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MANAGEMENT OF HORSES WITH ACUTE RENAL FAILURE

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Summary
Acute renal failure (ARF) is characterized by a rapid increase in serum creatinine. The most common causes include nephrotoxic drugs and vasomotor or ischemic nephropathy. Clinical signs are ill defined and often related to the concurrent disease. Distinction between prerenal, renal and post renal azotemia is based on history, clinical signs, urinalyses, and serum biochemistry. Conventional treatment involves increasing glomerular filtration rate and providing supportive care to the affected horse along with removal or correction of the inciting cause. Intravenous administration of large volumes of fluids (except in instances of urinary tract obstruction or post-renal azotemia) is often required, and diuretics and renal vasodilators may be necessary to establish diuresis. Peritoneal dialysis is a practical option in cases of refractory ARF.

Introduction
Acute renal failure (ARF) is characterized by a rapid decrease in glomerular filtration rate (GFR) resulting in azotemia and fluid homeostasis abnormalities. ARF may be separated into prerenal, renal, and postrenal azotemia. Both prerenal and postrenal azotemia may result in renal cell injury and intrinsic ARF. Prerenal azotemia is commonly associated with conditions causing dehydration and decreased renal perfusion such as diarrhea, endotoxemia, septic shock and acute blood loss. Postrenal azotemia is uncommon in adult horses except in foals with ruptured bladder. The main causes of intrinsic ARF in horses are nephrotoxins and vasomotor nephropathy. The pathogenesis differs between these two causes and thus, may require different therapy. Frequently, intrinsic ARF is caused by a combination of nephrotoxic drugs and ischemic nephropathy associated with severe systemic diseases. In horses, lesions associated with ARF are usually characterized by acute tubular necrosis.(1) Interstitial and glomerular diseases are rare causes of ARF in horses. The following discussion is focused on intrinsic ARF.

Causes of ARF

Toxic nephropathies

Medications
Aminoglycoside antibiotics are the most commonly implicated in cases of toxic nephropathies. Among aminoglycosides, the most nephrotoxic is neomycin, followed by gentamicin, kanamycin and amikacin with streptomycin being the least nephrotoxic. Aminoglycosides are eliminated by glomerular filtration but a fraction of the drug is reabsorbed in the proximal tubule where its accumulation may result in cell dysfunction, tubular swelling and sloughing, and preglomerular vasoconstriction leading to decrease in GFR and ARF.(2) Overdosing of aminoglycosides may result in ARF, however most cases are caused by predisposing conditions such as concurrent illness (e.g. diarrhea, septicemia, endotoxemia), dehydration, or the use of several potentially nephrotoxin drugs in combination (e.g. aminoglycoside and non-steroidal antiinflammatory drugs). Oxytetracycline has been incriminated in cases of ARF in foals treated for contracted limbs.(3) In those cases, nephropathy may be the result of a combination of factors including oxytetracycline toxicity, hypovolemia, and decreased renal blood flow due to propylene glycol which is the vehicle for oxytetracycline.
Non-steroidal antiinflammatory drugs (NSAIDS), and in particular phenylbutazone, may be nephrotoxic when used in high dosages or when drug administration is prolonged. Phenylbutazone is toxic at a dose
≥ 8 mg/kg/day if administered for several days or at recommended dosages if administered to dehydrated or hypovolemic horses.(4) However, some horses have been treated with 2 g/day orally of phenylbutazone for months to years without developing clinical or hematological abnormalities. Renal prostaglandins (PG-E2, PG-I2) act locally as vasodilators to maintain renal blood flow and GFR.(1) However, the role of prostaglandins is only important when renal perfusion is reduced. Therefore, NSAIDS renal toxicity is enhanced in dehydrated or toxemic horses. In these patients, prostaglandins inhibition may cause renal medullary crest and papillary ischemia and subsequently necrosis. Often, these lesions are incidental findings and do not result in clinical disease. However, high doses of NSAIDS or their use in compromised horses may result in ARF.

Vitamin D toxicosis may occur from parenteral administration (vitamins D2 and D3) or ingestion of feed additives or plants (e.g. Cestrum diurnum) containing large amounts of vitamin D or its metabolites.(5) The toxicity is related to the dose and duration of treatment or ingestion. Vitamin D toxicosis result in disseminated soft tissue mineralization including renal epithelial tubular cells.

**Pigment nephropathy**

Endogenous pigments, in particular hemoglobin and myoglobin have nephrotoxic and vasomotor effects. Pigments are released into the circulation following mild to severe episodes of rhabdomyolysis or extensive intravascular hemolysis.(5) Hemoglobin and myoglobin can produce tubular nephrosis and ARF. Causes of myoglobinemia include exertional rhabdomyolysis (tying-up), post-anesthetic myopathies, compartmental muscle syndrome, extensive burns and heatstroke. Causes of intravascular hemolysis include infections (Babesia caballi, B. equi), toxin ingestion (e.g. phenothiazine, onion, red maple), neonatal isoerythrolysis, fulminant hepatic failure, and immune-mediated hemolytic anemia.

**Heavy metals**

The most nephrotoxic heavy metals are mercury, lead, arsenic, and cadmium. Accidental ingestion may lead to renal tubular necrosis and ARF. Both organic and inorganic forms of mercury are toxic to horses.(5) However, cases of poisoning are rare and include ingestion of mercury containing blister and ARF following application of a mercury-DMSO sweat.

**Plants**

Several toxic plants can cause renal nephrosis (e.g. Oak leaves and acorn, oxalate containing plants) but these plants are in general unpalatable to animals unless pastures are overgrazed or animals are starving.

**Vasomotor nephropathies**

Conditions associated with marked hypotension or release of endogenous pressor agent may trigger hemodynamically-mediated ARF.(6) Causes include septic shock, severe dehydration, coagulopathies, and blood loss. The decrease in renal perfusion may be worsened by tubular obstruction secondary to cast accumulation or epithelial cell swelling.

**Clinical signs**

Clinical signs associated with ARF are mild and non-specific and usually masked by the manifestation of the underlying disease such as colitis, sepsis, rhabdomyolysis, or coagulopathies.(1) Anorexia, depression, mild colic, dehydration and oliguria are commonly observed.(2) In severe cases, laminitis, diarrhea and hematuria or hemoglobinuria may be seen. Pigmenturia is often observed with severe tying-up however, ARF may develop without gross discoloration of the urine. Horses with NSAIDS toxicosis may present with ulcerations of the oral mucosa or brick-red discoloration. Vitamin D toxicosis may result in lameness and heart murmur due to calcification of soft tissue. Acorn poisoning in horses is accompanied by diarrhea, edema and body cavity effusion.
Diagnosis

The cardinal indicator of ARF is azotemia i.e. increased blood urea nitrogen (BUN) and serum creatinine concentrations. Measurement of urine specific gravity (SG) is essential in differentiating prerenal from renal azotemia. In an azotemic patient, urine SG > 1.025 is consistent with prerenal azotemia and isosthenuria (1.008 < SG < 1.014) is suggestive of intrinsic ARF. Postrenal obstruction is usually diagnosed by examination of historical and clinical findings. Also, prerenal azotemia improves rapidly with fluid therapy but not with intrinsic ARF. By the time azotemia develops, approximately 75% of nephrons are nonfunctional. Early indicators of renal damage are enzymuria (gamma glutamyl transferase [GGT]), proteinuria, cast formation, impaired concentrating ability, and abnormal electrolyte excretion. In experimental models of toxic nephropathy, increased urine GGT activity was the earliest indicator of renal insult followed by proteinuria, glucosuria and presence of casts. In addition, urine-serum ratio of creatinine (reference range [2.0 - 344]; prerenal azotemia [51 - 241]; renal azotemia [3 - 37]) and fractional clearance of sodium (reference range [0.01 - 0.7%]; prerenal azotemia [0.02 - 0.5%]; renal azotemia [0.8 - 10%]) are useful indices of the ability of renal tubules to reabsorb water and electrolytes, respectively.

Beside BUN, serum creatinine and urinalysis, the minimum database should include serum electrolytes, proteins, glucose and muscle enzymes (creatine phosphokinase [CPK]; aspartate aminotransferase [AST]). Intrinsic ARF is usually accompanied by hyponatremia and hypochloremia. Serum potassium may be normal or elevated with ARF, but hyperkalemia is often pronounced in cases of postrenal ARF in particular with uroperitoneum. Calcium and phosphorus concentrations are variable. Rectal examination may reveal an enlarged left kidney. Ultrasonographic examination of both kidneys is helpful in assessing size and structure of the organ. However, abnormalities are not commonly observed in horses with ARF except for some cases of kidney enlargement, perirenal edema, widening of renal cortex, and loss of clear corticomedullary junction. Renal biopsy should only be considered if non-invasive diagnostic tests are inconclusive and histopathology results may affect therapy and prognosis.

Treatment

The goals of therapy are to restore GFR, treat the inciting cause, and provide supportive care. Initially, nephrotoxic agents should be removed and underlying conditions treated aggressively. In parallel, renal perfusion should be restored by providing fluid replacement and correcting electrolyte and acid-base abnormalities. Fluids of choice are isotonic saline solution, especially in hyperkalemic patients or a balanced electrolyte solution. Fluid deficit should be corrected within the first 6-12 hours and followed by maintenance therapy (40 - 80 ml/kg/day) until azotemia decreases significantly. If the horse is polyuric, fluid therapy is reduced (10 - 20 ml/kg/day) only when serum creatinine is close to the normal range. If the horse is still oliguric after 6-12 hours of fluid therapy, administration of diuretic agents (furosemide [0.5 - 1 mg/kg q 2 - 6 hours IV]; 20% mannitol [0.25 - 1 g/kg over 15 min IV]) and dopamine (3 - 5 μg/kg/min IV in 5% dextrose solution) should be considered. Monitoring of systemic blood pressure (normal indirect arterial pressures are: systolic [80 - 145 mmHg], diastolic [50 - 106 mmHg]), central venous pressure (normal < 8 cmH2O), and body weight are useful to adjust therapy and prevent complications such as peripheral edema, pulmonary edema and hypertension. The risk of aminoglycoside nephrotoxicity is diminished by reducing frequency of administration to once daily (gentamicin 6.6 mg/kg; amikacin 15-20 mg/kg) and by monitoring trough and peak levels. Diets reach in calcium (e.g. alfalfa) or intravenous calcium supplementation appear to lessen aminoglycoside-induced nephrotoxicosis. Anti-ulcer medication and nutritional support should also be considered to alleviate the catabolic state and support the animal's body function.

Hemodialysis and peritoneal dialysis (PD) should be considered in cases of ARF refractory to the above therapy. Hemodialysis requires specialized equipment, is expensive, time consuming, and may result in
complications. (3) In the case of PD, the peritoneum acts as a dialyzer membrane that allows passage of toxins out of and nutrients into the blood. Diffusive and convective forces move substances down their concentration gradient to achieve correction of electrolyte and acid-base abnormalities and toxin removal, and ultrafiltration facilitates normalization of fluid balance. Peritoneal dialysis can be safely used in patients in which vascular access is difficult or volume overload is detrimental. Intermittent peritoneal dialysis is performed by inserting a catheter (e.g. 24-28 F pezzar or chest tube) placed in the ventral aspect of the abdomen of the horse while it is standing. Ten to 15 liters of warmed sterile parenteral fluid is infused into the abdomen via gravity flow and then the catheter is clamped; the horse is then walked during 30-minute to allow fluid dwell time, after which the catheter is unclamped and the fluid allowed to drain out of the abdomen. Intermittent PD may be performed once or twice daily. Continuous-flow PD has been reported to increase clearance of toxins that accumulate as a result of uremia in humans and in the horse. (11) An additional catheter has to be inserted in the upper left flank area. A standard dialysate solution of 1.5% glucose in sterile parenteral fluid is continuously infused through catheter into the left flank at a rate of approximately 3 L/h and fluid is collected into a sterile closed collection system from the catheter in the ventral midline region of the abdomen. The quantity of intra-abdominal fluid may be regulated by positioning the collection bags at the level of the withers to maintain a constant and modest intraperitoneal pressure. Most of the common complications-catheter failure, subcutaneous edema as a result of leakage of fluid around the catheter, and aseptic peritonitis-are minor and easily dealt with. Contraindications of PD would include abdominal surgery, trauma, abdominal adhesions, and hypoalbuminemia.

Prognosis

Several factors affect the prognosis including the cause of ARF, duration, response to therapy, and secondary complications (e.g. laminitis, coagulopathies, hemolysis, etc.). The prognosis is fair to good if the animal becomes quickly polyuric after initiation of therapy. Prolonged anuria or oliguria (> 12 hours) despite aggressive therapy carries a poor prognosis. (1) Prevention of ARF is essential and requires identification of high-risk patients (e.g. sepsis, diarrhea), careful use of nephrotoxic drugs (e.g. aminoglycoside drug levels), and monitoring of hydration status and early indicators of renal damage (serum creatinine q 2-3 days and urine protein, GGT, casts).

References

