals.

An important *sequela* to leptospiral infection of horses is uveitis, or so called “moon blindness”. While leptospiral uveitis is not restricted to horses, it is far more common in this species and is discussed in detail in Section 3 below.

2.3. Diagnosis, treatment and prevention

The diagnosis of leptospirosis in horses does not differ from that for other species. The unequivocal gold standard remains the culture and identification of the infecting leptospiral isolate. PCR provides a more convenient alternative in many cases, with primer sets described which can discriminate at genus level or which are specific for pathogenic *Leptospira* spp. (Adler and de la Peña Moctezuma, 2010). A current search of the literature would reveal in excess of 200 publications reporting the use of PCR for the detection or identification of *Leptospira*, although only a very small number of these have been properly validated. Leptospire can also be demonstrated

in the placenta or foetal kidney by the fluorescent antibody test (FAT) or silver staining. Szeredi and Haake (2006) used polyvalent whole-cell leptospiral antiserum and antiserum against the major outer membrane leptospiral protein LipL32 in FAT and found that FAT is a more sensitive technique than silver staining and more specific than the microscopic agglutination test (MAT). (Donahue and Williams, 2000; Newman and Donahue, 2007; Szeredi and Haake, 2006)

For serological diagnosis, the MAT remains the test of choice. As with all serological tests the issue of starting dilution must be considered, with 1:100 being the most common. Additionally, in an endemic area the value of a single positive specimen is limited; hence the usual requirement of a four-fold rise in titre in paired sera is important for unequivocal diagnosis. In cases of leptospiral abortion, MAT on foetal fluids and maternal serum usually gives a very high titer and is diagnostic (Donahue and Williams, 2000). However, the inclusion of appropriate prevalent serovars as test antigens requires a knowledge of the local epidemiology of equine leptospirosis; this information is lacking in many parts of the world. There is no commercially available enzyme immunoassay (EIA, ELISA) available for detection of equine anti-leptospiral antibodies.

Treatment of leptospirosis in horses is the same as for other animal species. However, treatment regimens for horses have mostly been derived by extrapolation from other species, with very little specific information available for horses. Streptomycin (10 mg/kg) and/or penicillin (10,000–15,000 IU/kg) are most commonly the antibiotics of choice, with tetracyclines as an alternative. If a mare has a high titer of leptospiral antibodies, a high dose of penicillin G (20 million units, twice daily) is recommended for preventing the intra-uterine infection of the foetus. It should be noted that the use of streptomycin in horses is on a decline due to severe toxic side effects of this antibiotic (Bernard, 1993; Newman and Donahue, 2007).

There is no leptospirosis vaccine licensed for use in horses. Cattle vaccines have occasionally been administered to horses “off label”; this practice is not recommended and may be illegal in some countries. Additionally, the serovars contained in cattle vaccines will almost certainly not be appropriate for the prevention of equine leptospirosis. Our studies on leptospiral uveitis (see Section 3 below) suggest molecular mimicry between leptospiral proteins and equine ocular tissues and it is likely that vaccination with whole-cell bacterin may actually prime animals with these cross-reacting leptospiral antigens resulting in stronger antibody responses in subsequent exposures and development of ocular inflammation. A future leptospirosis vaccine should therefore exclude such cross-reacting leptospiral antigens. Numerous individual leptospiral antigens have been investigated for protective capacity, with variable results (Adler and de la Peña Moctezuma, 2010; Murray et al., 2013). None has been tested in horses. Thus, the only currently licensed vaccines consist of whole cell bacterins with immunity restricted to antigenically related serovars. Prevention must therefore revolve around normal husbandry and hygiene practices, vaccination of other animals on the

farm, minimising contact with rodents and other wildlife carriers and other infected horses.

3. Leptospiral equine uveitis

Ocular manifestations of leptospirosis appear in the form of equine recurrent uveitis (ERU), also referred as moon-blindness or periodic ophthalmia. *Leptospira*-associated uveitis forms an important subset of ERU cases, and *Leptospira* spp. is considered as the most common infectious cause of ERU (Halliwell et al., 1985; Hartskeerl et al., 2004). ERU is characterized by bouts of inflammation of the vascular tunic or uvea of the eye alternating with symptom-free intervals of low or no inflammation (Cook and Harling, 1983). ERU has a worldwide prevalence of around 10% and is a major cause of blindness in horses (Hartskeerl et al., 2004; Schwink, 1992). While Appaloosa breed and horses with MHC-I haplotype ELA-A9 are considered to be at increased risk of developing ERU, Standard breeds are believed to be on the other end of the spectrum (Deeg et al., 2004; Dwyer and Gilger, 2005).

Leptospira-associated equine uveitis is a painful condition that develops weeks to months after systemic leptospirosis. Early signs of the disease include miosis,

blepharospasm, lacrimation, photophobia, oedema of the eyelid, swollen conjunctiva and corneal oedema. As the disease progresses, aqueous flare and hypopyon may also be seen. A good prognosis is contingent on an early therapeutic intervention during this phase of the disease. The acute phase is followed by a period of low inflammation (Cook and Harling, 1983). Subsequent recurrences of inflammation are marked with much severe inflammatory response resulting in serious injury to ocular components. Secondary cataract, anterior or posterior attachment of iris, lens luxation, vitreous exudates and retinal detachment are seen as a result of a pronounced inflammatory insult to the eye components (Cook and Harling, 1983; Gilger et al., 2000; Gilger and Michau, 2004; Rebhun, 1979). A thick hyaline membrane adjacent to the posterior aspect of the iris and the eosinophilic linear cytoplasmic inclusion bodies in the nonpigmented ciliary epithelial cells are considered pathognomonic for ERU (Cooley et al., 1990; Dubielzig and Morreale, 1997).

Diagnosis of *Leptospira*-associated recurrent uveitis is based on the presence of classical signs of uveitis, a history of recurrence and seropositivity by MAT. There is no specific test available exclusively for the diagnosis of leptospiral uveitis. Because of a prolonged time gap

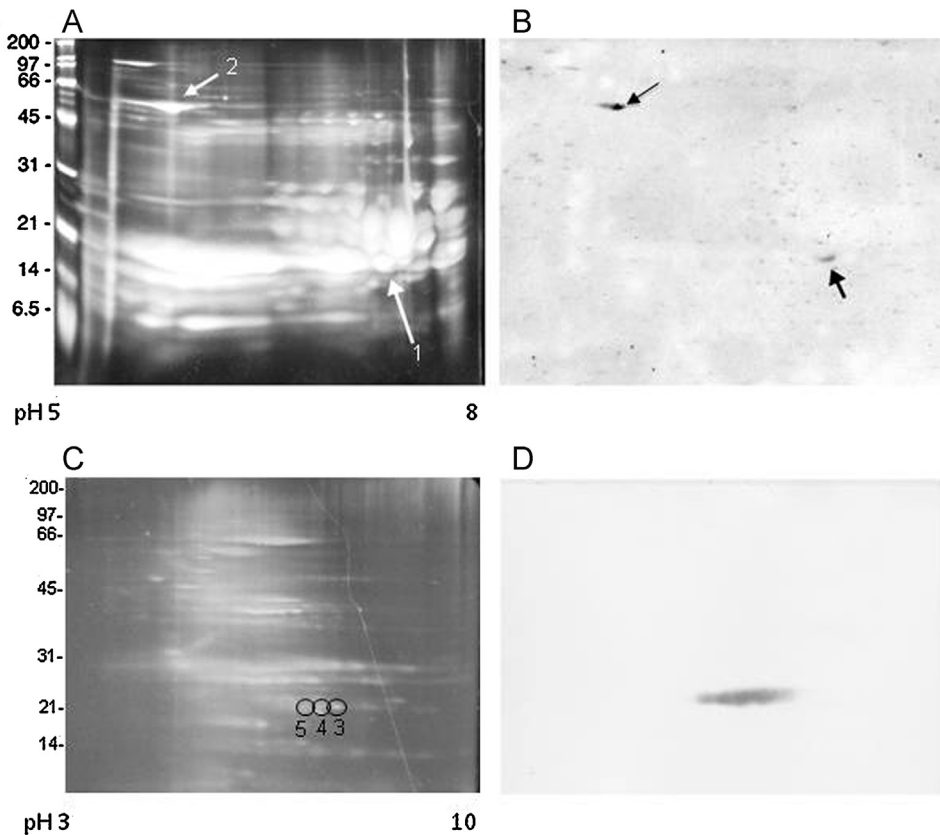


Fig. 3. Two-dimensional electrophoretic analysis of proteins in equine lenticular and retinal tissue extracts. (A) Lens extract separated on a polyacrylamide gel stained with the fluorescent dye SYPRO-Ruby. (B) Lens proteins transferred from a second gel to nitrocellulose membrane and blotted with LruA-antiserum. The arrowheads indicate the protein spots excised from the stained gel for analysis by mass spectrometry. (C) Retinal extract separated on a polyacrylamide gel stained with SYPRO-Ruby. (D) Retinal proteins transferred from a second gel to nitrocellulose membrane and blotted with LruB-antiserum. Three protein spots (numbered 3, 4 and 5) were excised from the stained gel for analysis by mass spectrometry. Reproduced with permission from Verma et al. (2010), PLoS Negl Trop Dis, 4, e778.

between systemic leptospiral infection and onset of uveitis, negative MAT titers may not always indicate absence of leptospiral etiology. Unlike human leptospiral uveitis, currently there is no clinical criteria or point system for the diagnosis of MAT-negative cases of equine leptospiral uveitis.

Treatment of ERU is primarily aimed at reducing inflammation. An intraocular device containing cyclosporine A, which blocks the transcription of interleukin-2 (IL-2), and pars plana vitrectomy have been shown to be effective in long term control of the disease. (Werry and Gerhards, 1991; Gilger and Michau, 2004). Usefulness of antibiotics in treating the infection is not clear.

ERU is an immune-mediated disease and regardless of the inciting factor it is characterized by alternate periods of severe and low inflammation. Parma and colleagues gave the initial evidence of an antigenic relationship between *Leptospira* spp. and equine eye and proposed cross-reactivity as a mechanism of disease progression (Parma et al., 1987, 1985, 1997). However, neither the leptospiral nor the ocular proteins involved were identified in those studies. In 2005, Verma et al. described intraocular expression of two leptospiral proteins, LruA and LruB, in uveitic horses. Intraocular levels of LruA- and LruB-antibodies were significantly higher than in the sera, indicating local production of antibodies in uveitic eyes. More importantly, LruA and LruB directed antibodies were shown to cross-react with normal eye components (Verma et al., 2005). Subsequently, the lens proteins cross-reacting with LruA antiserum were identified to be α -crystallin B and vimentin, and the retinal protein cross-reacting with LruB-antiserum was found to be β -crystallin B2 (Verma et al., 2010) (Fig. 3). Moreover, uveitic eye fluids contained significantly higher levels of antibodies that recognized α -crystallin B, β -crystallin B2 and vimentin than did eye fluids from healthy horses. The presence of antibodies recognizing α -crystallin B, β -crystallin B2 and vimentin in uveitic, but not normal eye fluids, suggests a role for these antibodies in *Leptospira*-associated recurrent uveitis (Verma et al., 2010). In a uveitic eye, the early phase of leptospiral infection may involve an immune response to LruA and LruB and resulting antibodies may interact with crossreacting proteins in lens and retinal tissues thus triggering autoimmune events by dequiescing normal eye proteins. These studies suggest that cross-reactivity between leptospiral and ocular proteins may contribute to immunopathogenesis of *Leptospira*-associated recurrent uveitis.

Conflict of interest

The authors declare that they have no conflict of interest with regard to the manuscript: Leptospirosis in horses.

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