Received: 12 April 2019 | Accepted: 12 January 2020

DOI: 10.1111/jvim.15713

CASE REPORT

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Acute kidney injury due to *Leptospira interrogans* in 4 foals and use of renal replacement therapy with intermittent hemodiafiltration in 1 foal

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Abstract

Four 2-month-old foals were presented to an equine hospital with acute kidney injury caused by *Leptospira interrogans* infection. Clinical signs were nonspecific and included lethargy, fever, and unwillingness to nurse. The most important hematologic and clinicopathologic findings were azotemia, anemia, thrombocytopenia, hyponatremia, and hypochloremia. The diagnosis was based on urinary real-time PCR, serology using a microscopic agglutination test, or both. The most important serovars involved were *L. interrogans serogroup australis serovar Bratislava* and *Australis*. Treatment consisted of IV fluid therapy and antimicrobial treatment. Renal replacement therapy with hemodiafiltration was performed in 1 of the foals. All foals survived to discharge. This report highlights the importance of early diagnosis and treatment in foals with acute kidney injury caused by *L. interrogans* infection.

KEYWORDS

horse, infection, leptospirosis, renal failure

1 | INTRODUCTION

Leptospirosis in adult horses most commonly is associated with abortion[1] or recurrent uveitis.[2,3] In contrast, foals seem to be particularly susceptible to acute kidney injury[4-6] or acute respiratory failure[7] after leptospiral infection, comparable to clinical findings in small animals.[8] Interestingly, leptospirosis rarely is mentioned as a differential diagnosis for renal disease in foals in textbooks of equine medicine. Treatment recommendations are therefore sparse and include IV fluid therapy in conjunction with appropriate antibiotic treatment.[4-6] Renal replacement therapy (RRT) is recommended in dogs with the severe renal form of leptospirosis.[8] Indications to perform RRT include "oliguria or anuria with subsequent life-threatening hyperkalemia or severe volume overload and advanced uremia refractory to medical management."[8] Renal replacement therapy is not considered a routine treatment for foals with acute kidney injury and specific recommendations for its use in horses are not available because of the low number of documented cases.[9-15] Hemodiafiltration (HDF) has been described in adult horses[11] and in 1 foal with post-resuscitation acute renal failure,[10] whereas hemodialysis has only once been reported as treatment for oxytetracycline-induced acute renal failure in a foal.[9] The latter foal was treated under general anesthesia on 3 occasions over a 4-day period.[9] With the potential to decrease inflammatory mediators and other uremic toxins in the mid-molecular range, HDF often is considered a more advanced technique than hemodialysis and is preferred for the treatment of acute kidney injury of infectious origin,

Abbreviations: BW, body weight; EDTA, ethylenediaminetetraacetic acid; ERU, equine recurrent uveitis; HDF, hemodiafiltration; LPHS, leptospirosis pulmonary hemorrhage syndrome; MAT, microscopic agglutination test; MCV, mean corpuscular volume; RRT, renal replacement therapy; USG, urinary specific gravity; γGT, gamma-glutamyltransferase.

when available. It is typically well tolerated and considered superior to hemodialysis with less overall and cardiovascular mortality.[16]

In this report, we describe 4 foals presented to an equine hospital with acute kidney injury caused by *Leptospira interrogans* infection, of which 1 foal was treated using RRT and HDF under sedation.

2 | CASE HISTORY

2.1 | Case 1

A 2-month-old Arabian colt was referred for evaluation of lethargy, fever, and unwillingness to nurse of several days' duration. Upon presentation, the foal was obtunded and febrile (rectal temperature, 39.6°C) and had loose feces. Heart and respiratory rates were normal. A CBC and serum biochemistry profile disclosed microcytic anemia, hyponatremia, hypochloremia, hypoproteinemia, hypoalbuminemia, and severe azotemia (Supplementary Tables 1 and 2). Urinalysis showed hyposthenuria (USG, 1.006), moderately increased fractional excretion of sodium (6.14%; reference range, 0.02%-1%) and severely increased gamma-glutamyltransferase (γGT)-to-creatinine ratio (214.7 IU/g; reference range, <25 IU/g). Serologic microscopic agglutination test (MAT; performed at ZOBA, Center for Zoonoses, Animal Bacterial Diseases and Antimicrobial, University of Bern, CH) showed increased titer for *L. interrogans serogroup australis serovar Australis* (1:800) and *L. interrogans serogroup australis serovar Bratislava* (1:800), whereas serology of the mare was negative for detection of leptospira antibodies. Ultrasonography of the kidneys was unremarkable. Treatment consisted of IV fluid therapy using 0.9% sodium chloride (100 mL/kg/d, followed by a progressive reduction; Natrium chloratum «Bichsel», Grosse Apotheke Dr. G. Bichsel AG, Interlaken, CH), sucralfate (20 mg/kg PO q6h; Sucralan, G.L. Pharma GmbH, Lannach, CH), penicillin (20 000 IU/kg IV q6h; Penicillin Natrium Streuli ad us. vet., Streuli Pharma AG, Uznach, CH) for 7 days followed by 3 weeks of PO doxycycline (10 mg/kg q12h; Primadox 50 ad us. vet., ufamed AG, Sursee, CH). During the first 3 days, the foal remained lethargic and was not nursing the mare. On day 4, the foal's general condition improved and regular nursing resumed. The mare and foal were stabled during the treatment period and monitoring included daily weight measurement, physical examination, and repeated evaluation of serum biochemistry variables. Azotemia resolved within 7 days (Supplementary Table 1) and the foal was discharged 12 days after presentation to the hospital. One year later, the foal was presented again to the hospital for evaluation of a traumatic injury to its leg and was in a good general condition.

2.2 | Case 2

A 2-month-old Swiss Warmblood filly was presented for evaluation of sudden onset lethargy and unwillingness to nurse. Upon presentation, the foal was dull but vital signs were within normal limits. Respiratory sounds were slightly increased on auscultation. Laboratory evaluation disclosed microcytic anemia, mild hyponatremia, hypochloremia, hypoalbuminemia, increased serum amyloid A concentration, as well as severe azotemia (Supplementary Tables 1 and 2). The urine was isosthenuric (USG, 1.008), fractional excretion of sodium (27.8%; reference range, 0.2%-1%), potassium (441.6%; reference range, 15%-65%), and chloride (44.05%; reference range, 0.04%-4%) were markedly increased and γGT-to-creatinine ratio was increased (35.18 IU/g). Real-time PCR was positive for pathogenic Leptospira. The MAT serology showed increased titers for *L. interrogans serogroup australis serovar Australis* (1:1600), *L. interrogans serogroup australis serovar Bratislava* (1:400), and *L. interrogans serogroup pyrogenes serovar Pyrogenes* (1:200), whereas serology of the mare was negative for the detection of leptospira antibodies. Upon ultrasound examination of the kidneys, only mild renal enlargement and hypoechoic medulla were observed. Treatment consisted of IV fluid therapy using 0.9% sodium chloride (100 mL/kg/d for 6 days, followed by 50 mL/kg/d for 1 day), sucralfate (20 mg/kg PO q6h), cefquinom (2 mg/kg IV q12h for 10 days; Cobactan IV 4.5% ad us. vet., MSD Animal Health GmbH, Luzern, CH), followed by doxycycline (10 mg/kg PO q12h for 3 weeks). Twenty-four hours after beginning treatment, the foal started nursing the mare. During the first 6 days, the foal remained quiet, but alert. By day 7, the foal was brighter and more active. During the first 7 days, the mare and foal were stabled on box rest with regular monitoring (daily weight measurement, physical examinations, repeated evaluation of serum biochemistry variables). Azotemia progressively decreased, but failed to resolve completely during 10 days of hospitalization, and serum creatinine concentration was still mildly increased at discharge (Supplementary Table 1). The foal was discharged in a good general condition, but then was lost to follow-up.

2.3 | Case 3

A 2-month-old Swiss Warmblood colt was presented for evaluation of lethargy and unwillingness to nurse of 1 day's duration. Upon presentation, the foal was quiet and alert, but not nursing the mare. Vital signs were within normal limits. Laboratory evaluation disclosed microcytic anemia, hyponatremia, hypochloremia, hypoproteinemia, hypoalbuminemia, increased serum amyloid A concentration, and azotemia (Supplementary Tables 1 and 2). The urine was isosthenuric (USG, 1.008). Real-time PCR was positive for pathogenic leptospira. The MAT serology of the foal showed increased titers for *L. interrogans serogroup canicola serovar Canicola* (1:400), *L. interrogans serogroup pyrogenes serovar Pyrogenes* (1:400), *L. interrogans serogroup australis serovar Australis* (1:200), *L. interrogans serogroup australis serovar Bratislava* (1:100), and serology of the mare was negative for the detection of leptospira antibodies. No abnormalities were detected on abdominal ultrasound examination. Treatment consisted of IV fluid therapy using 0.9% sodium chloride (100 mL/kg/d for 6 days, followed by 50 mL/kg/d for 1 day), sucralfate (20 mg/kg PO q6h), cefquinom (2 mg/kg IV q12h for 7 days), followed by doxycycline (10 mg/kg PO q12h for 3 weeks). One day after initiation of treatment, the foal was bright and alert and regularly nursing the mare. Because of rapid improvement, mare and foal were turned out

once daily in a small paddock. Patient monitoring was similar to that used in case 1 and 2. Azotemia resolved completely within 7 days (blood urea concentration, 4.87 mmol/L and serum creatinine concentration, 166 μmol/L) and the foal was discharged from the hospital. The foal presented 3 months later for evaluation of edematous swelling in the inguinal region. The foal was otherwise in a good general condition and serum creatinine and blood urea concentrations were within normal limits (Supplementary Table 1).

2.4 | Case 4

A 2-month-old Swiss Warmblood colt was presented for evaluation of diarrhea, fever, and lethargy of 1 day's duration, and evaluation of serum biochemistry variables performed by the private veterinarian had shown azotemia (serum creatinine concentration, 1200 μmol/L; blood urea concentration, 30 mmol/L). Upon presentation at the hospital, the foal had normal feces and was lethargic, but was still nursing the mare. The foal no longer had diarrhea and vital signs were within normal limits. A CBC and serum biochemistry profile disclosed microcytic anemia, thrombocytopenia, hyponatremia, hypochloremia, hypoalbuminemia, increased serum amyloid A concentration, and azotemia (Supplementary Tables 1 and 2). The urine was hyposthenuric (USG, 1.006) and fractional excretion of electrolytes was as follows: sodium (39.26%), potassium (486.92%), and chloride (60.41%). The γGT-to-creatinine ratio was increased (31.5 IU/g). Real-time PCR was positive for pathogenic leptospira. The MAT serology of the foal showed increased titers for *L. interrogans serogroup australis serovar Bratislava* (1:1600), *L. interrogans serogroup australis serovar Australis* (1:200), *L. interrogans serogroup canicola serovar Autumnalis* (1:100), and serology of the mare was positive for *L. interrogans serogroup australis serovar Australis* (1:200) and *L. interrogans serogroup australis serovar Bratislava* (1:400). On ultrasonographic examination, both kidneys were enlarged (approximately 16 cm long in the longitudinal plane) with thickened cortex of increased echogenicity and normal to increased corticomedullary distinction. A small amount of anechoic free fluid surrounded both kidneys, but the renal pelves were not dilated. Initial treatment included 0.9% sodium chloride (100 mL/kg/d), di-tri-octahedral smectite (1 4-oz scoop PO q12h; Bio-Sponge, Platinum Performance, Inc., Buellton, California) and penicillin (20 000 IU/kg IV q6h for 7 days). After 2 days, the foal developed ventral edema, was lethargic, but started nursing the mare. The foal remained apathetic and edema persisted. On day 4, the foal still had marked azotemia (Supplementary Table 1), its general condition had declined, and the foal was more lethargic. Renal replacement therapy with veno-venous HDF was began. For this purpose, a 13.5-French 28 cm double lumen central venous catheter (Medcomp, Harleysville, Pennsylvania) was placed in the right jugular vein under sedation using detomidine (0.01 mg/kg IV; Equisedan ad us. Vet., Dr. E. Graeub AG, Bern, CH) and butorphanol (0.01 mg/kg IV; Morphasol-10 ad us. vet., Dr. E. Graeub AG). Dialysis was performed using a Gambro AK 200^{R} Ultra S machine with a Fresenius FX 80 filter and Gambro BL200BD blood tubing with total extracorporeal volume of 241 mL. Bicarbonate-based dialysate (A341G, Dr G. Bichsel Laboratory, Interlaken, CH; and BiCart^{R}, Gambro Lundia AB, Sweden) was used, and heparin-free regional citrate anticoagulation was performed, adapted from a protocol used for intermittent hemodialysis in dogs, using trisodium citrate (Trisodium citrate 30 g/L, 102 mmol/L, Dr G. Bichsel Laboratory; initial rate of 2.5 mmol/L blood or 4.6 μmol/kg/min at the chosen blood flow rate) and calcium chloride (Calcium chloride 50 g/L, 340 mmol/L, Dr G. Bichsel Laboratory; initial rate of 0.85 mmol/L blood or 1.6 μmol/kg/min at the chosen blood flow rate) as citrate and calcium sources, respectively.[17] The dialysis prescription was designed to provide a urea clearance of approximately 1.5 mL/kg/min for 4 hours, corresponding to a blood flow rate of 200 mL/min. Initial citrate and calcium flow rates were 300 and 30 mL/h, respectively, and no adjustment was needed based on monitoring of ionized calcium concentration from the patient and the extracorporeal circuit.

A total of 52 L blood (0.43 L/kg body weight) were processed with 26 L of filtration (0.21 L/kg BW) over 240 minutes, resulting in a urea reduction ratio of 36%, a creatinine reduction ratio of 35%, and a fractional clearance (spKt/V) of 0.5. One litter of excess water was removed by ultrafiltration. Relevant details of blood variables at the end of the hemodialysis treatment are presented in Supplementary Table 1. The general demeanor and the renal variables of the foal (Supplementary Table 1) significantly improved after 1 session of HDF. On day 6, 2 days after HDF, the foal developed thrombophlebitis of the right jugular vein. Considering the progressive improvement in kidney function, no further HDF treatment was needed and the dialysis catheter was removed. Similar to standard procedure in dogs, a tight wrap was applied for 3 hours over the jugular vein, followed by a loose bandage for 2 days. Treatment was changed to broad-spectrum antibiotics with cefquinom (2 mg/kg IM q12h for 7 days) and dalteparin sodium (90 IU/kg SC q12h, 90 IU/kg SC q12h, Fragmin, Pfizer PFE Switzerland GmbH, Zürich, CH) was added. Intravenous fluid therapy was discontinued 1 day after the development of thrombophlebitis because of concern about the contralateral jugular vein. The foal was discharged after 19 days in good general condition and with moderate azotemia (Supplementary Table 1). Antibiotic treatment was continued for 3 weeks after discharge from the hospital (doxycycline, 10 mg/kg PO q12h). According to the owner, the foal remained slightly smaller than expected during the first few months after discharge but was in very good general condition and was developing normally at a 2-year follow-up.

3 | DISCUSSION

The incidence of leptospirosis in dogs has increased over the last several years,[18] which potentially may lead to an increased number of affected horses in the future. Risk factors for clinical disease that have been described for people[19] and dogs[20] include contact with outdoor water sources as might occur with swimming in and consumption of outdoor water sources. Risk factors for clinical disease in horses have not been described, but seropositivity was associated with geographic location, increased age, drinking of river water and the presence of

dogs in the adjacent properties in horses in Ethiopia.[21] Another study identified exposure to rodents and wildlife among other factors to be associated with seropositivity in horses.[22]

The foals described here were of the same age, showed similar clinical signs, and all of the animals survived to discharge. Hematologic and clinicopathologic findings in these foals (anemia, thrombocytopenia, azotemia, hyponatremia, and hypochloremia) were similar to those described in dogs. Anemia occurs in approximately 50% of dogs with leptospirosis with possible causes including bleeding in the respiratory or gastrointestinal tract and anemia of inflammatory disease.[8] Although clinical signs of blood loss were not observed in our patients, some degree of internal bleeding cannot be excluded. Hemorrhage as a cause for the anemia would be supported by the low total protein and albumin concentrations in all 4 foals. With regard to thrombocytopenia, we cannot exclude that these results were artifactual, because they were performed on EDTA and not citrated blood. However, thrombocytopenia commonly occurs in other species[8,23] and might be associated with immune-mediated platelet destruction.[24] Thrombocytopenia formerly has been described in horses to occur as a sequela of infectious diseases such as anaplasmosis.[25,26] Azotemia, hyponatremia, and hypochloremia are sequelae of acute renal injury and are also commonly seen in dogs with leptospiral infection.[8] Abnormalities in the urinalysis indicated glomerular and tubular damage, which again is comparable to findings in affected dogs.[8] Foals with acute kidney injury typically have hyposthenuric urine because of loss of renal concentrating ability.[27] The calculated fractional excretion results of electrolytes in the 4 foals were markedly increased, even above normal values reported in neonatal foals, which are higher than in adult horses.[28] Renal injury in acute leptospirosis is thought to occur from the direct effect of leptospiral organisms resulting in a combination of acute tubulointerstitial inflammation, tubular epithelial damage, and parenchymal hemorrhage. Additional mechanisms include secondary injury as a result of hypotension and hypovolemia as well as immune-mediated processes.[29] Acute renal failure after leptospiral infection in humans is characterized by urinary wasting of potassium and sodium and non-oliguria or polyuria,[29] similar to the foals described here.

Hepatic involvement does not seem to play a major role, and none of the foals in this report showed signs of hepatic disease or had increased activities of hepatic enzymes on serum biochemistry profiles.

Diagnosis based on urinary real-time PCR, although commonly used in small animals,[8] does not seem to be part of the routine diagnostic evaluation in horses suspected of leptospiral infection.[1,4,5] Seropositivity occurs commonly in healthy horses. On its own, it is not a good indicator for clinical disease and only points to recent exposure and seroconversion. Seroprevalence of *Leptospira* in the equine population has been examined in different areas of the world,[30-32] including the geographic region of the foals presented here, and indicates a seroprevalence for *Leptospira spp*. of approximately 58.5%, with 20.3% of the horses having titers ≥400.[30] Real-time PCR previously has shown to be an effective method for the diagnosis of leptospiral abortion in horses when compared to MAT and fluorescent antibody testing (FAT).[33] The combination of PCR and antibody testing seems to be the diagnostic method of choice for acute infections in affected humans and "can be used to confirm the diagnosis, early on in the acute stage of the infection."[34] Real-time PCR based on identification of *lipl32* in combination with MAT for the identification of the serogroup therefore is our choice in suspected cases. In the absence of available laboratories to perform urinary PCR for leptospirosis, seroconversion in paired serum samples would confirm infection retrospectively. This is of potential importance because leptospirosis is a zoonosis. Antibody testing of paired samples in suspected cases is recommended in dogs.[35,36]

The serology MAT results in all 4 foals were lower than previously reported.[5,6] The foals presented in those reports had a longer history of clinical signs and we assume that the low MAT serology results in the foals presented here reflect the acute onset of disease. Similarly, low MAT serology results were described in 2 foals with acute respiratory failure in Belgium.[7] The MAT is considered the gold standard for the diagnosis of leptospirosis in humans because of high test sensitivity and the identification of group-specific antibodies, although the test is known to have inferior sensitivity during the acute onset of disease.[34] Ideally, paired serum samples should have been sent to confirm the diagnosis, as previously mentioned. Other potential diagnostic tests to confirm the diagnosis include urine culture, renal biopsy, and FAT of urine. Culture of leptospiral organisms takes a long time and is therefore impractical for the diagnosis of acute infections,[34] and renal biopsy was not performed because of rapid clinical improvement after the initiation of treatment. This procedure is not without risk for complications and should therefore only be performed if the results are likely to change management of the patient.[37]

The most important serovars involved in the leptospiral infection of these foals were *L. interrogans serogroup australis serovar Bratislava* and *L. interrogans serogroup australis serovar Australis*, although there may have been some crossreactivity because both belong to the same serogroup. Both serovars are increasingly associated with clinical disease in dogs in Switzerland.[18] *Leptospira interrogans serogroup australis serovar Australis* and *L. interrogans serogroup australis serovar Bratislava* are the third and fourth most commonly identified serovars in horses in Switzerland, with seroprevalence of 19.2 and 15.9%, respectively.[30] It is unknown if different serovars of *L. interrogans* are associated with different clinical presentations although the serovar most commonly involved in recurrent uveitis in horses (ERU) in a study conducted in Germany was *L. interrogans serogroup australis serovar Grippothyposa*.[3] This observation is in accordance with the authors' clinical experience of horses with ERU.

Treatment included administration of an appropriate antimicrobial agent and IV fluid therapy using 0.9% sodium chloride. Foals 1-3 responded quickly to this treatment, whereas foal number 4 remained lethargic. Foal number 4 was considered to be a good candidate for HDF and responded well to the treatment, leading to rapid improvement in its clinical condition.

All foals in this report survived to discharge. Chances of survival in previous case reports was good if the foals were affected only by renal injury,[4-6] but worse if pulmonary hemorrhage was diagnosed.[7] Thoracic examination including ultrasonography and radiography (or possibly thoracic computed tomography) therefore might be recommended to

establish a prognosis for the affected animal, particularly in animals with clinical signs localized to the respiratory tract. Thoracic radiography was not described in a report about acute respiratory failure in foals,[7] but changes such as a mild interstitial pattern to a mild to severe reticulo-nodular pulmonary pattern with focal alveolar infiltrates in the caudodorsal parts of the lung field, described as leptospiral pulmonary hemorrhage syndrome might be expected based on findings in dogs and humans.[8,38,39] Leptospiral pulmonary hemorrhage syndrome is not the direct result of infection of the lungs with leptospires because leptospires typically cannot be found in lung tissue by PCR. The main hypothesis is that of a secondary immune reaction involving the pulmonary membrane, resulting in permeability changes and flooding of the alveolar space with blood. Alternatively, alveolar permeability changes could result from circulating bacterial products of the leptospires. A third hypothesis related to a systemic hemostatic disorder has mostly been ruled out.[40] Cases 2 and 4 of our report had thoracic radiographs performed with mild bronchointerstitial lung pattern without caudodorsal enhancement, thus it was unclear if changes were related to the leptospiral infection or not.

Hemodiafiltration treatment has been documented in a foal with post-resuscitation renal failure[10] and in healthy adult horses using a continuous RRT machine.[11] Both reports describe successful treatment without major adverse effects in the patients.[10,11] Hemodiafiltration is a well-established treatment in dogs, and monitoring protocols used for dogs performed very well for this foal, including regional citrate anticoagulation. The main difficulty would have been if further treatment was required, because of development of thrombophlebitis and the necessity to keep a patent large-bore dialysis catheter for the duration of dialysis support. For treatment to become more efficient, higher blood flow rates or longer sessions of dialysis, ideally with 120-240 L of blood being processed, would be required. To our knowledge, RRT with HDF using an intermittent renal replacement machine in a foal suffering from leptospirosis has not been described previously.

In conclusion, leptospiral infection should be considered in foals with nonspecific clinical signs including lethargy, fever, and azotemia. The diagnostic evaluation should include urinary real-time PCR and serology, ideally including paired samples to confirm seroconversion, and possibly thoracic imaging because respiratory involvement should be considered. Treatment including IV fluid therapy and antimicrobials should be implemented as early as possible and RRT with HDF or hemodialysis may be a valid option in refractory cases or foals with anuria or oliguria.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Consent was gained from the owners for all diagnostic procedures and use of case material for teaching and research purposes.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Fouché N, Graubner C, Lanz S, Schweighauser A, Francey T, Gerber V. Acute kidney injury due to *Leptospira interrogans* in 4 foals and use of renal replacement therapy with intermittent hemodiafiltration in 1 foal. *J Vet Intern Med*. 2020;34:1007–1012. https://doi.org/10.1111/jvim.15713