Received: 26 April 2024 | Accepted: 26 April 2024

DOI: 10.1111/jvim.17101

CONSENSUS STATEMENT

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Consensus Statements of the European College of Equine Internal Medicine (ECEIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ECEIM Board oversees selection of relevant topics, identification of panel members for each topic with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ECEIM membership which may be incorporated into the statement. It is then submitted to the Journal of Veterinary Internal Medicine, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

ECEIM consensus statement on equine kidney disease

Gaby van Galen[1,2] | **Thomas J. Divers**[3] | **Victoria Savage**[4] | **Harold C. Schott II**[5] | **Natalia Siwinska**[6]

[1]Goulburn Valley Equine Hospital, Congupna, Victoria, Australia

[2]Sydney School of Veterinary Science, University of Sydney, Sydney, New South Wales, Australia

[3]College of Veterinary Medicine, Cornell University, Ithaca, New York, USA

[4]Three Counties Equine Hospital, Gloucestershire, United Kingdom

[5]College of Veterinary Medicine, Michigan State University, East Lansing, Michigan, USA

[6]Faculty of Veterinary Medicine, Wroclaw University of Environmental and Life Sciences, Wroclaw, Poland

Correspondence
Gaby van Galen, Goulburn Valley Equine Hospital, Congupna, VIC, Australia.
Email: gaby@equinespecialists.eu

Abstract

The aim of this consensus statement is to summarize and appraise scientific evidence and combine this with the clinical experience of a panel of experts to optimize recommendations on how to recognize and manage kidney disease in horses.

KEYWORDS
acute kidney injury, chronic kidney disease, horse, renal

1 | AZOTEMIA

Azotemia is the term for increased blood concentrations of urea, serum creatinine (sCr), and other nonprotein nitrogenous substances. Prerenal (decreased renal blood flow [RBF], e.g., dehydration, hypovolemic shock, cardiac failure), renal (decreased glomerular filtration rate [GFR] caused by renal injury), or postrenal azotemia (failure of excretion, with urinary tract obstruction or rupture) should be differentiated. Prerenal causes for azotemia are frequently mentioned; however, in the panelists' opinions, many are linked with inflammatory changes, toxic insults, or associated with acute kidney injury (AKI). Furthermore, there is a continuum between prerenal and renal azotemia, where poor perfusion eventually leads to intrinsic kidney damage.

Abbreviations: ^{99m}Tc, 99-metastable technetium; AKI, acute kidney injury; ARF, acute renal failure; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRF, chronic renal failure; DTPA, diethylenetriaminopentaacetic acid; ESKD, end-stage kidney disease; FE, fractional excretion; GFR, glomerular filtration rate; GN, glomerulonephritis; IRH, idiopathic renal hematuria; IRIS, International Renal Interest Society; IVFT, intravenous fluid treatment; NSAIDs, nonsteroidal anti-inflammatory drugs; PD, polydipsia; PPID, pituitary pars intermedia dysfunction; PU, polyuria; RBF, renal blood flow; RTA, renal tubular acidosis; sCr, serum creatinine; SDMA, symmetric dimethylarginine; USG, urine specific gravity.

In horses sCr is freely filtered by the glomerulus and is neither reabsorbed nor secreted.[1] Therefore, sCr is inversely proportional to GFR and a functional marker. In advanced disease, a small decrease in GFR results in a large sCr increase. In early renal disease, a large decrease in GFR results in only a small sCr increase, and sCr does not increase above reference limits until GFR is reduced by nearly 75%.[2] As creatinine is formed by muscle, heavily muscled animals can have sCr values above reference limits.[3,4] In humans, production of creatinine is reduced in sepsis.[5] This has not been demonstrated in horses but could limit detection of AKI in critically ill horses.

Because of the multifactorial influences on blood urea nitrogen (BUN), including dietary protein and protein metabolism, BUN is a less specific estimator of GFR and has not been found useful to diagnose AKI.

2 | RENAL SYNDROMES

2.1 | Acute kidney injury

AKI represents a continuum of inapparent nephron injury or loss to acute renal failure (ARF).

2.1.1 | Prevalence

Prevalence studies in horses are lacking; however, estimates are that 3% to 23% of a hospitalized population are affected (published[6] and unpublished data from panelists).

2.1.2 | Risk factors

Decreased renal blood flow and hypoxia

The kidney is particularly susceptible to ischemic injury, especially the less perfused medulla. Hypotension, dehydration, hypovolemia, or anemia are risk factors for AKI because of decreased RBF and hypoxia.

Systemic inflammatory response syndrome

Systemic inflammation accompanying sepsis and endotoxemia can result in hypotensive injury, renal microcirculatory dysfunction, thrombotic injury, infarction, fibrin deposition, and renal cortical necrosis in horses.[7,8]

Nephrotoxicity

Nephrotoxic agents described in horses include aminoglycosides, oxytetracycline, bisphosphonates, and nonsteroidal anti-inflammatory drugs (NSAIDs). Many other medications, including omeprazole and hydroxyethyl starches, are nephrotoxic in humans; however, there is currently no evidence for this in horses. Endogenous nephrotoxins, such as myoglobin and hemoglobin, can also induce AKI (Table 1).[26,27]

As recognized in humans,[28] foals and geriatric horses are likely at greater risk for nephrotoxic AKI. With hypovolemia, IV fluid treatment (IVFT) should be commenced before, or soon after, administration of potentially nephrotoxic drugs. The panelists agree that clinical judgment should be used to decide if benefits of prompt administration of a potentially nephrotoxic compound before initiating fluid treatment outweigh the risk of AKI. Simultaneous use of several nephrotoxic drugs increases the risk of AKI. In noncritically ill human patients, escalating the burden of nephrotoxic drugs from 2 to 3 more than doubles the risk of developing AKI, and 25% of those receiving 3 or more develop AKI.[29]

Other causes

AKI can be caused by immune-mediated glomerular barrier injury (e.g., purpura hemorrhagica), idiosyncratic hypersensitivity reactions causing acute interstitial nephritis, *Actinobacillus* spp. infections in foals,[30] and leptospirosis.[31]

2.1.3 | Diagnosis

Clinical signs of AKI are often difficult to discern from signs from the primary disease. Careful attention to urine output must be paid to detect oliguria (<0.5 mL/kg/h). Inappetence and lethargy persisting longer than expected as the primary disease resolves should raise suspicion. Neurological signs (uremic encephalopathy) are occasionally seen with severe azotemia.[32]

In human and small animal medicine, scoring systems have been developed to document AKI based on sCr and urine output.[33-35] The Veterinary Acute Kidney Injury system has been applied to hospitalized horses (Table 2).[6] Although unvalidated, the panelists consider scoring systems worth implementing in practice with a focus on *detecting small increases in sCr from baseline even when it remains within reference ranges*.

Electrolyte abnormalities are not present in all cases with AKI but are common in ARF, especially hyponatremia and hypochloremia. Marked hyperkalemia is seen in peracute oliguric/anuric ARF, postrenal obstruction, or uroabdomen. Calcium and phosphorus concentrations are variable.

Measurement of urine output is challenging in adult horses. Collection of a urine sample before IVFT can be helpful to evaluate renal function. With adequate tubular function, urine specific gravity (USG) is increased (>1.035) in hypovolemic states. In ARF, concentrating ability can be lost and urine becomes dilute (USG <1.020) despite hypovolemia. Urinalysis can identify microscopic hematuria, casts and glucosuria.

Panelists do not consider renal rectal palpation a reliable diagnostic tool. Renal ultrasonography is often unremarkable with AKI (see Imaging 3.3). Renal biopsy results rarely alter management of ARF, and biopsy is not recommended by the panelists.

2.1.4 | Treatment

Initial treatment focuses on correcting the primary disorder. Intravenous fluid treatment is the therapeutic cornerstone to normalize intravascular volume and blood pressure, and subsequently RBF and GFR

TABLE 1 Evidence for potential nephrotoxic agents commonly used in equine practice.

Agent	Mechanism of nephrotoxicity	Evidence of nephrotoxicity in humans	Evidence of nephrotoxicity in horses	Panel recommendation, other than cautious use in at risk patients
Aminoglycosides	Accumulation in proximal tubular cells. Caused by sustained drug exposure (frequent dosing), not individual high doses.[9]	Risk factors include age, hypovolemia, preexisting renal dysfunction, combination with furosemide.[10] Gentamicin is more nephrotoxic than amikacin.[11]	Reported.[12] Dosing schedules should be altered in neonates.[13,14]	
Oxytetracycline	Unknown	Rare	AKI caused by high dose for flexural limb deformities in foals[15] and normal antimicrobial doses in adults.	Evaluate sCr before administration of high doses to foals.
NSAIDs	Inhibition of COX blocks renal autoregulatory response to hypoperfusion. Causing medullary crest necrosis and interstitial nephritis.	Uncommon	In healthy horses, phenylbutazone induced medullary crest necrosis with prolonged supraphysiological doses[16] and AKI with normal doses.[17,18] COX2 selective drugs carry a similar[19,20] to lower risk for nephrotoxicity.[18]	NSAIDS, especially phenylbutazone should be avoided in at risk horses.
Bisphosphonates	Proximal tubule degeneration, segmental glomerulosclerosis and apoptosis.	Reported	AKI reported and may be more common with concurrent NSAIDs.[21]	Evaluate sCr before use. Caution with concurrent NSAIDs.
Polymyxin B	Accumulation in proximal tubular cells causes acute tubular necrosis.	Reported. No longer recommended for sepsis.	Reported in hospitalized horses and when coadministered with gentamicin.[22,23]	Avoid concurrent aminoglycosides.
Vitamin D	Hypercalcemia and renal mineralization.	Reported	Toxicity observed in horses fed grain diets high in cholecalciferol.[24]	Avoid supplementation in at risk horses.
Vitamin K3	Renal tubular nephrosis.	Observed, not used in humans.	Toxicity observed clinically and induced experimentally when administered at recommended doses.[25]	Avoid use.

Note: Antimicrobial stewardship should be considered when selecting antimicrobials.
Abbreviations: AKI, acute kidney injury; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; sCr, serum creatinine.

TABLE 2 Veterinary Acute Kidney Injury (VAKI) scoring system for horses (unvalidated).[6]

Stage	Change in serum creatinine from baseline (baseline = 100%)
0	<150%
1	150%-199% *or* absolute increase of >0.3 mg/dL (>26.5 µmol/L)
2	200%-299%
3	300% *or* absolute increase to >4.0 mg/dL (>354 µmol/L)

(see Principles Intravenous Fluid Therapy). For persistent hypotension after adequate fluid replacement, inotropes and vasopressors can be used (Table 3).

Within the initial 24 to 72 hours of treatment of reversible AKI, sCr can be expected to decrease by 30% to 50%. With nephrotoxic AKI panelists have observed that it can take longer for sCr to decline. Urine output during IVFT should be observed. For anuric or oliguric cases, the aim of IVFT is to induce diuresis and polyuria. Failure to produce urine within 12 hours after IVFT is considered a "red flag" for oliguria and patients should be evaluated for obstructive disorders. With oliguria unrelated to obstruction, use of a diuretic agent can be considered (Table 3). A furosemide challenge test can be performed in a euvolemic AKI patient. In human medicine, this test is a predictor of AKI severity and outcome.[43] No further doses are advised unless a favorable response with urine production is witnessed. Mannitol is no longer recommended as it can be nephrotoxic. Supportive evidence for dopamine agonists is weak. Other than IVFT, all other medical

TABLE 3 Therapies to consider for oliguric/anuric acute renal failure.

Drug	Dose	Mechanism of action	Evidence in humans	Evidence in horses	Adverse effects	Consensus for use in foals	Consensus for use in adult horses
Diuretics							
Furosemide	Bolus 0.5-2 mg/kg IV/IM q2h-q6h or CRI 0.25-2 mg/kg/h	Decreases sodium, chloride, and potassium tubular reabsorption.	Induces diuresis but without clinical benefit in AKI.	Unavailable.	High dose can be nephrotoxic. Increase in sCr can occur through tubuloglomerular feedback. Electrolyte disturbances.	Single high dose furosemide test is 1st-line treatment of normotensive foals with anuria/oliguria.	Single high dose furosemide test is 1st-line treatment of normotensive adults with anuria/oliguria.
	Single high dose advised (furosemide test; 2 mg/kg). No further doses unless good response. If positive response switch to CRI.						
Mannitol	0.25-1 g/kg IV q4h-q6h (20% solution).	Increases osmotic pressure in renal tubules.	Associated with increased risk of AKI.	Unavailable.	Osmotic renal tubular injury.	Not recommended.	Not recommended.
Inotropes / vasopressors							
Dobutamine	2–20 μg/kg/min	Beta-1 agonist: inotropic effect.	Beneficial effect on renal function for cardiorenal syndrome.	Increased blood pressure.[36]	Arrhythmias	1st-line treatment for hypotension despite IVFT, and for anesthesia induced hypotension.	Common treatment for anesthesia induced hypotension.
					Not witnessed.[a]		Can be used in selected hypotensive nonanesthetized adults. Limited.[a]
Norepinephrine	0.2-0.3 μg/kg/min	Alpha-1 agonist: peripheral vasoconstriction.	Recommended for treatment and prevention of AKI in humans with distributive shock.	Increased blood pressure in anesthetized horses[37] and critically ill foals.[38] Improved renal function in healthy foals.[39] No evidence in standing horses.	Arrhythmias	Common treatment for hypotension despite IVFT and dobutamine. Usually in conjunction with dobutamine. Interchangeable with AVP.	Possible vasopressor, especially for distributive shock.

(Continues)

TABLE 3 (Continued)

Drug	Dose	Mechanism of action	Evidence in humans	Evidence in horses	Adverse effects	Consensus for use in foals	Consensus for use in adult horses
					Not witnessed.[a]		None in nonanesthetized adults.[a]
Arginine vasopressin (AVP)	0.1-2.5 mU/kg/min	Increase water reabsorption in distal tubule and collecting duct. Vasoconstriction at high doses.	Similar effect to norepinephrine for treatment and prevention of AKI in humans with distributive shock.	Increased blood pressure and urine output in hypotensive foals.[38]	Arrhythmias, hyponatremia	Treatment for hypotension despite IVFT and dobutamine. Usually in conjunction with dobutamine. Interchangeable with norepinephrine.	Possible vasopressor, especially for distributive shock.
					Not witnessed.[a]		None in nonanesthetized adults.[a]
Fenoldopam mesylate	0.04 mg/kg/min	Selective dopamine (D_1) agonist: renal vasodilation.	Not recommended for treating/preventing AKI.	Increased urine output in healthy foals.[40] No additional benefit to renal function when combined to norepinephrine.[39]		Potential treatment for normotensive foals with anuria/oliguria.	Potential treatment for normotensive adults with anuria/oliguria.
						Limited.[a]	None (cost-prohibitive)[a]
Low-dose dopamine	1–5 μg/kg/min	Renal dopamine receptors-agonist: renal vasodilation and natriuresis.	Not recommended for treating/preventing AKI.	Increased renal blood flow and urine production in healthy horses.[41]	Arrhythmias	2nd-line treatment after unsuccessful furosemide challenge in normotensive foals with anuria/oliguria.	2nd-line treatment after unsuccessful furosemide challenge in normotensive adults with anuria/oliguria.
				Anecdotal clinical success in adult horses with oliguric ARF. Oliguria may return when discontinued.	Not witnessed.[a]	Some have moderate experience.[a]	Some have moderate experience.[a]

TABLE 3 (Continued)

Drug	Dose	Mechanism of action	Evidence in humans	Evidence in horses	Adverse effects	Consensus for use in foals	Consensus for use in adult horses
Adenosine antagonists							
Aminophylline	2–5 mg/kg slow IV q8h-q12h	Afferent arteriole vasoconstrictor. Less potent and shorter acting than theophylline.	Lowers sCr in pediatric patients with AKI but without improvement of urine production or outcome.	Induced diuresis in healthy adult horses.[42] Anecdotal success treating oliguric ARF in neonates.	Dose-related tachycardia, tachypnoea and nervous signs.[42]	Potential treatment for normotensive foals with ARF.	Potential treatment for normotensive adults with ARF.
						1 has experience.[a]	None.[a]
Theophylline	8 mg/kg IV q12h	Afferent arteriole vasoconstrictor.	Prophylactic single dose helped prevent AKI in neonates with severe birth asphyxia.	Unavailable.	Dose-related tachycardia, tachypnoea and nervous signs.[42]	Potential prophylactic treatment.	Potential prophylactic treatment.
						None.[a]	None.[a]

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; AVP, arginine vasopressin; CRI, continuous rate infusion; IVFT, IV fluid treatment; sCr, serum creatinine.
[a]Panelists' experience.

treatments for AKI remain unproven because no drug has obtained evidence of improving outcome of AKI/ARF in human clinical trials. In equine medicine, large trials are unlikely, but case reports on treating oliguric ARF can give guidance to treatment decisions.

If oliguric ARF cannot be converted to polyuria, renal replacement (dialysis) can be considered in select cases.[15,44] Peritoneal dialysis has been described[45-47]; its therapeutic success can be questioned in some of these cases as urination was present before dialysis,[47] however, high aminoglycoside concentrations and azotemia were effectively reduced.[46] The panelists recommend consideration of peritoneal dialysis in select cases with persistent oliguria and high blood concentrations of nephrotoxic drugs despite appropriate IVFT. However, the procedure can be challenging, lead to complications and should only be performed in a hospital setting.

2.1.5 | Prognosis

Azotemia has been identified as a poor prognostic indicator when identified secondary to many conditions[48-50] but is often disregarded as "prerenal" instead of being an indicator of AKI. As equine intensive care expands, AKI will likely be increasingly recognized as an outcome-limiting factor. In humans, early detection of AKI, before progression to ARF and need for dialysis, improves patient outcome.[29] Although there are no data for horses, panelists agree that *early detection of AKI likely improves outcome and failure to recognize and manage AKI early can result in ARF*.

Prognosis is largely dependent on success in treating the primary disease process. *Severe increases in sCr do not necessarily equate to a poor prognosis*, and panelists have observed that *response to IVFT is a better prognostic indicator*. If within 72 hours of starting treatment, the patient is producing adequate urine and sCr is decreasing, prognosis can be favorable.[51] Horses with persistent azotemia that remain oliguric or anuric have a guarded to poor prognosis. Prognosis is grave for uremic encephalopathy.[32]

Final sCr may not be reached until 2 to 6 months postinjury, as remaining functional nephrons hypertrophy. If sCr returns to near normal, the horse likely has sufficient renal function for a relatively normal and athletic lifespan. *Despite clinical recovery, affected horses may have residual structural damage and decreased function, which can reduce their tolerance to future insults, and which can eventually progress to chronic kidney disease (CKD).*[52] Based on personal observations of 1 of the panelists on response to treatment in horses with ARF, approximately 60% recover, 30% are euthanized and 10% improve but develop CKD.

2.1.6 | Prevention

In at risk patients, sCr concentration should be closely monitored, primary disease and hypovolemia and hypotension corrected as soon as possible, nephrotoxic drugs used cautiously, and simultaneous use of several nephrotoxic drugs avoided.

Intravenous sodium bicarbonate is often suggested in human medicine to protect against pigment nephrosis through urine alkalinization; however, it has not been shown to be superior to IVFT without sodium bicarbonate.[53] To limit the risk for aminoglycoside induced AKI, IV, or PO calcium (feeding alfalfa or other legume hays can be a practical way to increase calcium intake) and vitamin C administration have been described.[54,55] These treatments are not well documented, are not routinely used by the panelists, and no consensus was reached about them.

2.2 | Chronic kidney disease

CKD is an irreversible, progressive disease of the kidneys, with a duration greater than 3 months. The International Renal Interest Society (IRIS) has developed a staging system for CKD for dogs and cats based on sCr, and a similar system been suggested for horses (Table 4).[56]

2.2.1 | Causes

Anomalies of development

Congenital disorders include renal agenesis, hypoplasia, dysplasia, and polycystic kidney disease. Affected equids are born with decreased renal functional reserve and are at increased risk of developing chronic renal failure (CRF).[57]

Chronic interstitial nephritis

Tubulointerstitial disease is *usually a consequence of acute tubular necrosis* secondary to ischemia or nephrotoxicity[8] and rarely also develops as adverse drug reaction. Subsequent loss of vasculature around tubules coupled with cell cycle arrest can lead to progressive interstitial fibrosis.[52] *CKD may not be recognized for months to years after prior AKI.*

Chronic interstitial nephritis (CIN) can also be caused by ascending urinary tract infection resulting in pyelonephritis.

Nephrolithiasis is commonly found with CIN. Equine nephroliths are almost exclusively composed of calcium carbonate. These crystals can be found in collecting ducts of normal equine kidneys but can deposit and grow at sites of renal parenchymal damage and form nephroliths, which are rarely obstructive. Thus, unlike nephrolithiasis in humans in which obstructive calcium oxalate stones are often the primary problem, the panelists consider nephroliths in horses a consequence of CKD, rather than the inciting cause. However, when bilateral obstructive disease occurs after calcification of necrotic renal papillae and lodging of the stones in the ureters (ureterolithiasis) this can result in chronic interference to urine flow and has been associated with renal failure.[58,59]

Glomerulonephritis

Glomerulonephritis (GN) is initiated by immune-mediated inflammation consequent to deposition of immune complexes along the glomerular barrier. It is commonly recognized with chronic infectious disease (e.g., *Streptococcus equi*[60] and equine infectious anemia virus), but autoimmune glomerular damage can also occur. Glomerulonephritis causes increased glomerular barrier permeability characterized by proteinuria and microscopic (and occasionally macroscopic) hematuria. Focal glomerular disease is a common histopathologic finding consequent to subclinical glomerular injury; however, progression to CRF remains rare.[61] Panelists have observed that GN can occur in patients with infectious disease or vasculitis syndromes but remain unrecognized because of lack of azotemia unless urinalysis is performed revealing hematuria and proteinuria.

Infiltrative causes

Infiltrative causes of CKD include neoplasia (lymphoma, carcinoma),[62] nephroblastoma, amyloidosis, and *Halicephalobus gingivalis*.[63] Occasionally these can lead to CRF.

End-stage kidney disease

End-stage kidney disease (ESKD) describes the final stages of CKD where kidneys are pale, shrunken, and firm, with an irregular surface and adherent capsule. It is often impossible to determine the inciting cause.

2.2.2 | Diagnosis

CKD can be subclinical. The most common clinical signs of CKD progressing into CRF are loss of body condition (86%) and mild to moderate polyuria and polydipsia (PU/PD; 42%).[57] Accumulation of dental tartar, especially on canine teeth, gingivitis, oral and gastro-intestinal ulcers, and decreased performance are other possible findings. Hypertension can be present[64] and panelists recommend measurement of indirect blood pressure. Ventral edema may be noted with GN.

Subclinical stages can be detected incidentally. Most horses usually have moderate to severe azotemia (IRIS stages III and IV) when clinical signs are initially recognized. Sodium and chloride concentrations are often mildly decreased. Hypercalcemia is unique to horses[65] and diet dependent; high values can return to normal within days of changing from legume to grass hay.[66] Concurrent hypophosphatemia is common and not caused by renal secondary hyperparathyroidism.[65] Mild anemia is commonly observed in CKD. Although there is currently no equine literature, based on other species this is most likely multifactorial in nature because of blood loss, decreased erythrocyte survival time, nutritional deficiencies, and decreased erythropoietin production. Proteinuria can cause hypoproteinemia and hypoalbuminemia. Isosthenuria (USG, 1.008-1.014) is a hallmark of CKD, although proteinuria can increase USG.

Small renal size and irregular surface are not always apparent on rectal palpation. Enlarged ureters can sometimes be palpated with ureteroliths. Ultrasound is useful for evaluation of CKD (see Imaging 3.3).

2.2.3 | Treatment

CKD is an irreversible process characterized by progressive decline in GFR and rise in sCr.[29,52] *IVFT is unlikely to reduce azotemia unless there is an AKI component or dehydration exacerbating CKD* (see Principles of

TABLE 4 An equine chronic kidney disease staging system, based on the small animal International Renal Interest Society (IRIS) staging system.

Stage	Serum creatinine concentration	Azotemia	Clinical signs of uremia
Normal	<180 µmol/L (<2.0 mg/dL)	No	Absent
1	<180 µmol/l (<2.0 mg/dL)	No	Some renal abnormalities are present, such as inadequate urinary concentrating ability, abnormalities in urinalysis, abnormal renal palpation or imaging, increasing creatinine in serial samples.
2	180-250 µmol/L (2.0-3.0 mg/dL)	Mild	Mild or absent
3	251-450 µmol/L (3.1-5.0 mg/dL)	Moderate	**Early Stage 3:** absent **Late Stage 3:** mild to moderate
4	>450 µmol/L (>6.0 mg/dL)	Severe	Moderate to severe

Source: Olsen and van Galen.[56]

Intravenous Fluid Therapy). Free access to fresh water is essential. Patients with GN may benefit from corticosteroids. Based on positive effects in people with CKD, treatment with an angiotensin converting enzyme inhibitor (benazepril 1 mg/kg PO; ramipril 0.8 mg/kg PO) could potentially help control blood pressure, attenuate proteinuria, and slow renal fibrosis in horses.[67] The panelists consider that *nephrolith removal is not indicated unless they are a focus of persistent sepsis, a suspected source of pain, or obstruct urine flow*. Erythropoietin administration is not recommended for anemic patients.

Maintaining appetite and body condition is the goal for management of horses with CKD. Access to good quality pasture, increasing carbohydrate intake, and adding fat to the diet can increase caloric intake. Panelists suggest allowing adequate protein access based on monitoring of BUN, BUN/sCr ratio, and serum total protein concentrations. Salt supplementation beyond a normal diet is not recommended by the panelists, as there is no evidence of efficacy, it could exacerbate edema and hypertension and lead to an increase in sCr as observed in other species.[68] For patients with edema or hypertension, a restricted salt diet is recommended. With hypercalcemia, low calcium feeds are recommended (grass hay instead of alfalfa). Omega-3 fatty acids[69] and vitamin E[70] slow progression of CKD in humans and small animals, but benefits are unknown for horses. Quality pasture is an excellent source of omega-3 fatty acids and of vitamin E. Many equine food supplements for renal support are commercially available; there is no evidence of their benefit. In humans with CKD, regular exercise is associated with improved health outcomes.[71]

2.2.4 | Prognosis

Progressive loss of nephron function with CKD precludes successful long-term treatment. Many horses with early CKD can continue in performance, breeding or as companion animals for months to years. In the panelists' experience, as long as sCr remains <4 to 5 mg/dL (<350-440 µmol/L), many maintain a fair attitude, appetite, and body condition. Once sCr exceeds this level, the progression rate typically accelerates and signs of uremia become apparent. *Each horse should be managed on an individual basis* until humane euthanasia becomes necessary.

2.3 | Pyelonephritis

Pyelonephritis is uncommon in horses and is a hematogenous or ascending bacterial infection of the renal pelvis and parenchyma. Predisposing factors are mechanical obstruction or functional impairments of urine flow and cases occur after urolithiasis, recurrent cystitis, bladder paralysis, ectopic ureter, lower urinary tract neoplasia, urinary surgery, and foaling injury to the urethra. Unilateral pyelonephritis is more common than bilateral.

Organisms isolated include *Escherichia coli*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., *Streptococcus* spp., *Staphylococcus* spp., *Pseudomonas aeruginosa*, and *Corynebacterium* spp.[72-76]

Clinical signs include fever, inappetence, lethargy, and weight loss. Renal hemorrhage,[75] sepsis,[72] renal failure,[76] and death can occur. Increased inflammatory markers are common. SCr can be increased or within reference ranges when disease is unilateral. Renal ultrasonography may demonstrate a dilated renal pelvis, distortion of the renal parenchyma, and nephroliths. Cystoscopy can assess the gross appearance of urine flowing from each ureter and allows ureteral urine collection. Urinalysis (including bacteriology and cytology) can confirm infection and whether the disease is unilateral or bilateral.

Empirical antimicrobial choices should consider stewardship, urinary drug concentrations, and nephrotoxicity. *Trimethoprim-sulfonamides are the treatment of choice.*[35,43] *Ongoing treatment should be guided by culture and susceptibility results*. Long-term antimicrobial treatment is often required and can be discontinued after negative culture results and resolution of clinical signs and blood work abnormalities. Panelists recommend repeating a urine culture 2 weeks after

discontinuation of treatment. When treatment of unilateral, nonazotemic, pyelonephritis is unsuccessful, nephrectomy is indicated.

Prognosis ranges from guarded to favorable and depends on underlying cause, concurrent nephrolithiasis (often difficult to cure), and extent of renal damage.

2.4 | Renal hematuria

Hematuria most commonly originates from the lower urinary tract. Hematuria originating from the upper urinary tract can be a consequence of lithiasis, pyelonephritis, neoplasia, drug toxicity (NSAIDs), idiopathic renal hematuria (IRH), and occasionally intense exercise.

Idiopathic renal hematuria is characterized by sudden onset of gross hematuria. Arabian or part-Arabian horses are over-represented, suggesting a genetic predisposition.[77,78] Hematuria can resolve spontaneously but can be followed by recurrent hemorrhage months to years later. A diagnosis is made by exclusion of systemic disease, coagulopathy and other causes of hematuria. Small neoplastic masses can be difficult or impossible to diagnose antemortem and can also cause renal hemorrhage. Cystoscopy confirms that hematuria originates from the upper urinary tract and whether hemorrhage is unilateral or bilateral. Treatment is supportive for acute blood loss. With severe hematuria of unilateral origin, a nephrectomy can be considered. However, in some of the panelists' experience, hematuria from the contralateral kidney can develop within days postprocedure.

2.5 | Renal tubular acidosis

Renal tubular acidosis (RTA) is a rare disorder categorized as Type I (impaired hydrogen excretion by the distal tubule) and Type II (impaired reabsorption of bicarbonate by the proximal tubule).[79] Type IV (impaired excretion of potassium), a mixture of Type I and Type II, and Fanconi syndrome (Type II RTA with widespread proximal tubular dysfunction causing urinary loss of glucose, phosphate, uric acid, amino acids and protein) are also described in horses.[80,81] RTA occurs as a primary disorder, or secondary to kidney injury, systemic diseases, or drug administration.

The predominant clinical features, regardless of type, include anorexia, lethargy, and weakness associated with severe metabolic acidosis. If the condition is chronic, weight loss occurs. *The nearly pathognomonic serum chemistry findings include metabolic acidosis and hyperchloremia with a normal anion gap.*[79] Azotemia is sometimes noted because of dehydration or a predisposing renal injury. Serum potassium concentration is frequently low.[79] Some cases have increased serum parathyroid hormone and 25-hydoxyvitamin D concentrations.[79] Urine is often alkalotic (7.5-9), despite metabolic acidosis, although some cases have acidic urine. Bicarbonate or ammonium chloride challenge tests are used in humans and dogs to determine the RTA type but are rarely used in horses because treatment is identical.

Initial treatment should focus on correcting metabolic acidosis by administering IV sodium bicarbonate.[79] Hypokalemia should be treated with potassium chloride supplementation; further decreases can occur during sodium bicarbonate administration. Most horses with RTA have a favorable clinical response within 24 to 72 hours to treatment.[4] Treatment can then be changed to oral sodium bicarbonate, with or without potassium chloride supplementation depending on appetite and serum potassium concentration. Duration of treatment is unpredictable, but many require treatment for months.[79] RTA can recur, especially with ongoing renal disease.[79]

2.6 | Renal causes for PU/PD

PU/PD is not common in horses, except for temporary iatrogenic causes and pituitary pars intermedia dysfunction (PPID). Physiological causes of PD (>100 mL/kg/day) are hot weather, intense exercise, and lactation. Physiological causes of PU are excessive dietary salt consumption, or iatrogenic causes such as administration of

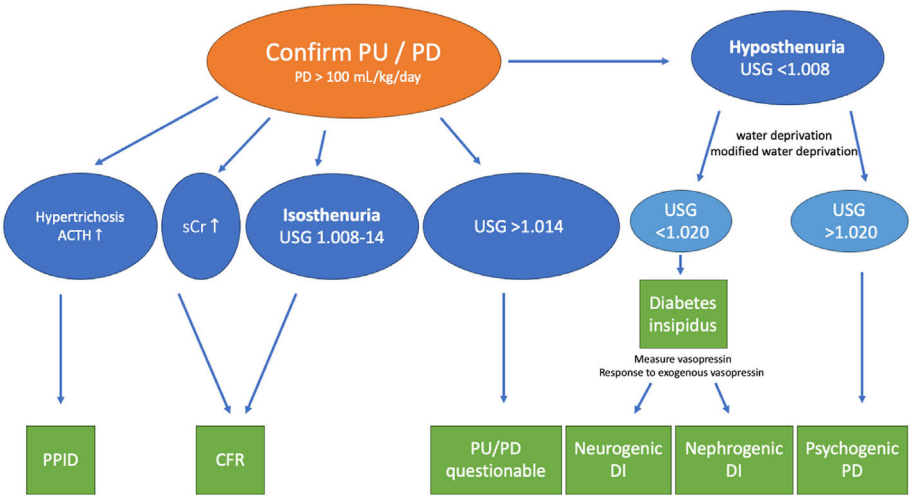

FIGURE 1 Diagnostic approach to polyuria/polydipsia (PU/PD). CFR, chronic renal failure; DI, diabetes insipidus; PPID, pituitary pars intermedia dysfunction; sCr, serum creatinine concentration; USG, urinary specific gravity.

alpha2-agonists, corticosteroids, glucose, diuretics, and IVFT. Pathological causes of PU/PD are as follows:

1. Psychogenic polydipsia: The most common cause and typically the most dramatic PU/PD.
2. Chronic kidney disease.
3. Diabetes insipidus (DI): Neurogenic DI (vasopressin deficiency) or nephrogenic DI (vasopressin insensitivity of collecting ducts).
4. Diabetes mellitus (DM): Chronic hyperglycemia leading to glucosuria. Primary DM is rare in horses.
5. PPID: The mechanism of PU/PD in PPID is currently unclear. Overall, 31% of PPID horses had PU/PD in 1 study[82]; however, this is likely underreported.
6. Sepsis and endotoxemia.
7. Hepatic insufficiency: Although described in literature and anecdotally reported, panelists have not recognized this as a cause of PU/PD.

Medullary washout is a commonly described phenomenon with PU/PD and could occur after psychogenic polydipsia, IVFT, or sepsis. The panelists are unaware of documentation of medullary washout in horses because of inability of measuring medullary osmolality.

The diagnostic approach to PU/PD includes blood and urine analyses and water deprivation tests (Figure 1).

Psychogenic polydipsia is treated by water intake restriction, slow feeding, and reducing boredom. Neurogenic DI has been treated with hormone replacement (desmopressin acetate),[83,84] but there are no reports of treatment of nephrogenic DI in horses.

2.7 | Foal specific renal problems

Neonatal kidneys receive less RBF than adult kidneys, although being a larger percent body mass.[85] However, GFR is similar to that of adult horses.[86] In normal foals, BUN and sCr are variable and often above the adult reference range at birth but return to adult reference ranges within 24 to 72 hours. Low BUN and sCr values are normal in nursing foals because of high fluid intake. Urination is expected within 12 hours of birth. Initial USG is variable, but urine rapidly becomes hyposthenuric (<1.008). Urine pH is neutral and passive transfer of colostral antibodies can cause proteinuria in the first 24 to 72 hours.

AKI in foals follows similar principles as in adults. It can occur as isolated organ dysfunction, secondary to sepsis, periparturient hypoxia, nephrotoxicity, or a combination of these factors. Foals can be lethargic, with fluid retention resulting in subcutaneous edema, most commonly in axillary or inguinal regions. In humans, a *higher proportion of oliguric/anuric AKI* is seen in neonates than adults, and the panelists also recognize this in horses. *Electrolyte derangements in foals with ARF are more common and often more severe than in adults* and severe hyponatremia can result in encephalopathy.[87] Measuring urine output is feasible via a closed urinary collection system; however, catheterization can lead to ascending infection. Treatment of foals with AKI should focus on maintaining effective circulatory volume and RBF without fluid overload while correcting acid-base and serum electrolyte abnormalities and allowing renal tissue time to repair (see Principles of Intravenous Fluid Therapy; and Table 3). In neonates with ARF and persistent oliguria, panelists find dialysis more feasible than in adult horses.[31] Panelists consider AKI affected foals at risk for developing CKD later in life.[52]

Failure to urinate, azotemia, or both do not equate to AKI in all neonates. Congenital abnormalities, uroperitoneum or a dysfunctional bladder as a component of perinatal asphyxia syndrome can be confused with oliguria because of ARF. Spurious hypercreatininemia reflects placental insufficiency or maternal renal failure, with in-utero fetal accumulation of nitrogenous products.[88] Azotemia, at times with sCr up to 20 mg/dL (1770 µmol/L), is found with this syndrome. *As the foal's kidney function is normal, electrolyte concentrations are normal in spurious hypercreatininemia, and sCr typically drops without IVFT by >50% in the first 24 hours providing the foal is adequately nursing*. Although the term "spurious" is used to describe this syndrome, panelists consider this syndrome to include a range of mild to severe azotemia. Therefore, they *suggest a new name focusing on pathophysiology: "materno-placental induced neonatal azotemia."*

Further investigation of oliguria and azotemia in neonates includes transabdominal ultrasonography (renal presence, size and structure, bladder size, free abdominal fluid volume), serum biochemistry, and urinalysis. An increased BUN relative to sCr can be caused by increased gastrointestinal protein absorption with gastrointestinal ulceration or enterocolitis.

Regardless of cause, *azotemia in sick foals has been associated with lower survival rates*,[89,90] *although in the panelists experience many azotemic foals can be managed with favorable outcomes*.

3 | DIAGNOSTICS

3.1 | Conventional diagnostics

SCr remains the recommended biochemical test to estimate GFR; BUN is unreliable. SCr results should be interpreted based on laboratory reference ranges, body condition, age, breed and sex of the horse.

Stall side urinalysis can be performed with reagent test strips and refractometer analysis (USG). In select cases biochemical testing (protein, creatinine, gamma-glutamyl transferase), as well as microscopic sediment evaluation, can be pursued (Table 5).

Fractional excretions (FE) assess tubular reabsorption of electrolytes.[91] When azotemia is present, normal sodium and chloride FE support a prerenal cause, whereas higher values occur with tubular dysfunction. *Fractional excretions have limited diagnostic value once IVFT has started.*

$$FE_{el} = U_{el}/P_{el} \times P_{Cr}/U_{Cr} \times 100\%,$$

where U_{el}, urinary electrolyte concentration, P_{el}, plasma/serum electrolyte concentration, U_{Cr}, urinary creatinine concentration, P_{Cr}—sCr.

Normal: Na <1%, Cl <1.7%, and K 24% to 75%.

3.2 | Novel biomarkers

Data on novel biomarkers of renal function or injury in horses is limited and restricted to AKI (Table 6).

Serum symmetric dimethylarginine (SDMA; a functional biomarker) and sCr concentrations are highly correlated, but *superiority of SDMA over sCr to support changes in GFR in horses has not been documented.*[93,94] Measurement of SDMA is currently *not recommended in foals less than 6 months of age* because of lack of established reference ranges.[92] As SDMA is not affected by muscle mass, it could prove to be more accurate to assess GFR in heavily muscled horses with sCr above reference ranges.

Biomarkers for glomerular and tubular injury, such as cystatin C,[95] podocin,[96] neutrophil gelatinase–associated lipocalin[95,97] and N-acetyl-β-d-glucosaminidase[99] show potential as early indicators of kidney injury, but more research is needed, and assays are not commercially available. *No novel biomarkers currently replace conventional biomarkers of kidney function or injury.*[92]

3.3 | Imaging

With AKI, kidneys may be normal in size (15-18 cm in length for Thoroughbreds)[100] or enlarged. Abnormalities of parenchymal detail are often not detected but can include diffuse or focal increased echogenicity of the renal cortex and (rarely) subcapsular edema. With CKD, especially ESKD, kidneys are usually small, have increased echogenicity, and may have nephroliths or cystic cavitation. Doppler assessment of intrarenal blood flow can be performed, also allowing measurement of renal resistive index. Doppler studies are time consuming, require skill, and results are unlikely to change patient management.[101]

Nuclear scintigraphy can be performed with radiopharmaceuticals labeled with 99-metastable technetium (^{99m}Tc). When ^{99m}Tc is tagged to diethylenetriaminepentaacetic acid (DTPA), both disappearance of ^{99m}Tc-DTPA activity in serial blood samples and sequential gamma camera images of the kidneys can be used to assess GFR.[102] Scintigraphy with ^{99m}Tc tagged to mercaptoacetyltriglycine can evaluate individual kidney function in horses with suspected unilateral disease.[103]

Computed tomography provides excellent anatomical detail. Patient size and requirement for general anesthesia restrict its use.

Endoscopic viewing of the ureteral openings can determine if hematuria or pyuria originates from 1 or both kidneys and ureteral catheterization allows urine sampling from each kidney. Smaller diameter endoscopic equipment (6 mm or less outer diameter) allows ureteroscopy and pyeloscopy. When ureteral orifices are damaged and open, a larger diameter endoscope can sometimes be advanced to the renal pelvis.[104]

3.4 | Renal biopsy

Although renal biopsies have a low reported mortality (0.6%) in horses, complications were observed in 11.3%, and include colic signs (likely associated with perirenal hemorrhage) and hematuria. Occasionally hemorrhage is severe.[105] In humans, hypertension is a risk factor for hemorrhage.[106]

As compared with humans often suffering from glomerular disease for which renal biopsy can yield a definitive diagnosis and prognostic information, renal biopsy is rarely helpful in horses with predominantly tubulointerstitial disease. *Panelists do not recommend renal biopsy for routine evaluation of either AKI or CKD and agree it should only be performed when information gained from the biopsy could change patient management or prognosis*. Renal biopsy technique is described elsewhere in detail.[105]

4 | TREATMENT AND PREVENTION

4.1 | Principles of Intravenous Fluid Therapy (IVFT)

The goals of IVFT in patients with AKI are (1) to establish and maintain euhydration, circulatory volume, and RBF, (2) to replace ongoing fluid loss, and (3) to promote diuresis. In patients with stable CKD, azotemia may have been present for weeks to months and diuresis is established (polyuria). Therefore, if the patient is drinking adequately, IVFT might not be needed or indicated. *Intravenous fluid treatment in horses with CKD is unlikely to reduce azotemia unless there is an AKI component or dehydration exacerbating CKD*.

Fluid selection warrants consideration. In human medicine, 0.9% saline remains a common initial choice as it does not contain potassium. Because hyperkalemia is less common in horses, except for foals, *polyionic replacement solutions are a reasonable choice*. Furthermore, the large amount of chloride administered with 0.9% saline can worsen GFR.[107]

Maintenance rates of IVFT (2-3 mL/kg/h) typically induce increased output of dilute urine. Thus, unless additional fluid requirements are identified, maintenance rates or slightly more are sufficient. Overzealous IVFT should be avoided as it can lead to renal interstitial edema, worsening rather than improving RBF and GFR.[108,109] Large volume IVFT also presents a large sodium load. Because sodium is eliminated slower (days) compared to water (minutes to hours), a sodium load can result in edema formation.[108,109] *It is the panelists strong opinion that avoidance of fluid overload should receive the same consideration as providing adequate fluid support*.

Panelists agree that in most cases, *IVFT is only needed short-term and not until azotemia fully resolves*. Once euhydration is achieved, appetite improves, voluntary drinking returns, and sCr has appreciably declined, there is little benefit to continuing IVFT. SCr might not return to normal values within a few days in all cases, and can even increase slightly after discontinuation of IVFT because of return of intravascular volume to normal.

TABLE 5 Urinalysis testing and interpretation.

Parameter	Analysis method	Reference value	Abnormalities	Process	Suggestive of (not exhaustive listing)	Next diagnostic step
USG	Refractometry	Adults: 1.025-1.040 Foals: <1.025	Hyposthenuria (<1.008)	Water excretion.	Psychogenic polydipsia; diabetes insipidus; medullary washout.	WDT, if needed followed by modified WDT. Measure plasma AVP concentration after negative WDT. Response to administration of exogenous AVP.
			Isosthenuria (1.008–1.014)	No excretion, no concentration.	CKD (USG is more variable with AKI)	Further renal diagnostics.
			Concentrated (USG may vary; more concentrated than plasma)	Ability to concentrate urine.	Normal renal function or dehydration.	Assess hydration status.
pH	Reagent strip	Adults: 8–9 Foals: <8	Aciduria (pH <7)	Potassium deficiency and increased excretion hydrogen in distal tubules. Urinary excretion of methylenecyclopropyl acetic acid (atypical myopathy). Systemic or local acid production.	Strenuous exercise; diet; metabolic acidosis (alkaline urine with severe metabolic acidosis can be suggestive of renal tubular acidosis); bacteriuria; anorexia; atypical myopathy.	Blood analysis; blood gas analysis; urine culture.
Protein Urine protein to creatinine ratio	Biochemistry analyzer (or reagent strip) Biochemistry analyzer	<100 mg/dL <0.5	Proteinuria	Damage to glomerular filtration membrane; reduced reabsorption in tubules; protein excretion.	Glomerular injury; bacterial infection; hematuria; post colostrum absorption; postexercise; false reagent strip results.	Blood analysis; urine culture; further diagnostics for hematuria and glomerular injury.
Glucose	Reagent strip or biochemistry analyzer	Not present	Glucosuria	Hyperglycemia; tubular damage.	Diabetes mellitus; endotoxemia; iatrogenic (glucose/dextrose, steroids, alpha-2-agonists, sodium glucose cotransporter 2 inhibitor); Strenuous exercise.	Blood glucose analysis; evaluation of tubular injury.
GGT or GGT to urinary creatinine ratio	Biochemistry analyzer	GGT/uCr <25 U/g	Enzymuria	Leakage from proximal tubular brush border cells.	Tubular damage (mostly nephrotoxic insults).	Evaluation of tubular injury.
RBC	Microscopic sediment or reagent strip	5000 RBC/mL or <5 RBC/hpf	Hematuria Microscopic: 10 000-2 500 000 RBC/mL or 10-20/hpf	Bleeding from urinary tract.	Bacterial infection; uroliths; cystitis;	Further diagnostics of hematuria; urine culture.

(Continues)

TABLE 5 (Continued)

Parameter	Analysis method	Reference value	Abnormalities	Process	Suggestive of (not exhaustive listing)	Next diagnostic step
	Note: reagent strips do not distinguish between hemoglobin and myoglobin.		Macroscopic: >2 500 000-5 000 000 RBC/mL or approximately 0.5 mL of blood per liter of urine		idiopathic renal hemorrhage; neoplasm; parasite migration; iatrogenic (catheterization, nephrotoxic drugs); strenuous exercise. Note: red coloration on snow or shavings can occur physiologically because of pyrocatechin.	
WBC	Microscopic sediment	<5 WBC/hpf	Pyuria: >5 WBC/hpf	Inflammation or infection.	Bacterial infection (pyelonephritis, septic nephritis); Inflammation; Uroliths; Neoplasm.	Urine culture; Urinary tract ultrasonography and endoscopy.
Casts	Microscopic sediment	Absent	Casts formed off the following: hyaline, myoglobin, WBC, RBC, tubular epithelial cells.	Protein and cells aggregate after tubular damage or high concentration.	Renal pathology (tubular/glomerular injury, pyelonephritis); hematuria; pyuria; hemolysis; rhabdomyolysis.	Further diagnostics of renal disease; blood analysis.
Crystals	Microscopic sediment	Normal	Crystalluria	Physiological process.	Physiological (crystalluria or visible sedimentation does not equal presence of a stone or pyuria). Less abundant with acidic or dilute urine. More abundant in bladder paralysis syndromes.	If abundant: neurological examination, endoscopy.

Note: Systemic and lower urinary tract–induced findings are included in this table but are not further discussed in the article.

Abbreviations: AKI, acute kidney injury; AVP, arginine vasopressin; CKD, chronic kidney disease; GGT, gamma-glutamyltransferase; hpf, high powerfield; RBC, red blood cell; USG, urine specific gravity; WBC, white blood cell; WDT, water deprivation test.

TABLE 6 Novel biomarkers of renal function and injury investigated in horses.[92]

Biomarker		Characteristics	Cause of increase	Sample type	Evidence in humans and small animals	Evidence in horses	Reference value for horses	Availability for commercial/ clinical use
SDMA	Symmetric dimethylarginine	Endogenous, methylated form of arginine.	Renal dysfunction or GFR decrease.	Serum	Early detection of CKD.	Higher in azotemic than in nonazotemic horses.[93]	Adults: <14-19 µg/dL[4,93] or <0.8 µmol/L[94] Foals: ND (>adults)	Yes
Cystatin C		Cysteine protease inhibitor.	Renal dysfunction or GFR decrease.	Plasma /serum	Early detection of AKI.	Higher in horses with AKI, and at AKI risk than in healthy horses.[95]	ND	No
Podocin		Maintenance protein for glomerular podocytes (glomerular barrier).	Podocyte damage.	Urine	Promising diagnostic tool for glomerular diseases.	Higher in horses with AKI than healthy horses.[96]	ND	No
NGAL	Neutrophil gelatinase–associated lipocalin	Lipocalin protein.	Tubular damage.	Serum / urine	Early detection of AKI. Indicator of degree of damage.	Increase with azotemia. Potential to detect AKI earlier than sCr.[95,97]	ND	No
MMP-2, MMP-9	Matrix metalloproteinase 2 and 9	Zinc-dependent proteinases (remodeling extracellular matrix).	Damage to tubules or glomeruli.	Urine	Early detection in some nephropathies.	Effectiveness of use not confirmed.[98]	ND	No
NAG	N-acetyl-β-d-glucosaminidase	Lysosomal protein of proximal tubules.	Tubular damage.	Urine	Early detection of AKI. Correlation with severity of lesions.	Higher in azotemic than in nonazotemic horses.[99]	ND	No

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; ND, not determined or lack of sufficient data; sCr, serum creatinine.

4.2 | Drug adjustments

If drugs that are primarily eliminated or metabolized by the kidney are used in horses with AKI or CKD, toxic serum and tissue concentrations can be reached because of impaired renal function. To avoid systemic or renal toxicity, drug dosage or interval adjustments might be indicated. Adjustments are often needed for nephrotoxic drugs and occasionally for non-nephrotoxic drugs (e.g., digoxin, amphotericin, enalapril, sotalol, morphine, pregabalin, levetiracetam, acyclovir, and quinidine).

For concentration dependent antibiotics (aminoglycosides), prolonging the interval between doses to equal the estimated percentage decrease in GFR is preferred. For most other potentially toxic drugs, including some time dependent antibiotics (oxytetracycline), a decrease in dosage is preferred.[110] A reduction in a loading dose is rarely recommended.[111]

Before adjustments, risk of toxicity without adjustment versus risk of subtherapeutic dosing, especially for antimicrobials, should be considered. Therapeutic drug monitoring can be useful to monitor plasma drug concentrations, especially when clinical effects or toxicity are related to plasma drug concentrations (e.g., aminoglycosides).

These adjustments are most appropriate for horses with CKD; rapid changes in GFR with AKI/ARF make drug adjustments difficult.

4.3 | Limiting further renal damage

In patients with existing renal disease, it is important to *avoid further insults to the kidney*. The panelists recommend avoiding use of potentially nephrotoxic drugs (Table 1). Drugs with a similar therapeutic effect but lower nephrotoxicity can sometimes be selected. If nephrotoxic drugs are needed, not exceeding recommended drug dosages, using the lowest effective dose, shortening duration of use, avoiding use during hypovolemia or dehydration, and avoiding simultaneous use of multiple nephrotoxic drugs are recommended.

Recent studies in cats and humans suggest NSAIDs may not worsen progression of CKD and could be appropriate medications for treatment of concurrent osteoarthritis.[112] The panelists support judicious use of NSAIDS, preferring cyclooxygenase-2 selective agents, in patients with CKD if treatment could improve quality of life. There is weak evidence in humans that misoprostol reduces the risk of NSAID-induced kidney injury.[113]

4.4 | Future therapeutics

Temporary renal replacement treatment has infrequently been performed in horses with unresponsive oliguric/anuric ARF[15,44] and will in the future likely be used in a more expanded manner.

For CKD, except for controlling hypertension, there are no proven medical treatments that effectively prevent progression of fibrosis, but several medications are currently the subject of experimental investigation.[67] In humans with CKD, sodium glucose cotransporter 2 inhibitors slow the decline in GFR and decrease proteinuria[114]; this effect should be evaluated in horses. Also, renal or artificial kidney transplants can be expected.

ACKNOWLEDGMENT

No funding was received for this study. The authors acknowledge the important work that has been done by other authors on the topic of equine kidney disease.

CONFLICT OF INTEREST DECLARATION

Harold C. Schott, II has accepted funding from IDEXX for research on symmetric dimethylarginine. No other authors declare a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

The authors have taken antimicrobial stewardship principles into account for antimicrobial treatment suggestions in this manuscript and strongly advise clinicians to consider stewardship for antimicrobial drug selection.

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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

ORCID

Gaby van Galen https://orcid.org/0000-0002-0689-7141
Thomas J. Divers https://orcid.org/0000-0001-7125-636X
Victoria Savage https://orcid.org/0000-0003-0654-8627
Harold C. Schott II https://orcid.org/0000-0002-7728-5409
Natalia Siwinska https://orcid.org/0000-0002-5205-5826

REFERENCES

1. Finco DR, Groves C. Mechanism of renal excretion of creatinine by the pony. *Am J Vet Res*. 1985;46:1625-1628.
2. Osborne CA, Polzin DJ. Azotemia: a review of what's old and what's new. I. Definition of terms and concepts. *Compend Contin Educ Pract Vet*. 1983;5:497.
3. Baxmann AC, Ahmed MS, Marques NC, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol*. 2008;3:348-354.
4. Schott HC 2nd, Gallant LR, Coyne M, et al. Symmetric dimethylarginine and creatinine concentrations in serum of healthy draft horses. *J Vet Intern Med*. 2021;35:1147-1154.
5. Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol*. 2009;20:1217-1221.
6. Savage VL, Marr CM, Bailey M, Smith S. Prevalence of acute kidney injury in a population of hospitalized horses. *J Vet Intern Med*. 2019;33:2294-2301.
7. Cotovio M, Monreal L, Armengou L, Prada J, Almeida JM, Segura D. Fibrin deposits and organ failure in newborn foals with severe septicemia. *J Vet Intern Med*. 2008;22:1403-1410.
8. Divers TJ, Whitlock RH, Byars TD, Leitch M, Crowell WA. Acute renal failure in six horses resulting from haemodynamic causes. *Equine Vet J*. 1987;19:178-184.
9. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. *Kidney Int*. 2011;79:33-45.
10. Fabrizii V, Thalhammer F, Horl WH. Aminoglycoside-induced nephrotoxicity [German]. *Wien Klin Wochenschr*. 1997;109:830-835.

11. Lerner SA, Schmitt BA, Seligsohn R, Matz GJ. Comparative study of ototoxicity and nephrotoxicity in patients randomly assigned to treatment with amikacin or gentamicin. *Am J Med*. 1986;80:98-104.
12. Riviere JE, Traver DS, Coppoc GL. Gentamicin toxic nephropathy in horses with disseminated bacterial infection. *J Am Vet Med Assoc*. 1982;180:648-651.
13. Bucki EP, Giguère S, Macpherson M, Davis R. Pharmacokinetics of once-daily amikacin in healthy foals and therapeutic drug monitoring in hospitalized equine neonates. *J Vet Intern Med*. 2004;18:728-733.
14. Burton AJ, Giguère S, Warner L, Alhamhoom Y, Arnold RD. Effect of age on the pharmacokinetics of a single daily dose of gentamicin sulfate in healthy foals. *Equine Vet J*. 2013;45:507-511.
15. Vivrette S, Cowgill LD, Pascoe J, Suter C, Becker T. Hemodialysis for treatment of oxytetracycline-induced acute renal failure in a neonatal foal. *J Am Vet Med Assoc*. 1993;203:105-107.
16. MacAllister CG. Effects of toxic doses of phenylbutazone in ponies. *Am J Vet Res*. 1983;44:2277-2279.
17. Costa LRR, Swiderski C, Palm C, Aleman M. Preliminary evaluation of hepatitis a virus cell receptor 1/kidney injury molecule 1 in healthy horses treated with phenylbutazone. *J Vet Emerg Crit Care (San Antonio)*. 2023;33:481-486.
18. Kunkle BN, Saik JE, Attebery DK, Targa NL, Larsen DL, Hanson PD Effects of firocoxib and phenylbutazone dosed for 42 days in horses. In: proceedings of American Association of Equine Practitioners (AAEP); 2010:54.
19. White JM, Colbath AC, Schott HC 2nd. Effects of phenylbutazone, firocoxib, and dipyrone on the diuretic response to furosemide in horses. *J Vet Intern Med*. 2023;37:2544-2551.
20. Raidal SL, Hughes KJ, Charman AL, Nielsen SG, Phillips JK, Noble GK. Effects of meloxicam and phenylbutazone on renal responses to furosemide, dobutamine, and exercise in horses. *Am J Vet Res*. 2014;75:668-679.
21. Edwards L, Magdesian KG. Retrospective evaluation of acute kidney injury in horses treated with nonnitrogenous bisphosphonates (2013-2020): 8 cases. *J Vet Emerg Crit Care (San Antonio)*. 2023;33:685-695.
22. van Spijk JN, Beckmann K, Wehrli Eser M, et al. Preliminary investigation of side effects of polymyxin B administration in hospitalized horses. *Antibiotics (Basel)*. 2023;12:12.
23. van Spijk JN, Beckmann K, Wehrli Eser M, et al. Adverse effects of polymyxin B administration to healthy horses. *J Vet Intern Med*. 2022;36:1525-1534.
24. Harrington DD, Page EH. Acute vitamin D3 toxicosis in horses: case reports and experimental studies of the comparative toxicity of vitamins D2 and D3. *J Am Vet Med Assoc*. 1983;182:1358-1369.
25. Rebhun WC, Tennant BC, Dill SG, King JM. Vitamin K3-induced renal toxicosis in the horse. *J Am Vet Med Assoc*. 1984;184:1237-1239.
26. Norman TE, Chaffin MK, Johnson MC, Spangler EA, Weeks BR, Knight R. Intravascular hemolysis associated with severe cutaneous burn injuries in five horses. *J Am Vet Med Assoc*. 2002;2005(226):2039-2043.
27. Hunyadi L, Sundman EA, Kass PH, Williams DC, Aleman M. Clinical implications and hospital outcome of immune-mediated myositis in horses. *J Vet Intern Med*. 2017;31:170-175.
28. Chang-Panesso M. Acute kidney injury and aging. *Pediatr Nephrol*. 2021;36:2997-3006.
29. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13:241-257.
30. Layman QD, Rezabek GB, Ramachandran A, Love BC, Confer AW. A retrospective study of equine actinobacillosis cases: 1999-2011. *J Vet Diagn Invest*. 2014;26:365-375.
31. 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.
32. Bouchard PR, Weldon AD, Lewis RM, Summers BA. Uremic encephalopathy in a horse. *Vet Pathol*. 1994;31:111-115.
33. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179-c184.
34. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. *Crit Care Med*. 2010;38:933-939.
35. Lee YJ, Chang CC, Chan JP, Hsu WL, Lin KW, Wong ML. Prognosis of acute kidney injury in dogs using RIFLE (risk, injury, failure, loss and end-stage renal failure)-like criteria. *Vet Rec*. 2011;168:264.
36. Meier M, Bettschart-Wolfensberger R, Schwarzwald CC, Portier K, Gysler A, Ringer SK. Effects of dobutamine on cardiovascular function and oxygen delivery in standing horses. *J Vet Pharmacol Ther*. 2020;43:470-476.
37. Dancker C, Hopster K, Rohn K, Kästner SB. Effects of dobutamine, dopamine, phenylephrine and noradrenaline on systemic haemodynamics and intestinal perfusion in isoflurane anaesthetised horses. *Equine Vet J*. 2018;50:104-110.
38. Dickey EJ, McKenzie H III, Johnson A, Furr MO. Use of pressor therapy in 34 hypotensive critically ill neonatal foals. *Aust Vet J*. 2010;88:472-477.
39. Hollis AR, Ousey JC, Palmer L, et al. Effects of norepinephrine and combined norepinephrine and fenoldopam infusion on systemic hemodynamics and indices of renal function in normotensive neonatal foals. *J Vet Intern Med*. 2008;22:1210-1215.
40. Hollis AR, Ouseyxya JC, Palmer L, Stoneham SJ, Corley KTT. Effects of fenoldopam mesylate on systemic hemodynamics and indices of renal function in normotensive neonatal foals. *J Vet Intern Med*. 2006;20:595-600.
41. Trim CM, Moore JN, Clark ES. Renal effects of dopamine infusion in conscious horses. *Equine Vet J Suppl*. 1989;21:124-128.
42. Errecalde JO, Button C, Mulders MS. Some dynamic and toxic effects of theophylline in horses. *J Vet Pharmacol Ther*. 1985;8:320-327.
43. McMahon BA, Chawla LS. The furosemide stress test: current use and future potential. *Ren Fail*. 2021;43:830-839.
44. Wong DM, Ruby RE, Eatroff A, Yaeger MJ. Use of renal replacement therapy in a neonatal foal with Postresuscitation acute renal failure. *J Vet Intern Med*. 2017;31:593-597.
45. Gallatin LL, Couetil LL, Ash SR. Use of continuous-flow peritoneal dialysis for the treatment of acute renal failure in an adult horse. *J Am Vet Med Assoc*. 2005;226(756–759):732-759.
46. Sweeney RW, Macdonald M, Hall J, Divers TJ, Sweeney CR. Kinetics of gentamicin elimination in two horses with acute renal failure. *Equine Vet J*. 1988;20:182-184.
47. Han JH, McKenzie HCI. Intermittent peritoneal dialysis for the treatment of acute renal failure in two horses. *Equine Vet Educ*. 2008;20:256-264.
48. Dondi F, Lukacs RM, Gentilini F, Rinnovati R, Spadari A, Romagnoli N. Serum amyloid a, haptoglobin, and ferritin in horses with colic: association with common clinicopathological variables and short-term outcome. *Vet J*. 2015;205:50-55.
49. Staempfli HR, Townsend HG, Prescott JF. Prognostic features and clinical presentation of acute idiopathic enterocolitis in horses. *Can Vet J*. 1991;32:232-237.
50. Arroyo MG, Slovis NM, Moore GE, Taylor SD. Factors associated with survival in 97 horses with septic pleuropneumonia. *J Vet Intern Med*. 2017;31:894-900.
51. Groover ES, Woolums AR, Cole DJ, LeRoy BE. Risk factors associated with renal insufficiency in horses with primary gastrointestinal disease: 26 cases (2000-2003). *J Am Vet Med Assoc*. 2006;228:572-577.

52. Canaud G, Bonventre JV. Cell cycle arrest and the evolution of chronic kidney disease from acute kidney injury. *Nephrol Dial Transplant*. 2015;30:575-583.
53. Scharman EJ, Troutman WG. Prevention of kidney injury following rhabdomyolysis: a systematic review. *Ann Pharmacother*. 2013;47:90-105.
54. Brashier MK, Geor RJ, Ames TR, O'Leary TP. Effect of intravenous calcium administration on gentamicin-induced nephrotoxicosis in ponies. *Am J Vet Res*. 1998;59:1055-1062.
55. el-Ashker M, Abdelhamid F, Risha E, Salama M, el-Sebaei M. Vitamin C ameliorates gentamicin-induced acute kidney injury in equines: an experimental study. *J Equine Vet*. 2015;35:238-243.
56. Olsen E, van Galen G. Chronic renal failure-causes, clinical findings, treatments and prognosis. *Vet Clin North Am Equine Pract*. 2022;38:25-46.
57. Schott HC, Patterson KS, Fitzerald SD. Chronic renal failure in 99 horses. Proceedings of *43rd Annual Convention of the American Association of Equine Practitioners (AAEP)*; 1997:345.
58. Ehnen SJ, Divers TJ, Gillette D, Reef VB. Obstructive nephrolithiasis and ureterolithiasis associated with chronic renal failure in horses: eight cases (1981-1987). *J Am Vet Med Assoc*. 1990;197:249-253.
59. Laverty S, Pascoe JR, Ling GV, Lavoie JP, Ruby AL. Urolithiasis in 68 horses. *Vet Surg*. 1992;21:56-62.
60. Divers TJ, Timoney JF, Lewis RM, Smith CA. Equine glomerulonephritis and renal failure associated with complexes of group-C streptococcal antigen and IgG antibody. *Vet Immunol Immunopathol*. 1992;32:93-102.
61. Banks KL, Henson JB, McGuire TC. Immunologically mediated glomerulitis of horses. I. Pathogenesis in persistent infection by equine infectious anemia virus. *Lab Invest*. 1972;26:701-707.
62. Vienenkötter J, Siudak K, Stallenberger L, Herden C. Renal neoplasia in horses - a retrospective study. *Tierarztl Prax Ausg G Grosstiere Nutztiere*. 2017;45:290-295.
63. Akagami M, Shibahara T, Yoshiga T, et al. Granulomatous nephritis and meningoencephalomyelitis caused by Halicephalobus gingivalis in a pony gelding. *J Vet Med Sci*. 2007;69:1187-1190.
64. de Solis CN, Slack J, Boston RC, Reef VB. Hypertensive cardiomyopathy in horses: 5 cases (1995-2011). *J Am Vet Med Assoc*. 2013;243:126-130.
65. Tennant B, Bettleheim P, Kaneko JJ. Paradoxic hypercalcemia and hypophosphatemia associated with chronic renal failure in horses. *J Am Vet Med Assoc*. 1982;180:630-634.
66. LeRoy B, Woolums A, Wass J, et al. The relationship between serum calcium concentration and outcome in horses with renal failure presented to referral hospitals. *J Vet Intern Med*. 2011;25:1426-1430.
67. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. *Nat Rev Nephrol*. 2020;16:269-288.
68. Kirk CA, Jewell DE, Lowry SR. Effects of sodium chloride on selected parameters in cats. *Vet Ther*. 2006;7:333-346.
69. Li WL, Zhang NH, Ge SW, Xu G. Dietary omega-3 fatty acid intake and mortality in CKD population: a 1999-2014 NHANES analysis. *Am J Nephrol*. 2021;52:909-918.
70. Saran R, Novak JE, Desai A, et al. Impact of vitamin E on plasma asymmetric dimethylarginine (ADMA) in chronic kidney disease (CKD): a pilot study. *Nephrol Dial Transplant*. 2003;18:2415-2420.
71. Pei G, Tang Y, Tan L, Tan J, Ge L, Qin W. Aerobic exercise in adults with chronic kidney disease (CKD): a meta-analysis. *Int Urol Nephrol*. 2019;51:1787-1795.
72. Scala E, van Galen G, Skärlina EM, Durie I. Do post-surgical multiresistant urinary infections occur in horses? Case of unilateral pyelonephritis caused by extended-spectrum beta-lactamase-producing bacteria as a complication of cystotomy. *Vet Med Sci*. 2023;9:2042-2052.
73. Roberts MC. Ascending urinary tract infection in ponies. *Aust Vet J*. 1979;55:191-193.
74. Graves EA. Unilateral pyelonephritis in a miniature horse colt. *Vet Clin North Am Equine Pract*. 2006;22:209-217.
75. Kristhardt KK, Schumacher J, Finn-Bodner ST, Carson-Dunkerley S, Williams MA. Severe renal hemorrhage caused by pyelonephritis in 7 horses: clinical and ultrasonographic evaluation. *Can Vet J*. 1999;40:571-576.
76. Held JP, Wright B, Henton JE. Pyelonephritis associated with renal failure in a horse. *J Am Vet Med Assoc*. 1986;189:688-689.
77. Schott HC 2nd, Hines MT. Severe urinary tract hemorrhage in two horses. *J Am Vet Med Assoc*. 1994;204:1320.
78. Vits L, Araya O, Bustamante H, Mohr F, Galecio S. Idiopathic renal haematuria in a 15-year-old Arabian mare. *Vet Rec*. 2008;162:251-252.
79. Aleman MR, Kuesis B, Schott HC, Carlson GP. Renal tubular acidosis in horses (1980-1999). *J Vet Intern Med*. 2001;15:136-143.
80. van der Kolk JH, de Graaf-Roelfsema E, Joles JA, et al. Mixed proximal and distal renal tubular acidosis without aminoaciduria in a mare. *J Vet Intern Med*. 2007;21:1121-1125.
81. Ohmes CM, Davis EG, Beard LA, Vander Werf KA, Bianco AW, Giger U. Transient Fanconi syndrome in quarter horses. *Can Vet J*. 2014;55:147-151.
82. Ireland JL, McGowan CM. Epidemiology of pituitary pars intermedia dysfunction: a systematic literature review of clinical presentation, disease prevalence and risk factors. *Vet J*. 2018;235:22-33.
83. Durie I, van Galen G. Long-term hormone replacement treatment in a horse with central diabetes insipidus. *J Vet Intern Med*. 2020;34:1013-1017.
84. Kranenburg LC, Thelen MH, Westermann CM, de Graaf-Roelfsema E, van der Kolk JH. Use of desmopressin eye drops in the treatment of equine congenital central diabetes insipidus. *Vet Rec*. 2010;167:790-791.
85. Holdstock NB, Ousey JC, Rossdale PD. Glomerular filtration rate, effective renal plasma flow, blood pressure and pulse rate in the equine neonate during the first 10 days post partum. *Equine Vet J*. 1998;30:335-343.
86. Brewer BD, Clement SF, Lotz WS, Gronwall R. A comparison of inulin, para-aminohippuric acid, and endogenous creatinine clearances as measures of renal function in neonatal foals. *J Vet Intern Med*. 1990;4:301-305.
87. Collins NM, Axon JE, Carrick JB, Russell CM, Palmer JE. Severe hyponatraemia in foals: clinical findings, primary diagnosis and outcome. *Aust Vet J*. 2016;94:186-191.
88. Chaney KP, Holcombe SJ, Schott HC 2nd, Barr BS. Spurious hypercreatininemia: 28 neonatal foals (2000-2008). *J Vet Emerg Crit Care (San Antonio)*. 2010;20:244-249.
89. Armengou L, Jose-Cunilleras E, Ríos J, Cesarini C, Viu J, Monreal L. Metabolic and endocrine profiles in sick neonatal foals are related to survival. *J Vet Intern Med*. 2013;27:567-575.
90. Sanchez LC, Giguere S, Lester GD. Factors associated with survival of neonatal foals with bacteremia and racing performance of surviving thoroughbreds: 423 cases (1982-2007). *J Am Vet Med Assoc*. 2008;233:1446-1452.
91. Morris DD, Divers TJ, Whitlock RH. Renal clearance and fractional excretion of electrolytes over a 24-hour period in horses. *Am J Vet Res*. 1984;45:2431-2435.
92. van Galen G, Olsen E, Siwinska N. Biomarkers of kidney disease in horses: a review of the current literature. *Animals (Basel)*. 2022;12:12.
93. Siwinska N, Zak A, Paslawska U. Detecting acute kidney injury in horses by measuring the concentration of symmetric dimethylarginine in serum. *Acta Vet Scand*. 2021;63:3.
94. Siwinska N, Zak A, Slowikowska M, Niedzwiedz A, Paslawska U. Serum symmetric dimethylarginine concentration in healthy horses and horses with acute kidney injury. *BMC Vet Res*. 2020;16:396.

95. Siwinska N, Zak A, Paslawska U. Evaluation of serum and urine neutrophil gelatinase-associated lipocalin and cystatin C as biomarkers of acute kidney injury in horses. *J Vet Res*. 2021;65:245-252.
96. Siwińska N, Pasławska U, Bąchor R, et al. Evaluation of podocin in urine in horses using qualitative and quantitative methods. *PLoS One*. 2020;15:e0240586.
97. Jacobsen S, Berg LC, Tvermose E, Laurberg MB, van Galen G. Validation of an ELISA for detection of neutrophil gelatinase-associated lipocalin (NGAL) in equine serum. *Vet Clin Pathol*. 2018;47:603-607.
98. Arosalo BM, Raekallio M, Rajamäki M, et al. Detecting early kidney damage in horses with colic by measuring matrix metalloproteinase −9 and −2, other enzymes, urinary glucose and total proteins. *Acta Vet Scand*. 2007;49:4.
99. Bayless RL, Moore AR, Hassel DM, Byer BJ, Landolt GA, Nout-Lomas YS. Equine urinary N-acetyl-beta-D-glucosaminidase assay validation and correlation with other markers of kidney injury. *J Vet Diagn Invest*. 2019;31:688-695.
100. Draper AC, Bowen IM, Hallowell GD. Reference ranges and reliability of transabdominal ultrasonographic renal dimensions in thoroughbred horses. *Vet Radiol Ultrasound*. 2012;53:336-341.
101. Siwinska N, Zak A, Slowikowska M, Szczepankiewicz B, Niedzwiedz A, Paslawska U. An assessment of the utility and repeatability of the renal resistive index in horses. *PLoS One*. 2019;14:e0226941.
102. Walsh DM, Royal HD. Evaluation of a single injection of ^{99m}Tc-labeled diethylenetriaminepentaacetic acid for measuring glomerular filtration rate in horses. *Am J Vet Res*. 1992;53:776-780.
103. Woods PR, Drost WT, Clarke CR, Rodebush CJ. Use of ^{99m}Tc-mercaptoacetyltriglycine to evaluate renal function in horses. *Vet Radiol Ultrasound*. 2000;41:85-88.
104. Moss AL, Acutt EV, Ullal T, Applegate TJ, Hackett ES. Ureteropyeloscopic removal of a nephrolith from a 19 year old Hanoverian gelding. *Vet Surg*. 2022;51(Suppl 1):O53-O59.
105. Tyner GA, Nolen-Walston RD, Hall T, et al. A multicenter retrospective study of 151 renal biopsies in horses. *J Vet Intern Med*. 2011;25:532-539.
106. Eiro M, Katoh T, Watanabe T. Risk factors for bleeding complications in percutaneous renal biopsy. *Clin Exp Nephrol*. 2005;9:40-45.
107. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *Br J Surg*. 2015;102:24-36.
108. Ding X, Cheng Z, Qian Q. Intravenous fluids and acute kidney injury. *Blood Purif*. 2017;43:163-172.
109. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol*. 2010;6:107-115.
110. Aloy B, Launay-Vacher V, Bleibtreu A, et al. Antibiotics and chronic kidney disease: dose adjustment update for infectious disease clinical practice. *Med mal Infect*. 2020;50:323-331.
111. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. *Am Fam Physician*. 2007;75:1487-1496.
112. Monteiro B, Steagall PVM, Lascelles BDX, et al. Long-term use of non-steroidal anti-inflammatory drugs in cats with chronic kidney disease: from controversy to optimism. *J Small Anim Pract*. 2019;60:459-462.
113. Mitsuboshi S, Kotake K, Takahashi T, Sato K, Sakamaki T. Association between misoprostol and nonsteroidal anti-inflammatory drug-induced kidney injury: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2023;89:2662-2670.
114. Wang M. Kidney benefits of SLGT2 inhibitors: evidence from clinical trials. *Nat Rev Nephrol*. 2023;19:3.

How to cite this article: van Galen G, Divers TJ, Savage V, Schott HC II, Siwinska N. ECEIM consensus statement on equine kidney disease. *J Vet Intern Med*. 2024;38(4):2008-2025. doi:10.1111/jvim.17101