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Unilateral left-sided nephrectomy in a horse with ureteropyelonephritis

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Summary: A 21-year-old Dutch Warmblood mare was presented for evaluation and treatment of suspected chronic renal insufficiency of three weeks duration. The mare was suffering from anorexia, polyuria, polydipsia and azotaemia. Abdominal palpation per rectum revealed that the left kidney was located further cranially than expected, marked enlargement of the associated ureter made digital palpation of this structure possible. Transabdominal ultrasonography of the left kidney revealed a completely deranged anatomy; normal renal structures could not be identified. The right kidney appeared to have a normal size and architecture, but was located more caudally than usual. Cystoscopy revealed outflow of urine mixed with purulent exudate from the left ureter (pyuria). The urine coming from the right ureter had a normal macroscopic appearance. Urine was collected from both ureters separately for bacteriologic, cytologic and fractional electrolyte excretion examination as well as for specific gravity. No bacteriological growth was observed from the left ureter, whereas *Pseudomonas* species, *Staphylococcus* sp. and *Stenotrophomonas maltophilia* were grown from the right ureter. The cytologic examination of urine from both ureters was consistent with purulent inflammatory changes within the urinary tract; no signs of neoplasia or concrements were identified. A tentative diagnosis of a bilateral (uretero)pyelonephritis, more severe in the left kidney, was made. Because after conservative treatment with antibiotics and fluid therapy the levels for creatinine and urea normalized, it was concluded that the right kidney at least partially had returned to normal function. That assumption was supported by the normal parameters of function fractional electrolyte excretion and urinary gamma glutamyl transferase (GGT):creatinine ratio, for the right kidney. Since those parameters of function were abnormal for the left kidney, and its transabdominal ultrasonographic appearance remained severely abnormal, chronic ureteropyelonephritis unresponsive to medical treatment was suspected. Consequently, a unilateral left-sided nephrectomy was recommended. The left kidney was successfully removed using a hand-assisted laparoscopic technique under standing sedation. This technique provides the surgeon with the access for a very good three-dimensional assessment using a combination of visual and tactile information. The approach is also less invasive than the traditional approach via a more extensive coeliotomy. The horse made an uneventful recovery and was discharged from the hospital 18 days post-operatively. Two years later the owner reported the mare to be in very good body condition, she returned to full work as a pleasure horse. In conclusion fractional electrolyte excretion and urinary GGT:creatinine ratio calculations, performed separately for urine from the left and from the right kidney, can be very useful and valuable tools in determining renal function.

Keywords: renal insufficiency, kidney, hand-assisted laparoscopy, fractional electrolyte excretion, urinary GGT:creatinine ratio

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Introduction

Clinical signs of renal disease in horses are often unspecific, and the diagnosis and treatment of nephropathies can be challenging (*McLeland* 2015). During the early stages, renal disease is usually asymptomatic (*Schott II* 2007, *Schott II* and *Esser* 2020). Acute kidney injury (AKI) is diagnosed more frequently than chronic kidney disease (CKD) and is characterized by a sudden decrease in glomerular filtration rate (GFR) resulting in azotaemia and uraemia (*Geor* 2007, *Savage* et al. 2019, *Fouché* et al. 2020, *Schott II* and *Esser* 2020). Frequently this condition occurs secondary to enterocolitis and other gastrointestinal disease, sepsis, systemic inflammatory response syndrome (SIRS) or rhabdomyolysis; therefore, the main clinical signs in these patients are associated with the primary disease process and do not necessarily manifest as clinical signs specific to renal pathology (*Groover* et al. 2006, *Geor* 2007, *Schott II* and *Esser* 2020). Administration of potentially nephrotoxic medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, sulfonamides or tetracyclines can also lead to AKI (*McLeland* 2015). If recognized early, AKI can often be treated successfully, making a full recovery possible (*Geor* 2007, *Savage* et al. 2019, *Fouché* et al. 2020, *Schott II* and *Esser* 2020).

Chronic kidney disease is characterized by progressive loss of renal function resulting in decreased urinary concentrating ability, polyuria, polydipsia, lethargy, inappetence and weight loss (*Schott II* 2007). Endocrine functions of the kidney such

as production of erythropoietin and production of the active form of vitamin D are often diminished, and clearance time for hormones prolonged.

Both AKI and CKD result in azotaemia, which is characterized by increased levels of urea and creatinine in blood. During end stage CKD a multiple organ dysfunction termed "uraemia" develops (*Schott II* 2007). Differential diagnoses for CKD include (uretero)pyelonephritis, urolithiasis, polycystic kidneys, nephritis due to exposure to nephrotoxicants and renal neoplasia.

The diagnosis of pyelonephritis is usually reached by way of exclusion of other causes of CKD. Most clinical signs of pyelonephritis are non-specific and are the same as those encountered with AKI and with other causes of CKD. These include anorexia, weight loss, fever, polyuria, polydipsia and azotaemia (*Reed* et al. 2004). Urolithiasis, recurrent cystitis, bladder paralysis and urinary stasis are risk factors for the occurrence of pyelonephritis (*McLeland* 2015, *Reed* et al. 2004).

A complete physical examination, blood analysis, abdominal palpation per rectum, transabdominal ultrasound examination, cystoscopy, fractional excretion of electrolytes, and cytological and bacteriological examination of ureteral urine (to assess each kidney separately) are important for the successful and accurate diagnosis of renal disease in horses (*Reed* et al. 2004).

This case report describes the clinical presentation, diagnostic evaluation, surgical treatment, post-operative management and outcome of a mare that underwent unilateral left-sided nephrectomy to treat chronic ureteropyelonephritis. A special feature of this report is the comprehensive diagnostic evaluation of both kidneys before surgery, which allowed to accurately establish the presence of a normal functioning right kidney prior to unilateral left-sided hand-assisted laparoscopic nephrectomy, allowing the horse to return to a normal quality of life post-operatively.

Case history

A 21-year-old Dutch Warmblood mare used for pleasure riding was presented to the clinic for a third opinion for the evaluation and treatment of suspected CKD of three weeks' duration. Approximately four months prior to presentation the owner had started to appreciate a loss in body condition and a suspected polyuria. Three weeks prior to admission the owner reported a significant deterioration in the mare's condition. The referring veterinarian initially noted anorexia, polyuria, polydipsia and azotaemia and commenced treatment with trimethoprim sulfonamides. Due to a lack of improvement the horse was referred to a referral center where antibiotics (medication unknown) were continued and intravenous fluid therapy instituted. This did not lead to clinical improvement, prompting referral to our clinic. Reportedly eight years prior

Table 1 Hematology and Serum Chemistry | *Hämatologie und Serumchemie*

Parameter	Day 0	Day 8	Day 9	Day 15	Day 21	RR	Unit
Hematocrit	34,7	**25,4**	**25,2**	**28.2**	**24,6**	30–47	%
Erythrocytes	7.83	**5.87**	**5.84**	6.42	**5.65**	6.4–10.4	T/L
Hemoglobin	13.1	**9.9**	**9.7**	11	**9.6**	10.7–16.5	mmol/L
MCV	44.3	43.3	43.2	43.9	43.5	41.1–52.4	fL
MCH	16.7	16.9	16.6	17.1	17	14.1–18.6	fmol
MCHC	37.8	**39**	38.5	**39**	**39**	32.8–38.6	mmol/L
Leukocytes	**11.83**	8.35	**13.27**	8.85	7.87	4.9–11.1	G/L
Neutrophils	**8.55**	5.4	**11.4**	6.14	5.2	2.5–6.9	G/L
Total protein	7.4	7.1	6.7	6.8	6.3	5.6–7.9	g/dL
Albumin	3	3	2.7	2.7	2.6	1.9–3.2	g/dL
Urea	**54**	22	24	20	16	10–25	mg/dL
Creatinine	**3.8**	1.9	2.3	1.4	1.5	0.8–2.2	mg/dL
Calcium	**15**	12.4	**10.2**	11.1	11.3	10.4–12.9	mg/dL
Chloride	105		103	109	107	97–109	mmol/L
Potassium	4.2		3.1	3.6	4.3	3–5.3	mmol/L
Sodium	**129**			136	139	133–150	mmol/L
CK	92	117	**524**	176	86	10–350	U/L
Bilirubin	2.7	2.4	**3.6**	2.2	1	0–3.5	mg/dL
Glucose	122	114	**235**	90	111	64–150	mg/dL

Blood analysis results from admission (Day 0), the day of surgery (Day 8), and one day (Day 9), one week (Day 15) and two weeks (Day 21) after surgery. RR: Reference Range. Results outside the RR are underlined and in bold font. | *Resultate der Blutanalyse am Ankunftstag in der Pferdeklinik (Tag 0), am Operationstag (Tag 8), und ein Tag (Tag 9), eine Woche (Tag 15) und zwei Wochen (Tag 21) nach der Operation. RR: Referenzbereich. Resultate ausserhalb des RR sind unterstrichen und fett geschrieben.*

to referral a cystolith had been diagnosed and removed with an apparent good outcome. Since that time the mare had not shown any signs of disease of the urogenital system or of other body systems.

Clinical and diagnostic findings

On presentation at the clinic, the horse was quiet, but alert, with a heart rate of 40 beats/min, a respiratory rate of 12 breaths/min and a rectal temperature of 38.2 °C. Oral mucous membranes were pale pink with a normal capillary refill time of 2 seconds. Gastrointestinal motility was within normal limits.

Complete blood count (CBC) and serum biochemistry (SBC) on the day of presentation revealed a mild neutrophilic leukocytosis, marked azotaemia, hypercalcaemia and hyponatraemia (Table 1). These derangements are consistent with CKD associated with an inflammatory process.

Upon abdominal palpation per rectum the caudal pole of the right kidney could be palpated (a somewhat unusual finding, as this organ is not readily palpable in most horses) and felt firm to the touch. The caudal pole of the left kidney palpated as soft and was difficult to reach, giving the impression of being located too far cranially. The left ureter was enlarged and could be palpated as a thickened, firm and somewhat tortuous chord.

Transabdominal ultrasound examination using a 2 MHz curved array probe revealed that the left ureter had a diameter of 3 cm, while the size of the right ureter was within normal limits. The margins of the left kidney could not be distinguished. Subcapsular and central fluid accumulations were apparent. The right kidney had a normal size (17 cm long) and architecture. Abdominocentesis was performed to rule out secondary peritoneal changes due to renal disease. The cytological analysis of macroscopically normal clear pale amber abdominal fluid was unremarkable; there were no indications of peritonitis or neoplasia within the abdomen.

A cystoscopy performed under sedation with detomidine hydrochloride (Cepesedan®, 10 mgl/ml, intravenously (iv))[1] identified purulent mucus-particles in the urine within the urinary bladder, and linear petechiae on the mucosa of the vesical trigone. The mucosa around the left ureteral orifice was severely thickened and the outflow from the ureter appeared purulent (pyuria; Fig 1 and Fig 2). The urine outflow from the right ureter was normal; however, mild mucosal thickening was present around the right ureteral orifice (Fig 3). The remaining mucosal surface of the urinary bladder was pink and shiny with no signs of inflammation, and no signs of concrements or neoplasia were observed. Urine was collected from both ureters separately for specific gravity, bacteriologic, cytologic and fractional electrolyte excretion examination (Fig 2). No bacteriological growth was observed in the urine from the left ureter, whereas *Pseudomonas* spp., *Staphylococcus* sp. and *Stenotrophomonas maltophilia* were grown from the urine collected from the right ureter. The cytologic examination of urine from both ureters was consistent with purulent inflammatory changes in the urinary tract; no signs of neoplasia or urolithiasis were identified. The specific gravity of the ureteral urine was decreased bilaterally, with 1.018 for the left kidney and 1.012 for the right kidney (reference range (rr) > 1.024). This is consistent with loss of urinary concentrating ability of both kidneys. However, it is noted that the interpretation of urine specific gravity in a sedated horse is unreliable due to the known diuretic effects of alpha 2 receptor agonists. Urinalysis from the left ureter revealed increased fractional excretion (FE) of sodium (0.69 %, rr 0.04–0.52 %) and chloride (2.4 %, rr 0.7–2.1 %). The FE of potassium was slightly decreased (32 %, rr 35–80 %). Gamma glutamyl transferase (GGT) was 104 IU/L, and the GGT:creatinine ratio was markedly elevated with 119 IU/gCr (< 25 IU/gCr normal, > 100 IU/gCr indicating acute damage of the renal tubules). The FE of electrolytes was within normal limits in urine from

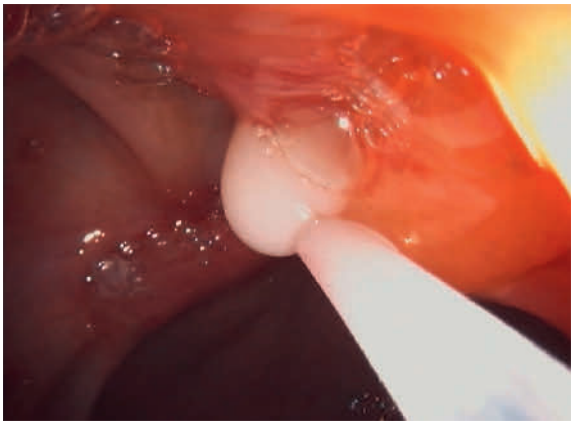

Fig. 1 Cystoscopic image of the severely thickened mucosa in the area of the left ureteral orifice and purulent urine outflow from the left ureter (pyuria) during trans-endoscopic urine collection from the left ureter. | *Zystoskopisches Bild der hochgradig verdickten Mukosa im Bereich der linken Ureter-Öffnung und eitriger Urin-Ausfluss aus dem linken Ureter (Pyurie) während der trans-endoskopischen Urin-Gewinnung aus dem linken Ureter.*

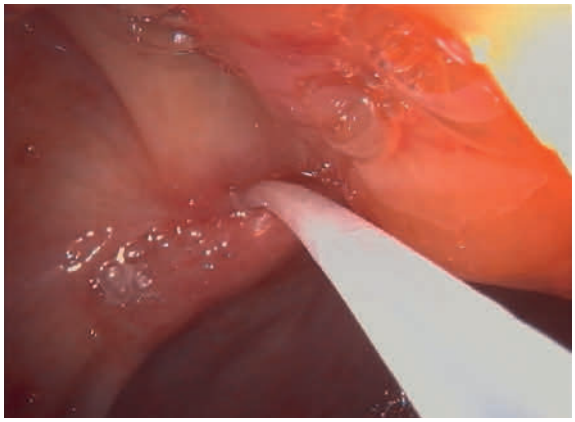

Fig. 2 Urine collection using a trans-endoscopic catheter (separately for both ureters) for specific gravity and for bacteriologic, cytologic and fractional electrolyte excretion examination. Severely thickened and oedematous mucosa in the area of the left ureteral orifice. | *Urin-Gewinnung mit einem trans-endoskopischen Katheter (separat aus beiden Ureteren) zur Bestimmung des spezifischen Gewichts sowie für eine bakteriologische und zytologische Untersuchung und für die fraktionelle Elektrolyt-Ausscheidung. Hochgradig verdickte und ödematöse Mukosa im Bereich der linken Ureter-Öffnung.*

the right ureter (FE of sodium 0.47 % and FE of chloride 1.7 %). The FE of potassium was decreased (29 %). GGT was 17 IU/L, and the GGT:creatinine ratio was within normal limits (24 IU/gCr). Based on the results of the clinical findings, blood analysis, abdominal palpation per rectum, transabdominal ultrasonography, cystoscopy and urinalysis, bilateral bacterial pyelonephritis was suspected. With normal fractional excretion of electrolytes and a normal urinary GGT:creatinine ratio of the right kidney, recovery of the right kidney was considered likely if the bacterial infection could be eradicated and the azotaemia subsided.

Antimicrobial treatment with sodium amoxicillin (10 mg/kg, iv, q12 h; Amoxisel-Trockensubstanz®)[2] and intravenous fluid therapy with NaCl 0.9 %[3] at a constant rate infusion (CRI) of 6 ml/kg/h was commenced. The horse also received metamizole (30 mg/kg, iv, q24 h; Novaminsulfon® 500 mg/ml)[4] to provide analgesia while avoiding non-steroidal anti-inflammatory drugs due to their potential nephrotoxic effects. A dietary supplement enriched with micronutrients and with a claim of supporting renal function was administered (25 g/600 kg, po, q12 h; Navalis Nephrosal®)[5]. Access to drinking water and water with a balanced electrolyte solution was provided. As the mare drunk well, intravenous fluids were discontinued after 24 hours. On day 3 after admission the subcapsular and central fluid accumulation visible via ultrasound of the left kidney were still present. Following 7 days of medical therapy, serum creatinine and urea levels returned to normal; but a normocytic, normochromic anaemia was identified (Table 1). The mare's mentation remained subjectively slightly reduced, but the anorexia had resolved and defecation was normal. Upon cystoscopy on day 8 after admission, pyuria was still present from the left ureteral opening, while urine with a normal macroscopic appearance was observed coming from the right. The mucosa at the caudal extent of the urinary bladder showed less linear petechiation, an accumulation of purulent material within the urinary bladder was no longer identifiable. Due to the severely abnormal ultrasonographic appearance, the abnormal fractional electrolyte excretion and GGT:creatinine ratio results, and the lack of apparent improvement in the above despite medical treatment, it was concluded that the left kidney was so severely compromised that return to function could not be expected. A laparoscopic unilateral left-sided nephrectomy was elected.

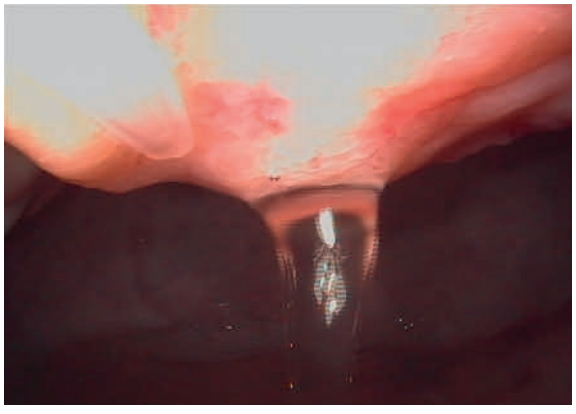

Fig. 3 Cystoscopic image of the macroscopically normal urine outflow from the right ureter. Mild mucosal thickening was present around the right ureteral orifice. | *Zystoskopisches Bild des makroskopisch normalen Urin-Ausflusses aus dem rechten Ureter. Die Mukosa im Bereich der rechten Ureter-Öffnung ist leichtgradig verdickt.*

Surgical treatment

Surgery was performed in the standing horse under sedation on day 9 after admission. Sedation was initiated using an intravenous bolus of detomidine hydrochloride (0.01 mg/kg, iv and butorphanol tartrate (0.025 mg/kg, iv; Butorgesic® 10 mg/ml)[1] and maintained by CRI of detomidine hydrochloride (0.16 µg/kg/minute) in Lactated Ringer's solution, as described by *van Dijk* et al. (2003). Intra-operative intravenous fluid therapy consisted of a CRI of NaCl 0.9 %[3] and Ursolyt®153[3†] (a hypertonic, isoionic solution containing in mmol/l Na^+ 140; K^+ 5; Ca^{2+} 2.5; Mg^{2+} 1.5; Cl^- 103; $Acetat^-$ 50). The procedure for laparoscopic surgery was performed as described previously by *Rijkenhuizen* and *Grinwis* (1999). Briefly, two portals were made in the left flank, using the standard portals for abdominal cryptorchid castration. Upon initial abdominal exploration, the left kidney seemed to be enlarged, bulging medially. After local subperitoneal infiltration of 10 ml lidocaine hydrochloride (Lidocainhydrochlorid 2 %, 20 mg/ml)[4] around the left kidney, medial to the nephrosplenic ligament, the peritoneum surrounding the kidney was incised using laparoscopic scissors (5 mm). Due to the large size of the kidney a hand-assisted laparoscopy was deemed necessary, and the instrumental portal was enlarged to accommodate the surgeon's hand using a modified grid incision technique. Manual blunt dissection was used to free the kidney from the retroperitoneal fat until it remained attached only by the renal artery, vein and ureter. The renal artery and the renal vein were individually isolated and double ligated using an extra corporal Roeders knot with lactomer 2 USP (Polysorb 2 USP)[7] and transected using the LigaSure™ device[7]. The renal artery was ligated first to reduce renal blood flow and prevent congestion. The ureter, which was markedly inflamed

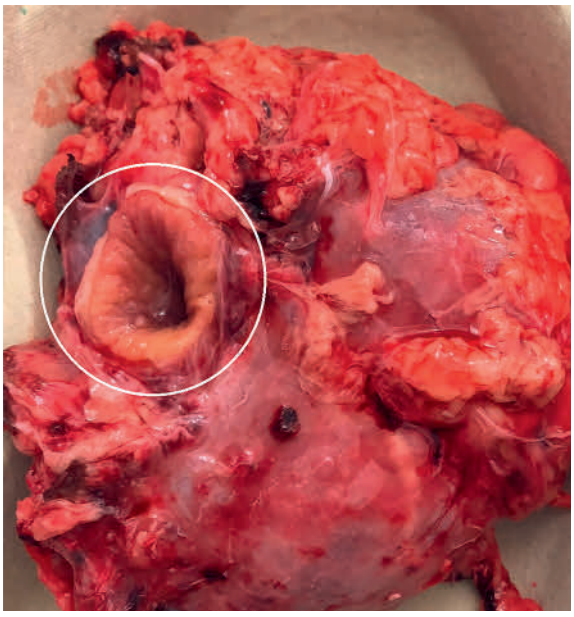

Fig. 4 The removed left kidney and its severely increased and inflamed ureter (circle). | *Die entfernte linke Niere und ihr hochgradig vergrößerter und entzündeter Ureter (Kreis).*

and thickened (estimated 3 cm diameter) was bluntly dissected in the direction of the urinary bladder until the kidney could be exteriorised from the abdomen using laparoscopic Babcock forceps (10 mm). Two transfixing ligatures were placed with absorbable multifilament suture (lactomer 2 USP) and the ureter was sharply transected extra-abdominally. The ureter was found to be filled with mucopurulent material (Fig 4). The lumen of the ureteral stump attached to the bladder was flushed with sterile saline solution prior to double-layer closure using a Lembert suture pattern (lactomer 0 USP) and being returned into the abdomen. The small laparotomy incision was closed routinely. The transverse and oblique abdominal muscles were sutured independently in a simple interrupted pattern (lactomer 2 USP), the subcutaneous tissue was closed in a simple continuous pattern with polyglecaprone 2/0 USP (Monocryl 2/0 USP)[8], and the skin was closed using a continuous intradermal pattern (poliglecaprone 2/0 USP). The laparoscopic portal was closed with two simple interrupted sutures (poliglecaprone 2/0 USP). An adherent soft foam bandage (Animal Polster®)[9] was placed over the surgical incisions. The whole procedure took two hours.

Gross examination of the nephrectomised kidney revealed it to be oval in shape, with approximate dimensions of $13 \times 12 \times 5$ cm and a reddened smooth external surface. The mucosa of the ureter appeared markedly inflamed and thickened. Dissection of the removed kidney revealed a continuous cavity surrounded only by an approximately 5 mm thin kidney wall, filled with copious amounts of mucopurulent material (Fig 4). The histopathologic findings of the left kidney were consistent with chronic pyelonephritis. A chronic active lymphocytic interstitial nephritis due to a longstanding ascending infection was reported: marked, chronic active, purulent and proliferative pyelonephritis with interstitial fibrosis, and atrophic, scarred glomerular structures. Bacteriological culture identified the gram-positive anaerobe *Propionibacterium acnes* and a gram-negative anaerobic bacterium similar to *Prevotella heparinolytica* which could not be completely identified. The left ureter was unfortunately not submitted for histopathological examination.

Post-operative care

Following surgery, the mare was bright, alert and responsive to stimuli. Two and 24 h after surgery, the hematocrit and total protein remained stable compared to preoperative values. A moderate neutrophilic leukocytosis was present, serum creatinine and urea concentrations were within normal limits (Table 1). The mare ate and drank well; the intravenous fluid therapy was discontinued after 24 h and Equistro® Haemolytan 400 (3 ml/100 kg, po, q24 h; a dietary supplement enriched with vitamins, folic acid, and the trace elements copper, iron and zinc)[10] was given with feed.

An addendum to the antibiotic sensitivity profile of the isolated *Pseudomonas* spp. (urine from the right ureter on initial cystoscopy) was received the day after surgery; antibiotic treatment was therefore changed to ceftiofur sodium (4.4 mg/kg, iv, q24 h; Excenel® 4g)[11] instead of amoxicillin and continued until day 10 post surgery. The bladder mucosa had a normal cytoscopic appearance 7 days post-operatively. The urine emanating from the right ureter and pooled within the urinary bladder had a normal macroscopic appearance (clear with a normal amber colour). Both ureteral openings were no longer hyperemic and swollen. As expected, left ureteral urine flow was absent. Anti-inflammatory treatment with metamizole was discontinued that day.

Except for a mild seroma at the surgical site observed on day 8 after surgery, which resolved completely following sterile drainage on days 9 and 12, the horse made an uneventful recovery and was discharged from the hospital 18 days after surgery. At the time of discharge the surgical site on the left flank had healed completely. A mild normocytic, normochromic anemia (Table 1) was still present. The owner was advised to continue supplementation with Equistro® Haemolytan 400 to support blood cell production, and to have the mare assessed by the house veterinarian, including a complete blood cell count and urea and creatinine levels once monthly for the following six months, and every six months thereafter if the mare remained in good health.

On follow up two years after the unilateral nephrectomy was performed, the owner reported the mare to be in very good health, with adequate body condition, and haematological and biochemstry examinations within normal limits. Six months after surgery the mare had returned to her normal pre-surgery use as a pleasure riding horse.

Discussion

Clinical signs of renal disease occur in advanced disease stages only, are nonspecific and often include lethargy, inappetence, weight loss and azotaemia (*Geor* 2007, *McLeland* 2015, *Schott II* and *Esser* 2020). Polyuria and polydipsia become apparent when > 75 % of renal tissue function has been lost (*Schott II* 2007, *Schott II* and *Esser* 2020). In the present case polyuria and polydipsia were reported; however, the daily water intake and the daily urine production were not measured. The mare displayed all of the clinical signs described above and bilateral renal disease was initially suspected. Although azotemia was present, the mare did not show possible severe consequences of uraemia such as multiple organ dysfunction. Therefore, recent, acute or subacute disease progression was thought likely, which is consistent with the sudden worsening in the horse's condition reported by the owner over the weeks preceding presentation to the clinic.

Complete blood count (CBC) and serum biochemistry (SBC) on the day of presentation revealed a mild leukocytosis due to mild neutrophilia, marked azotaemia and hypercalcaemia. Azotaemia can be caused by pre-renal, renal or post-renal problems (*Geor* 2007). Pre-renal azotaemia is most often due to hypovolemia and dehydration. Renal problems leading to azotaemia include glomerular diseases, tubulointerstitial diseases, (uretero)pyelonephritis, urolithiasis in the renal pelvis, neoplasia and congenital anomalies such as renal dysplasia, hypoplasia, polycystic kidney disease and horseshoe kidney (*McLeland* 2015). Post-renal azotaemia is most frequently seen in association with urolithiasis, inflammation, neoplasia or other diseases of the ureters, urinary bladder

or urethra (*Reed* et al. 2004). When a renal problem is suspected based on clinical signs, blood analysis, ultrasonography and abdominal palpation per rectum, a renal biopsy can aid in establishing a more accurate diagnosis (*Tyner* et al. 2011, *Hussein* et al. 2018). However, renal biopsy sampling is not without its risks, with reported complications such as haemorrhage and signs of colic in 11.3% of horses (similar to humans and companion animals; *Tyner* et al. 2011). Furthermore, only 72% or fair agreement between histopathological findings of biopsy specimens compared to postmortem findings has been reported (*Tyner* et al. 2011). Therefore, renal biopsy should only be performed when the benefits of the limited information it provides outweigh the risks and are truly necessary to guide further treatment and patient management decisions (*Tyner* et al. 2011). In our case the results of ultrasonography, cystoscopy, and separate urinalysis, cytology and bacteriological culture from both ureters, together with the response of the horse to medical treatment, led to the diagnosis of bilateral bacterial pyelonephritis and pyuria, and left hydronephrosis and ureteritis.

Hypercalcaemia in the presence of azotaemia, as seen in this horse, is consistent with CKD. In horses, concurrent azotaemia and hypercalcaemia, is considered to be pathognomonic for CKD (*LeRoy* et al. 2011, *Schott II* and *Esser* 2020). Horses with CKD have significantly higher serum calcium concentrations than horses with AKI (*LeRoy* et al. 2011). It has been suggested that urinary calcium excretion is reduced in horses with CKD (*Schott II* 2007), although the exact pathogenesis for hypercalcaemia in horses with CKD remains unknown (*LeRoy* et al. 2011). The low specific gravity of ureteral urine from both kidneys was consistent with the observed polyuria and polydipsia and was also compatible with the diagnosis of CKD. However, urinary specific gravity in a sedated horse is not reliable due to the known diuretic effects of alpha 2 receptor agonists, and must therefore be interpreted with caution.

Usually palpation of the urinary system per rectum in a healthy adult horse only allows for the caudal pole of the left kidney and the urinary bladder to be palpated, while the right kidney, both ureters and the urethra usually are not palpable. In this mare, the caudal pole of the left and of the right kidney, as well as the left ureter could be palpated. Normal equine ureters have a diameter of 6–8 mm (*Donawick* and *Uhlmann* 1998), therefore, they can only be palpated transrectally when they are enlarged or dilated due to an obstructive disease (*Carr* 2003). In our case the left ureter most likely had been dilated secondary to vesicoureteral reflux, which likely developed secondary to urinary stasis and bladder dilatation following urethral obstruction by the reported cystolith.

On transabdominal ultrasound examination the margins of the left kidney could not be distinguished and complete disruption of the tissue architecture was apparent, with only fluid-filled cavities within a thick capsule observed in the area of the normal acoustic window of this organ. These findings are consistent with hydronephrosis and characteristic of the structural changes that occur in a kidney with pyelonephritis, including decreased renal length, increased echogenicity, loss of corticomedullary distinction and pyelectasia (*Kisthardt* et al. 1999, *Bouillon* et al. 2018).

Cystoscopy before surgery revealed mucosal thickening around the left and right ureteral orifices, which had completely resolved upon reassessment one week following unilateral left-sided nephrectomy. In urine from the right ureter the fractional excretion of sodium and chloride, as well as the urinary GGT and the urinary GGT:creatinine ratio were within normal limits. As fractional excretion of sodium and chloride, and urinary GGT:creatinine ratio are indicators of renal tubular integrity and sensitive markers of active renal tubular disease (*Ferguson* et al. 2007, *Schott II* and *Esser* 2020), a normal function of the right kidney was presumed following initial antibiotic and fluid therapy with subsequent normalization of serum creatinine and urea concentrations. Normal function of the remaining kidney is a prerequisite for a successful outcome after unilateral nephrectomy (*Reed* et al. 2004, *Ferguson* et al. 2007). Unfortunately, urinalysis was not performed after surgery. A second urinalysis could have confirmed the health status of the right kidney, and a negative bacteriological examination could have guided cessation of antibiotic administration. However, the clinical improvement in the mare corroborated the sufficient function of the right kidney. The enzyme GGT is found in large quantities in the brush border of proximal tubular epithelial cells in the cortex of the kidney (*Geor* 2007, *Schott II* and *Esser* 2020). The urinary GGT:creatinine ratio is a sensitive indicator of tubular cell damage and necrosis (*Ferguson* et al. 2007), and a value > 25 is indicative of renal tubular disease (*Lameire* et al. 2005, *Geor* 2007, *Schott II* and *Esser* 2020) - as it was the case for the left kidney, but not the right, in our patient. As fractional excretion of electrolytes, urinary GGT and the urinary GGT:creatinine ratio was abnormal for urine from the left ureter, and the transabdominal ultrasonography demonstrated complete disruption of the parenchyma of the left kidney, a working diagnosis of chronic ureteropyelonephritis unresponsive to medical treatment was made and unilateral left-sided nephrectomy with the expectation of enabling the mare to live a normal life in terms of renal function after surgery was recommended. The left kidney could successfully be removed using a standing hand-assisted laparoscopic technique (*Rijkenhuizen* 2008).

Indications for unilateral nephrectomy include unilateral pyelonephritis, hydronephrosis, abscessation, neoplasia, nephrolithiasis, ureterolithiasis, ureteropelvic polyps, renal parasitic lesions, rupture of the renal capsule because of trauma, renal dysplasia, idiopathic renal haematuria and ectopic ureters (*Lilich* et al., 2006, *Ferguson* et al. 2007, *Rijkenhuizen* 2008, *Arnold* et al. 2013). Standing hand-assisted laparoscopy allows the surgeon a very good three-dimensional assessment using a combination of visual and tactile information, and enables the use of a modified minimally invasive surgical approach. In most cases where this approach is used, the duration of hospitalisation, the time to return to work and the risk of peritonitis are reduced compared to patients undergoing celiotomy (*Cokelare* et al. 2007). Complications described using the standing, hand-assisted laparoscopic approach include intra-operative bleeding from accessory branches of the renal artery if they are not well ligated before transection (*Keoughan* et al. 2003) and incisional seroma formation (*Röcken* et al. 2007). Our case developed a seroma at the left flank

incision, however, this was classified as a minor complication as it resolved following two sterile aspirates on days 9 and 12 post-surgery. *Arnold* et al. (2013) described a nephrectomy technique using a ventral median celiotomy approach. The main disadvantage of that technique is a very long surgery and anaesthetic time of 4 hours.

Bacteria isolated in diseases of the urinary system can include *Streptococcus equi* subspecies *zooepidemicus* and subspecies *equi*, *Staphylococcus* spp., *Escheria coli*, *Enterobacter* spp., *Pseudomonas aeruginosa*, *Proteus* spp., *Klebsiella* spp., *Actinobacillus equuli*, *Rhodococcus equi* or *Salmonella Enterica* spp. (*Reed* et al. 2004). In humans the etiologic agent in > 80% of pyelonephritis cases is *E. coli* (*Ramakrishnan* and *Scheid*, 2005). This was also the most common pathogen found in dogs and cats with pyelonephritis (37% of cases in dogs (*Bouillon* et al. 2018) and 39–59% of positive urine cultures in cats (*Dorsch* et al. 2019)). In our case bacteriological examination of urine from the right ureter revealed the presence of *Pseudomonas* species, *Staphylococcus* sp. and *Stenotrophomonas maltophilia*, while no bacteria could be isolated from the pyuria coming from the severely diseased left kidney. In the study of *Bouillon* et al. (2018) 32% of dogs with pyelonephritis did not have bacteriuria. Possible explanations for that finding include administration of antibiotics before taking the urine sample, bacterial adherence to the urothelium and host defence mechanism inhibiting bacteria (*Bouillon* et al. 2018).

Bacteriological culture from the nephrectomised left kidney identified the gram-positive anaerobe *Propionibacterium acnes* (skin flora) and a gram-negative anaerobic bacterium similar to *Prevotella heparinolytica*, which could not be completely identified. In humans the latter can cause urinary tract infections (UTI), respiratory infections or sepsis; in horses it may be associated with chronic lower airway problems. Why those bacteria could not be isolated from the left ureteral urine sample before surgery remains unexplained.

The normocytic, normochromic anaemia in the mare is likely attributable to a shortened lifespan of the erythrocytes due to uraemia (*Schott II* and *Esser* 2020), together with decreased erythropoiesis due to chronic disease and inflammation associated with the severe pyelonephritis (*Lester* et al. 2015). In CKD patients anaemia has been associated with blood loss and nutritional deficiencies, and in humans and small animals it has been linked to a decrease in erythropoietin activity (*Paganini* et al. 1989, *Schott II* 2007).

Pyelonephritis is often a consequence of an ascending UTI secondary to urine stasis due to bladder paralysis, pregnancy, urolithiasis, or urethral stricture (*Rooney* and *Robertson* 1996, *Schott II* 2007, *McLeland* 2015, *Bouillon* et al. 2018, *Dorsch* et al. 2019). The owner had reported that a bladder stone had been successfully removed via a direct urethral approach eight years prior to the onset of the clinical signs that lead to the diagnosis of CKD. As vesicoureteral reflux is a prerequisite for an ascending pyelonephritis (*Reed* et al. 2004), urolithiasis might have resulted in ascending ureteral infection and chronic left-sided pyelonephritis. An ascending, long-standing infection of the left kidney was suspected histopathologically. The inflammation of the renal pelvis had extended into the renal parenchyma, resulting in complete destruction of all renal tissues. Ascending UTI resulting in pyelonephritis and leading to chronic interstitial nephritis finally resulting in CKD has been described (*Schott II* 2007).

Although rare, hematogenous spread from a systemic infection is also possible (*Bouillon* et al. 2018). Haematogenous infection of the kidneys can occur in horses during episodes of bacteraemia associated with other infectious processes such as dental disease, hoof abscesses or endocarditis. In horses with haematogenous septic nephritis *Actinobacillus equuli*, *Streptococcus equi*, *Rhodococcus equi* and *Salmonella* spp. have been isolated (*Reed* et al. 2004).

It is considered likely that the sudden onset and rapid progression of clinical signs in this mare were the result of ascending or, less likely, hematogenous bacterial spread from a chronically affected left kidney into the right kidney. Once the right kidney's health was impacted to such a degree that it reached a functional threshold, clinical signs of renal insufficiency became apparent. Clinical signs of renal disease only become apparent when greater than 75% of renal function has been lost (*Bouillon* et al. 2018, *Schott II* and *Esser* 2020) and an increase in serum creatinine concentration only occurs following a reduction in GFR of more than 75% (*Relford* et al. 2016, *Schott II* and *Esser* 2020). Sudden secondary involvement of the right kidney in the weeks prior to presentation to the clinic offers a plausible explanation for the likely onset of left kidney pathology years earlier, with clinical signs of renal insufficiency becoming apparent only after the right kidney became secondarily affected.

The novel serum kidney biomarker symmetric dimethylarginine (SDMA) is now available for assessment of renal function in horses (*Siwinska* et al. 2020). SDMA is an end product of protein metabolism in all cells. More than 90% of this metabolite is excreted in urine and therefore reflects GFR (*Schott II* and *Esser* 2020). In dogs and cats, SDMA has been validated for detection of renal pathology during the early disease process, as serum levels start to increase when GFR decreases by 40% (*Relford* et al. 2016). Early recognition of renal disease and early detection of disease progression in renal patients is imperative when attempting to avoid further renal damage and monitor the speed of disease progression or regression (*Schott II* and *Esser* 2020). The inclusion of SDMA assessment is therefore advisable in routine equine blood work. In this case it would likely have also been a valuable parameter to use to monitor the horse's remaining kidney function following unilateral nephrectomy. However, more research is required to validate the use of SDMA for early detection of renal disease in asymptomatic equine patients (*Siwinska* et al. 2020, *Gratwick* 2021) and therefore it was not implemented in our therapeutic plan.

Conclusions

Hand-assisted laparoscopic nephrectomy is an effective, safe and minimally invasive surgical technique for unilateral kidney removal that offers an alternative to the formerly performed celiotomy technique with rib resection under general anesthesia (*Röcken* et al. 2007, *Rijkenhuizen* 2008). Normal

function of the remaining kidney is a prerequisite for a successful outcome after unilateral nephrectomy. Measurement of fractional excretion of electrolytes and urinary GGT:creatinine ratio, performed separately in urine from the left and from the right kidney, is useful in the assessment of individual renal function. The novel serum kidney biomarker SDMA may be useful to assess renal function before the onset of clinical signs of renal disease (*Schott II* and *Esser* 2020). After unilateral nephrectomy renally metabolized or excreted drugs must be prescribed only with clear indications and with caution regarding function of the remaining kidney (*Ferguson* et al. 2007).

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Footnotes

[T]Ursolyt®153: hypertonic, isoionic solution containing in mmol/l Na^+ 140; K^+ 5; Ca^{2+} 2.5; Mg^{2+} 1.5; Cl^- 103; Acetat$^-$ 50

Manufacturers' addresses

1 CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany
2 Selectavet Dr. Otto Fischer GmbH, Weyarn-Holzolling, Germany
3 Serumwerk Bernburg, Germany
4 Bela-Pharm GmbH & Co. KG, Vechta, Germany
5 navalis® nutraceuticals GmbH, Filderstadt, Germany
6 Deltamedica GmbH, Reutlingen, Germany
7 Medtronic, Minneapolis, Minnesota, USA
8 Ethicon, Inc., Raritan, New Jersey, USA
9 Norgesplaster AS, Dep. Snoog, Vennesla, Norway
10 Vétoquinol GmbH, Ismaning, Germany
11 Zoetis Deutschland GmbH, Berlin, Germany

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