Review of Azotemia in Foals

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1. Introduction
Azotemia in neonatal foals (≤7 days of age) may be an indicator of pre-renal failure, acute kidney injury (AKI), obstructive disease, congenital renal disorders, or disruption of the collecting system leading to uroperitoneum. Because clinical signs of renal failure may be similar to those with septicemia or asphyxia (weakness, recumbency, or poor nursing vigor), performing a serum biochemical analysis in compromised neonates is an essential part of the minimum database to detect azotemia. Spurious hypercreatininemia may also be a transient finding in asphyxiated foals or foals delivered from mares with placentitis.1 Neonates with spurious hypercreatininemia have normal serum electrolyte concentrations, supporting normal renal function, and creatinine concentration, which may exceed 20 mg/dL, typically drops by 50% or more over the first 1 to 2 days of life, as long as foals are well hydrated and nursing well (Fig. 1). In older foals, azotemia and renal failure are almost always a consequence of another primary disease process, although limited renal function with congenital anomalies may delay onset of renal failure until foals are several years old.

2. Neonatal Renal Development and Physiology
Nephrogenesis, in terms of nephron numbers, is essentially complete at birth, and, as foals grow, the kidneys increase in size through the first 1 to 2 years of life. Foals are born with about 10 million glomeruli in each kidney, and these enlarge in size as the kidneys grow.2 Of interest, low birth weight and premature infants may be born with fewer nephrons, and there is mounting evidence that this reduced renal endowment may increase the risk of developing hypertension and chronic kidney disease (CKD) in later life.3

Normal term colts typically first urinate between 5 and 6 hours of age, whereas fillies initially urinate later, at 10 to 11 hours of age.4 Initial urine may be dilute or concentrated (specific gravity up to 1.040), but hyposthenuria develops by 24 hours of age in all foals that are nursing well. Urine pH is nearly neutral, and significant proteinuria (2 to 3+ on reagent strips) is commonly observed from 24 to 48 hours of age in foals that received good passive transfer of colostral antibodies.5 Serum urea nitrogen (BUN) and creatinine (Cr) concentrations are variable during the initial 24 hours of life, with values in the range of 15 to 30 mg/dL (~5–10 mmol/L) and 2 to 4 mg/dL (~175–350 μmol/L), respectively. BUN generally drops below the lower limit of the adult reference range by 24 hours of age, whereas Cr may not drop below 2 mg/dL until 48 hours of age. By 1 to 2 weeks of age, BUN is typically below 10 mg/dL (~3.5 mmol/L) and Cr may fall below 1.0 mg/dL (~90 μmol/L). These low values...
Renal tubular function remains essentially normal with pre-renal failure. Thus, serum electrolyte concentrations are typically normal, and urine sodium concentration is <20 mEq/L. Depending on hydration status, urine specific gravity may be variable, but the classic finding that supports pre-renal azotemia is a specific gravity ≥1.025 and a urine osmolality (Uosm) exceeding 500 mOsm/kg.

4. Intrinsic Renal Failure
Intrinsic renal disease and acute renal failure (ARF) can develop as a consequence of hypoxic-ischemic injury associated with birth asphyxia, septicemia, or leptospirosis or treatment with nephrotoxic medications (aminoglycoside antibiotics and NSAIDs). It is often difficult to separate the effects of these factors because many compromised foals are routinely treated with nephrotoxic medications. Over the past decade, there has been a shift away from routine use of penicillin and an aminoglycoside for broad-spectrum antimicrobial therapy of neonatal foals (largely replaced by ceftriaxone), and this change has probably decreased the incidence of aminoglycoside nephrotoxicity in foals. Further, the shift away from multiple daily doses to once-daily dosing regimens for aminoglycoside antibiotics has been well documented to decrease the risk of nephrotoxicity in infants. Unfortunately, during the same time period there has been increased use of oxytetracycline in foals with contracted tendons, and tetracycline-associated ARF may go undetected in compromised neonates unless a serum chemistry profile is submitted as part of case management. The incidence of ARF in foals in neonatal intensive care units is not well documented, but human neonatal intensive care units have reported incidences ranging from 6% to 24%, with cardiac surgery and severe asphyxia being recognized risk factors. Of interest, ARF was nonoliguric, oliguric, and anuric in 60%, 25%, and 15% of patients, respectively. Consequently, adequate urine production cannot be used to exclude AKI and ARF in compromised equine neonates.

Although there are no specific values for BUN and Cr that separate pre-renal failure from intrinsic renal failure, azotemia is generally greater with intrinsic renal failure. Further, there is not a sudden transition from pre-renal failure to intrinsic renal failure; rather, these are overlapping conditions. To emphasize the point that some intrinsic renal damage probably occurs with simple renal hypoperfusion, the term acute kidney injury, characterized by a 50% increase in Cr, has been introduced to describe early damage with intrinsic renal disease. This predominantly tubular damage may be characterized by proteinuria, microscopic hematuria, glucosuria, increased urine sodium and chloride concentrations and excretion, increased urinary enzyme activities, and detection of novel biomarkers of tubular epithelial damage in urine (kidney injury molecule 1 and others).
iment may also reveal hyaline or granular casts. These urinary changes can develop a few days before onset of significant azotemia.

With both pre-renal and renal azotemia, acute changes are better assessed by the comparatively greater increase in Cr than BUN, due to the larger size of Cr that slows its diffusion out of the extracellular fluid (ECF) space. Thus, following changes in Cr over time is more reliable for assessment of changes in renal function than is monitoring BUN. However, it warrants emphasis that increases in Cr are insensitive for detection early changes in renal function (GFR must decrease by 75% or more before azotemia develops). Further, an occasional foal may have a more marked increase in BUN than Cr, and, in such cases, upper intestinal ulceration with blood loss into the intestine should be considered as a potential cause for the increase in BUN. Next, another simple question to ask is whether or not acid-base status and serum electrolyte concentrations are normal. These parameters typically remain normal with pre-renal azotemia, whereas alterations are common with intrinsic renal failure (hyponatremia, hypochloremia, hyperkalemia, and metabolic acidosis). A final hallmark of tubular damage associated with AKI and intrinsic renal failure is loss of concentrating ability. Urine of affected foals is typically hyposthenuric (specific gravity <1.008 and U_osm <300 mOsm/kg).

With AKI and intrinsic renal failure, it is important to determine whether or not affected neonates are oliguric (urine output <0.5–1 mL/kg/h) because oliguric AKI carries a more guarded prognosis than does nonoliguric AKI. However, most cases in neonates are nonoliguric, and these may only be detected by finding a progressive increase in Cr with serial serum biochemical analyses. Fortunately, neonatal kidneys are forgiving, and treatment can sometimes be successful with anuria/oliguria lasting up to 72 hours. Dialysis, either peritoneal or hemodialysis, is also feasible in foals as compared with full-sized adult horses when anuria/oliguria persists. However, recent reports of peritoneal dialysis as a treatment for oliguric renal failure in horses are not without controversy, as careful review of the reports reveals that urine output was not well documented and that Cr had already begun to decline before dialysis was initiated. The main challenge of treating patients with anuric/oliguric renal failure is not to control Cr; rather, it is to maintain acid-base balance and serum electrolyte concentrations within reasonable ranges while renal tissue is repaired and urine production returns. Of interest, recent evidence in management of ARF in people provides further support for cautious IV fluid support of compromised foals (so-called “running them dry”) because excessive fluid replacement may increase intrarenal pressure and further compromise restoration of renal function.

5. Post-Renal Failure

Azotemia arising from disruption of the urinary tract typically occurs in the face of nearly normal kidney function, but failure to eliminate urine leads to progressive abdominal distension and electrolyte alterations. Hyponatremia, hypochloremia, and hyperkalemia develop with “mixing” or “dialysis” of the expanded peritoneal fluid compartment with the remainder of the ECF compartment, including plasma. Again, because Cr does not diffuse out of the ECF compartment as rapidly as urea, finding a peritoneal fluid Cr to serum Cr ratio >2 is the clinical pathologic test of choice to confirm uroperitoneum. However, this test is being performed less frequently than in the past because detection of a large volume of hypoosmotic fluid within the abdomen via transabdominal ultrasonography is essentially a pathognomonic finding in foals with electrolyte alterations expected with uroabdomen.

The classic case of uroperitoneum occurs in 2- to 3-day-old colts that develop abdominal distension consequent to a dorsal bladder wall tear sustained as they pass through the pelvic canal with a full bladder. However, silent uroabdomen can also develop in compromised neonates in intensive care units, especially when they are unable to stand and void urine normally. Uroabdomen in these foals may develop as a consequence of bladder distension and leakage/rupture or can be due to a small leak in association with sepsis of the urachus. Uroabdomen in these foals may not become a problem until 4 to 7 days of age and is often first detected as an increase in free abdominal fluid during routine transabdominal ultrasonographic monitoring of sick neonates to assess intestinal motility and bladder size. At initial suspicion of uroabdomen, enough time may not have elapsed for electrolyte alterations to develop (or they may be attenuated by concurrent IV fluid therapy), but uroperitoneum can be confirmed by comparing peritoneal fluid Cr to serum Cr. Finally, another cause of “late onset” uroperitoneum can be a ruptured ureter. Most ureteral leaks occur near the kidney and may be associated with blunt abdominal trauma during parturition or after birth. The author has seen several cases of ureteral leakage in foals with multiple rib fractures, supporting birth trauma and possible delivery with the mare in a standing position as potential risk factors. Urine initially accumulates more slowly in the retroperitoneal space until it ruptures into the peritoneal cavity. Further, with unilateral ureteral rupture, the bladder continues to fill from the contralateral side and normal urination may still be observed.

6. Congenital Disorders

Anomalies of renal development reported in foals include agenesis/aplasia, hypoplasia, dysplasia, and polycystic kidney disease (PKD). Although present at birth, anomalies may not lead to azotemia and renal failure until later in life, especially renal
hypoplasia or PCKD. For example, the author diagnosed PCKD as the cause of CKD in a 19-year-old Arabian mare. Anomalies of the collecting system such as ureteral ectopia do not typically cause renal failure and azotemia unless complicated by obstruction or ascending urinary tract infection. Mega-vesica, or a markedly enlarged bladder, has been described in several foals in association with suspected urachal obstruction and can cause post-renal failure and abdominal distension (due to the large bladder) without actual disruption of the urinary tract.29

7. Evaluation and Management of Azotemia

When azotemia is detected in a neonatal foal, repeating the physical examination may detect subtle findings that may not have been appreciated during the initial exam. For example, mild edema or “looseness” of the skin in the axillary and inguinal regions may be appreciated with oliguria, and foals with hyperkalemia may have fine muscle tremors that may be easier to feel than to see. Evidence of incontinence may support ectopic ureter, and moistness of the umbilicus may support localized sepsis that may lead to subcutaneous urine accumulation and/or uroperitoneum. In addition to physical examination and a clinicopathologic database, abdominal ultrasonography should be a standard part of the work-up of neonatal foals. With regard to the urinary system, the first question to answer is whether or not the foal actually has two kidneys that are of normal shape and size (about 5 × 10 cm for a 50-kg foal, Fig. 2).30 Foals that have nursed well or that have started on IV fluid support and are producing adequate urine often have mild distension (to 1–1.5 cm) of the renal pelvis (Fig. 3), but this should be a symmetrical finding in both kidneys. Next, the bladder should be imaged to determine whether it is small (supporting oliguria) or possibly larger than normal (supporting intra-uteral urachal obstruction or lack of detrusor tone). If the bladder is larger than 10 cm in diameter and urination is not observed within 30 to 60 minutes after this finding, a catheter should be passed to collect a urine sample and to empty the bladder. Indwelling bladder catheters with closed collection systems are being used more frequently in recumbent neonates and are certainly helpful in documenting rate of urine production. However, even well-managed catheters are commonly colonized with multidrug resistance bacterial spp.; thus, short-term use (<3 days) is the goal and prophylactic antimicrobial treatment is warranted.

One of the hallmark treatments of azotemia is supportive fluid therapy. However, the approach should err on the side of caution. For example, with pre-renal azotemia and spurious hypercreatininemia, fluid support can often be limited to enteral milk feeding or close observation to ensure adequate nursing. With milk alone provided at 10% or more of body weight daily, foals will be receiving a fluid intake at a rate more than adequate for maintaining hydration. Although adequate nutritional support with enteral milk feeding can be accomplished in all neonates that tolerate milk feedings, it is important to remember that foals will produce dilute urine (specific gravity ≤1.005) when fed either 10% or 20% of body weight daily as milk. However, they will produce a greater amount of dilute urine when they are fed more. Thus, assessment of body weight gain daily is a superior method of assessing adequacy of either nursing or enteral feeding, as compared with only measuring urine specific gravity. When enteral feeding is not tolerated well and/or when acid-base balance or serum electrolyte concentrations are altered, judicious IV fluid therapy support may also be required. A potassium-free IV fluid (0.9% saline solution) should
be used when significant hyperkalemia (>5.5 mEq/L) is present, whereas a polyionic replacement fluid can be used when potassium concentration is not elevated. The goal should be to limit fluid replacement to maintenance to 1.5 times maintenance requirements (1.0–1.5 mL/kg/h), and patients on IV fluids should be monitored twice daily for development of edema and body weight change. Urine production can also be monitored with an indwelling collection system, and central venous pressure (CVP) can be monitored via the jugular venous catheter placed for fluid administration (as the catheter end is often near or in the right atrium). Ideally, CVP should be maintained below 10 cm H₂O. Further, the enteral route, when it is working, can also be used for administration of sodium chloride, sodium bicarbonate, potassium chloride, or potassium bicarbonate. Once foals are tolerating enteral feeding well or are nursing adequately, they will have a fluid intake that may be 3 to 5 times maintenance requirements, and there is little benefit of additional IV fluids. The resultant diuresis is generally adequate for resolution of azotemia, as long as damaged renal tissue undergoes repair. Thus, IV fluid therapy does not need to be continued until azotemia has fully resolved and can often be stopped once Cr concentration has stabilized at values <2.5 to 3 mg/dL (~250 μmol/L), although Cr concentration should be measured again 1 to 2 days after discontinuing IV fluids to make sure that it is not increasing again. What is difficult (or impossible) to know at the start of therapy is what the final Cr will be after repair of damaged renal tissue. Many cases will have Cr return to values within the reference range within 5 to 10 days, whereas others will be discharged with persistent elevations in Cr. In the latter cases, Cr should be monitored at monthly intervals and may still return to normal values over 1 to 3 months.

In foals with oliguric ARF, judicious fluid therapy is even more critical to prevent volume overload. Although efficacy remains unproven, furosemide (1–3 mg/kg, q 2 hours, IV) may be used in an attempt to increase urine flow rate. If no effect is observed, mannitol (0.25–1.0 g/kg, IV) has also been used as an osmotic diuretic but, again, supportive data are lacking in foals, and this treatment has fallen out of favor in human medicine. Similarly, use of a dopamine infusion in an attempt to increase renal blood flow is no longer recommended in human medicine because of the potential for development of arrhythmias and a lack of data substantiating improved long-term outcome. Despite the lack of clinical evidence for treatment of anuric or oliguric ARF, continuous rate infusion of pressor agents, including dopamine, norepinephrine, or dobutamine, may be of benefit to foals with systemic hypotension, as part of the overall neonatal supportive care although the electrocardiogram (ECG) should be closely monitored during use of these drugs. Finally, peritoneal dialysis can be considered with refractory oliguria and worsening azotemia. The goals of dialysis are to both correct electrolyte alterations and acid-base status along with controlling azotemia, but a more guarded prognosis should always be issued for owner consideration before this more invasive treatment is pursued.

Surgical correction of urinary tract disruption is generally the treatment of choice for uroabdomen, although small bladder rents may heal with placement of an indwelling bladder catheter alone. With uroabdomen, large volumes of urine in the abdomen may compromise ventilation, and moderate to severe hyperkalemia (>6.5–7.0 mEq/L) may

Fig. 3. Ultrasonographic appearance of normal kidneys of equine neonates receiving IV fluids showing distension of the renal pelvis to nearly 2 cm in diameter.
cause life-threatening cardiac arrhythmias. Thus, affected neonates must be stabilized before surgical treatment is pursued. Drainage of accumulated urine is indicated but can be challenging. The author prefers using a small trocar chest tube (16F), placed abaxial to the linea alba (Fig. 4), over a teat cannula or bitch catheter to allow more rapid removal of urine from the abdomen. Multiple holes in the chest tube also make occlusion with omentum or mesentery less of a problem.

Immediate treatment of hyperkalemia is directed at membrane stabilization by administration of potassium-free IV fluids supplemented with calcium and dextrose over 30 to 60 minutes (e.g., by addition of 50 mL of a 23% calcium boroguconate solution and 200 mL of a 50% dextrose solution to 1 L of 0.9% NaCl, after initially discarding 100–200 mL of the 0.9% NaCl solution). Calcium acts rapidly (within 2–5 minutes and lasting 30–60 minutes) to raise threshold membrane potential, thereby reestablishing the gap between resting membrane potential and threshold membrane potential to counteract the increased (less negative) resting membrane potential induced by hyperkalemia. The increase in glucose concentration consequent to dextrose administration stimulates endogenous insulin release that leads to increased activity of Na/K/ATPase pumps on cell membranes and redistribution of potassium into cells over a period of a few hours. ECG changes accompanying hyperkalemia typically progress from peaked T waves, loss of P waves, widening of the QRS complex, sine wave pattern, and ultimately to ventricular fibrillation as serum potassium concentration increases. Un fortunately, ECG changes are inconsistent, and ventricular fibrillation may be the initial arrhythmia while the ECG may remain normal in some patients with severe hyperkalemia. In foals with uroabdomen, drainage of urine that has accumulated in the abdo-

References


