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Acute kidney injury in horses

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Acute renal failure (ARF) usually develops as a complication of another disease process that causes decreased renal perfusion (colic, colitis, hemorrhage, or exhaustive exercise). Recently, there have also been reports of ARF developing with leptospirosis in equids. Treatment with nephrotoxic medications including aminoglycoside antibiotics, oxytetracycline (when administered for correction of flexural deformities in neonatal foals), and nonsteroidal anti-inflammatory drugs (NSAIDs) is an important risk factor for ARF in horses. Other nephrotoxins that can cause ARF include endogenous pigments (myoglobin or hemoglobin), vitamin D or vitamin K3, heavy metals (mercury, cadmium, zinc, arsenic, and lead), and acorns. Due to widespread use of aminoglycoside antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) in equine practice, potential nephrotoxicity with these medications will be discussed in further detail below.

Change in terminology: The term "prerenal failure" has long been used to describe reversible increases in BUN and Cr (azotemia) associated with compromised renal function. Although use of this term is firmly entrenched in both the human and veterinary medical literature, its use likely contributes to a lack of recognition of subclinical renal damage that accompanies a number of medical and surgical conditions. This can be attributed to a large renal functional reserve capacity. In many patients with reversible azotemia, changes in glomerular and tubular function and integrity can be demonstrated by pigmenturia, proteinuria, cast formation, or impaired concentrating ability (urine specific gravity of 1.015-1.030 in a markedly dehydrated patient), and an increase in urine sodium concentration (>20 mmol/L). Despite the reversible nature of these functional alterations, a degree of nephron loss may occur with prerenal failure. To increase awareness of subclinical renal damage in patients with decreased RBF and GFR, the term acute kidney injury (AKI) has been introduced in human and, subsequently, small animal medicine. AKI is defined as an increase in Cr of 0.3 mg/dL or a 50% increase from the baseline value, yet Cr may remain within the reference range. Hemodynamically-induced AKI is often associated with oliguria (urine output <0.5 ml/kg for 6 hours) while urine production with nephrotoxin-associated AKI often remains normal (nonoliguric AKI).

Aminoglycoside antibiotics: Aminoglycoside antibiotics exert their toxic effect by accumulating within proximal tubular epithelial cells. Once toxic amounts are sequestered within the cell, cellular metabolism is disrupted, and tubular cell swelling, death, and sloughing into the tubular lumen occur. Most cases of aminoglycoside nephrotoxicity are not the result of overdosing or administration of the drug to an azotemic patient. The healthy kidney can usually tolerate a single major overdose (10 times the normal amount) without detrimental effects. Toxicity is a result of the cumulative effect of repeated administration of aminoglycosides. When aminoglycosides are administered to high-risk patients (those with concurrent dehydration or neonates), volume deficits must be replaced and serum creatinine concentration (Cr) should be monitored closely. Because nephrotoxicity is a cumulative effect of repeated dosing, delay of administration of the initial nephrotoxicity to develop in horses receiving appropriate fluid therapy. Once daily
administration of aminoglycosides has become a standard practice that has reduced the risk of nephrotoxicity. Because aminoglycosides exert a concentration-dependent action against bacteria, once-daily dosing both ensures a higher peak serum concentration while also allowing for a longer period at which the drug concentration is below the trough value. Since renal tubular damage is usually sustained only when the drug is above the trough concentration, once-daily dosing can be considered “renoprotective”.

Nonsteroidal anti-inflammatory drugs: Most horses do not experience appreciable adverse effects from NSAID use as long as they are administered at the proper dose and animals are not dehydrated. When renal blood flow decreases as a consequence of dehydration, vasodilatory prostaglandins (PGI₂ and PGE₂) are produced within the kidney. Production of renal prostaglandins is several-fold greater in medullary tissue such that action of these mediators leads to a greater increase in medullary blood flow, regions of the kidney that normally function in a relatively hypoxic environment. Thus, it should not be surprising that the lesion associated with NSAID toxicity is medullary necrosis. Recent development of more COX-2 selective NSAIDs has received considerable attention and it would logical to assume that use of these NSAIDs may be less nephrotoxic than use of other non-specific NSAIDs. However, this new generation of more COX-2 selective NSAIDs has not been demonstrated to be renoprotective in studies in other species.

Clinical signs: Clinical signs in horses with AKI/ARF commonly reflect the primary disease process: colic, diarrhea, or restricted gait and pigmenturia due to rhabdomyolysis. Subtle clinical signs that should prompt investigation of possible secondary AKI/ARF include more severe lethargy or inappetance than are typically manifested with the primary disease, especially in patients with nonoliguric AKI/ARF. Persistent anuria or oliguria followed by development of edema in the face of supportive fluid therapy, along with weight gain due to fluid retention, are more obvious clinical signs of ARF. Occasionally, horses with severe ARF may develop marked conjunctival edema and they may also be ataxic or manifest neurological signs similar to hepatoencephalopathy. Diarrhea and laminitis may develop in more serious cases.

Diagnosis of AKI/ARF: As mentioned, AKI/ARF should be suspected in patients showing more lethargy and anorexia than would be expected with the primary disease process and in patients that fail to produce urine within 6-12 hours of initiating fluid therapy. Rectal palpation in horses with ARF may reveal enlarged, painful kidneys in some patient and enlargement can be confirmed by renal ultrasonography. Renal ultrasonography may also reveal perirenal edema, increased echogenicity of the renal cortex, and/or dilation of renal pelvis. Renal ultrasonography can also document presence of both kidneys, as well as underlying chronic kidney disease (e.g., unilateral nephrolithiasis). At necropsy, the renal cortex with AKI/ARF is typically pale and bulges on cut section due to edema.

A diagnosis of AKI/ARF is confirmed on the basis of history, potential exposure to nephrotoxins, clinical signs, and laboratory findings. With regard to the latter, the increase in Cr is often several-fold greater (to 5-15 mg/dL, 440-1320 μmol/L) than that for blood urea nitrogen concentration (BUN, to 50-100 mg/dL, 18-36 mmol/L). Hyponatremia, hypochloremia, and hypocalcemia are usually present and, in more severe cases, hyperkalemia, hyperphosphatemia, and metabolic acidosis may also be detected. With oliguria or anuria, hyperkalemia can be severe (>7 mmol/L) and may precipitate life-threatening cardiac arrhythmias.
Urinalysis should be performed on all horses in which AKI/ARF is suspected. Low urine specific gravity (<1.020) in the face of dehydration and gross or microscopic hematuria are common findings. Glucosuria may also be detected as a consequence of proximal tubular damage. Examination of urine sediment may reveal casts and increased numbers of erythrocytes and leukocytes while the amount of urine crystals may be decreased.

**Treatment of AKI/ARF:** Initial treatment of AKI/ARF should focus on judicious fluid therapy to replace volume deficits and correct electrolyte and acid-base abnormalities. Sodium and chloride replacement are often required in horses with polyuric ARF and can be accomplished by IV administration of a polyionic replacement fluid or through electrolyte supplementation in grain feedings or as oral pastes. Serum potassium concentration in horses with nonoliguric ARF is often normal, and, except for post-renal problems (obstruction or rupture), therapy intended to lower serum potassium is usually not necessary. Next, it is important to determine if the horse is oliguric or nonoliguric (normal urine output to polyuric) because prognosis for recovery is more favorable with nonoliguric ARF. In horses with prerenal failure, rather than intrinsic ARF, Cr should decrease by at least 30-50% within the initial 24 hours of fluid therapy. In contrast, Cr remains little changed, or may increase, with ARF.

In horses that remain oliguric after 12-24 hours of appropriate fluid and electrolyte replacement, furosemide (1-3 mg/kg, IV, q 2 h) should be administered. Unfortunately, furosemide treatment is often ineffective in increasing urine output in horses with ARF. If urine is not voided after the second dose, administration of mannitol (0.5-1 mg/kg as a 10-20% solution) can be instituted, although use of this osmotic diuretic is controversial. Renal arterioles contain dopamine type 1 receptors and a constant rate infusion of dopamine (3 µg/kg/min) increases RBF, GFR, and urine output by normal kidneys of several species including horses. Consequently, this drug has been used for several decades for treatment of anuric ARF in human intensive care units and is recommended in several equine texts. However, several large studies of human patients indicated that dopamine treatment had limited impact on improving survival while it also posed a risk of inducing or exacerbating cardiac arrhythmias. Thus, dopamine is no longer a recommended treatment and has been replaced by dopamine type 1 receptor agonists (e.g., fenoldopam) with more specific effects on renal arterioles and less adverse effects. In horses, oliguria should progress to polyuria within 48-72 hours after development of ARF for the prognosis for recovery to remain reasonable. Fortunately, the majority of horses with ARF are nonoliguric rather than oliguric and administration of furosemide or mannitol is not needed with nonoliguric ARF. When oliguria persists for more than 72 h, the prognosis becomes grave and peritoneal dialysis may be attempted but pursuit of this treatment should likely only be offered to clients that want to pursue all treatments as an alternative to euthanasia.

After volume deficits have been restored and polyuria has been achieved, patients usually only require continued fluid therapy to promote a continued decrease in Cr. During the week after fluid therapy is discontinued, Cr should be measured again to ensure that it has not increased. Occasionally, Cr may not decrease below the upper limit of the reference range despite fluid therapy. As long as the horse is eating and drinking well, IV fluids can be discontinued. In some horses Cr may return to the normal range over the next couple of months while in other patients a persisting elevation in Cr is indicative of a permanent loss of renal function.