This article discusses kidney disease in critically ill small animal patients. Critically ill patients may present to the clinician with kidney disease as the primary complaint, or kidney damage or dysfunction may arise as a complication or consequence of other illness. In the latter scenario, the clinician must carefully monitor parameters that assess renal function and be prepared to intervene to prevent irreversible injury.

NORMAL RENAL FUNCTION

The functions of the kidney are wide-ranging and critical for maintaining homeostasis. These functions include the regulation of electrolyte and acid-base balance, regulation of water balance, regulation of arterial blood pressure, excretion of metabolic wastes, excretion of hormones and exogenous compounds (eg, drugs), production of erythropoietin, synthesis of active vitamin D, and gluconeogenesis.1

The basic functional unit of the kidney is the nephron, which consists of the glomerulus, Bowman’s capsule, and the renal tubule.1 The glomerulus is interposed between an afferent and efferent arteriole within the renal cortex, and is the site of filtration of water and solutes from the blood. This filtrate passes into Bowman’s space and then is significantly altered as it traverses the renal tubule. The functions of the different segments of the renal tubule are reflected in the functional and structural specializations of the epithelial cells that line the tubule.

Central to the function of the kidney is the unique blood supply to this organ. The kidneys receive approximately 20% of cardiac output,2 all of which passes through the glomeruli. The blood enters the glomeruli through the afferent arterioles, 20% of the plasma passes into Bowman’s space, and 80% of the plasma leaves through the efferent arterioles. Of the blood leaving the glomerulus, 90% or more passes through the peritubular capillaries in the renal cortex and into the renal venous system. The remaining 5% to 10% flows into the medulla through the vasa recta. These bundles of parallel vessels play an important role in solute and water exchange in
the renal medullary interstitium. Although an in-depth review of renal vasculature, blood flow, glomerular filtration, and tubular function is beyond the scope of this article, an understanding of this area is important in understanding the role of the kidney in critical illness. The following facts are particularly noteworthy:

1. The vasculature of the renal cortex is highly unusual in that there are 2 arterioles (afferent and efferent) and 2 capillary beds (the glomerulus and the peritubular capillaries).
2. Glomerular filtration rate (GFR) reflects renal function.
3. The main factors affecting GFR are the permeability of the glomerular capillaries, the hydrostatic pressure in Bowman’s capsule, the oncotic pressure of the blood, and the hydraulic pressure in the glomerular capillaries.
4. The pressure in the glomerular capillaries is determined by the pressure in 2 arterioles that are in series: the afferent and efferent arterioles. Changes in the resistance of each of these arterioles allow the kidney to regulate GFR independently of renal blood flow. For example, if renal arterial pressure falls, constriction of the efferent arteriole will increase the pressure in the glomerulus, and preserve GFR.
5. Constriction of the afferent or efferent arteriole has opposite effects on GFR, but both decrease renal blood flow. Changes in renal blood flow are important because they affect the metabolic functions and the integrity of the tubules. Changes in GFR affect excretion of water and solutes.
6. The kidney has a remarkable ability to maintain renal blood flow and glomerular filtration within a narrow range in the face of alterations in mean arterial blood pressure. This effectively isolates the kidney from normal fluctuations in systemic blood pressure and allows the kidney to continue its necessary homeostatic functions. This property is known as autoregulation and is effective over mean arterial blood pressures ranging from 70 to 170 mm Hg.
7. As noted earlier, the renal cortex receives about 90% of renal blood flow, with the medulla receiving about 10%, which means that the cortex is particularly vulnerable to blood-borne toxins. In contrast, the medulla is more susceptible to ischemia.
8. Within the renal cortex, the most metabolically active nephron segments are most susceptible to ischemic damage, including the proximal tubule and the thick ascending limb of the loop of Henle.
9. The processes that alter the ultrafiltrate in the nephron tend to concentrate nephrotoxins.

AZOTEMIA, UREMIA, AND RENAL FAILURE

Azotemia is defined as an increase in serum creatinine or blood urea nitrogen (BUN) concentrations, or both. Thus it is defined by the results of laboratory tests. Uremia literally means the presence of urine constituents in the blood, but the term is generally used to refer to the clinical signs that develop as azotemia worsens. These clinical signs commonly include decreased appetite, vomiting, lethargy, and weight loss. As uremia progresses, affected patients may develop uremic gastritis, oral ulcers, and platelet dysfunction. Less common signs of severe uremia may include uremic pneumonitis, osteodystrophy, and encephalopathy. Other consequences of worsening renal function include polyuria/polydipsia, dehydration, electrolyte derangements, acidosis, anemia, systemic hypertension, and renal secondary hyperparathyroidism.

Azotemia, renal insults, renal disease, or renal failure are often classified as prerenal, renal, or postrenal; many patients may have a combination of more than 1 type of
azotemia or renal insult. The term prerenal implies normal renal morphology with a functional decrease in GFR, which may arise through decreased cardiac output, hypovolemia, hypotension, dehydration, decreased effective circulating volume, decreased plasma oncotic pressure, increased blood viscosity, or occlusion or constriction of the renal artery. When considering azotemia, the term prerenal also refers to an increase in BUN caused by increased protein intake or gastrointestinal bleeding. Renal azotemia or renal disease implies that the kidney itself is compromised and unable to perform its normal functions. Intrinsic renal disease can arise through a variety of different insults, many of which are discussed later. Postrenal azotemia implies that BUN and creatinine are increased because the urine does not exit the body through the normal route. This condition can arise through obstruction within the urinary tract, or rupture of the tract with subsequent leakage of urine into the abdomen.

**Differentiation Between Prerenal, Renal, and Postrenal Azotemia**

It is essential for the clinician to always consider prerenal, renal, and postrenal causes whenever a patient is newly diagnosed with azotemia, or whenever a previously stable azotemic patient experiences an unexpected increase in BUN or creatinine. This requirement is crucial because it may be possible to improve or fully reverse the prerenal or postrenal components of the azotemia. There is a continuum of damage between prerenal and renal azotemia, and between postrenal and renal azotemia. While it is diagnostically helpful, it is also vital, to consider the 3 components of azotemia, because failure to consider, and attempt to correct, prerenal and postrenal azotemia will eventually lead to intrinsic renal damage. For example, complete ureteral obstruction by a calcium oxalate nephrolith in a cat will initially reduce GFR because of increased hydrostatic pressure in Bowman’s capsule. In time, the pressure in the renal pelvis will lead to hydronephrosis and permanent damage to the renal parenchyma. This patient will therefore progress from postrenal disease to intrinsic renal disease. Similarly, a sustained decrease in renal artery pressure, if less than the limits of autoregulation, will result in renal ischemia, renal tubular cell damage, and eventually acute intrinsic renal failure. In this case, it may be argued that the distinction between prerenal and renal azotemia is artificial, because prerenal factors, if not addressed, can progress to cause renal damage.

A prerenal component of azotemia should be assumed if the patient has a history of excessive fluid losses or decreased fluid intake. A prerenal component is also likely to be present if the patient has clinical findings consistent with hypotension, hypovolemia, shock, dehydration, or inadequate peripheral perfusion. The clinician must therefore rely on the history and physical examination findings to ensure that prerenal azotemia is considered; there are few specific laboratory tests that can confirm the presence of prerenal azotemia. In some cases, examination of the BUN/creatinine ratio can raise suspicion of a prerenal component to the azotemia. Creatinine is freely filtered at the glomerulus, and is not significantly secreted or reabsorbed. Thus, serum creatinine levels are largely dependent on GFR. In contrast, urea is both secreted and reabsorbed, as well as freely filtered, and it plays an essential role in urine concentrating ability. In simple terms, urea can be considered to follow water in the distal renal tubule. In a state of hypovolemia, hypotension, or dehydration, the kidney attempts to conserve water through the actions of antidiuretic hormone (ADH), and the same water-conserving mechanisms also promote reabsorption of urea. Thus, when GFR is decreased by prerenal factors, both creatinine and BUN increase, but BUN may increase to a proportionally greater extent as the kidney attempts to conserve water.

Interpretation of urine specific gravity is helpful when determining whether a patient has renal azotemia. It is most important for the clinician to consider whether urine
specific gravity is appropriate for the patient, not whether it is normal. Kidneys respond appropriately to changes in body water balance by producing urine that allows excess water to be excreted, or by allowing water to be conserved in the face of dehydration. Water balance depends on 3 components: normal thirst, normal number and function of nephrons, and the action of ADH at the distal nephron. In renal disease, once approximately 66% of functional nephron mass is lost, renal concentrating ability is lost because the remaining nephrons must handle larger amounts of filtered solute, and this contributes to an osmotic diuresis. However, many other factors affect renal concentrating ability. Abnormal water intake leads to the production of a nonconcentrated urine; similarly, fluid therapy decreases urine specific gravity. Many drugs act to increase urine output. For example, diuretics are specifically used for this purpose. Other medications, such as glucocorticoids, may interfere with the action of ADH. Disease processes also interfere with renal concentrating ability without necessarily causing intrinsic renal damage. Examples include typical hypoadrenocorticism (Addison’s disease), hypercalcemia, diabetes mellitus, hyperadrenocorticism, and diabetes insipidus. In summary, if a patient is azotemic and the urine is concentrated (specific gravity >1.035 in a dog and >1.045 in a cat), renal azotemia is unlikely. If a patient is azotemic and the urine is not appropriately concentrated, that patient may have renal disease, but the clinician should consider other causes of failure to concentrate the urine: fluid therapy, medications, and concurrent diseases that cause polyuria. If the urine is hyposthenuric, renal failure is not ruled out because failing kidneys do retain diluting ability. However, renal tubular failure alone does not cause hyposthenuria, and the clinician must consider the presence of additional disease processes.

Addison’s disease is a classic example of a single disease that can cause a significant azotemia together with failure to appropriately concentrate the urine. A patient in an addisonian crisis is often azotemic because of the presence of marked hypovolemia, hypotension, and dehydration. This patient has prerenal azotemia. The urine is not appropriately concentrated because marked sodium (Na) depletion in this patient decreases the hypertonicity of the renal medulla, which is essential for the creation of a concentrated urine. The example of the patient with Addison’s disease illustrates another important feature of prerenal azotemia: it can be completely resolved with appropriate therapy. Thus, aggressive fluid therapy to restore volume in the patient with Addison’s disease typically completely resolves the azotemia within 24 to 48 hours. By appropriately correcting the prerenal component of azotemia, the clinician has shown that this patient does not have renal azotemia.

Postrenal azotemia can be considered to be a urine flow problem: the urine is not exiting the body because of obstruction to urine flow, or because of diversion as a result of a rupture of the duct system. Obstruction or rupture can occur at any level of the urinary tract. These problems are best diagnosed with imaging. In the case of urinary tract rupture, an effusion will be present. The creatinine and potassium (K) content of the effusion should be measured and compared with serum levels. If the creatinine or K levels in the fluid are more than twice those in the serum, the effusion likely contains urine. Because urinary tract obstruction can occur at any level, this cannot be ruled out in the patient that is able to urinate. The obstruction may be partial, or at the level of 1 ureter or renal pelvis. The combination of both abdominal radiographs and abdominal ultrasound gives the best diagnostic accuracy for detection of urinary tract obstruction. The obstruction of 1 kidney only leads to azotemia if the contralateral kidney is subnormal. The most common example of this scenario is ureteral obstruction in cats. For the development of azotemia, approximately 75% of functional nephron mass must be lost. Thus ureteral obstruction does not
cause azotemia if the remaining kidney is normal (because only 50% of renal mass has been lost). However, if ureteral obstruction occurs in a cat with preexisting renal disease, the remaining kidney may not be able to provide more than 25% of renal function, and azotemia will result. This patient has both renal and postrenal azotemia.

Many acutely azotemic patients have more than 1 type of azotemia. For example, the cat with ureterolithiasis described earlier may have preexisting chronic kidney disease causing renal azotemia, an obstructing ureterolith causing postrenal azotemia, and fluid deficits caused by anorexia and vomiting causing prerenal azotemia. It is the clinician’s responsibility to consider all forms of azotemia and their appropriate therapies. In Table 1, clinical questions are used to frame the approach to the azotemic patient, ensuring that the clinician considers the different potential causes of azotemia, as well as the tools used to detect them.

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Important Findings</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the azotemia prerenal?</td>
<td>History, Physical examination, BUN/creatinine ratio</td>
<td>Fluid support, Oncotic support, Blood pressure support</td>
</tr>
<tr>
<td>Is the azotemia postrenal?</td>
<td>Abdominal radiographs, Abdominal ultrasonography, Abdominocentesis and fluid analysis</td>
<td>Surgical or medical therapy, depending on cause</td>
</tr>
<tr>
<td>Is the azotemia renal?</td>
<td>History, Response to therapy for prerenal and postrenal causes, Urine specific gravity</td>
<td>Address prerenal and postrenal causes</td>
</tr>
<tr>
<td>Is renal azotemia acute or chronic or both?</td>
<td>History, Physical examination, Packed cell volume, Renal imaging</td>
<td>Assume acute component in the sick patient, Provide therapy for acute renal failure (see text)</td>
</tr>
<tr>
<td>If acute renal azotemia, is the cause a drug or toxin?</td>
<td>History, Specific testing where applicable</td>
<td>Remove drug or toxin, Specific antidotes when available</td>
</tr>
<tr>
<td>If acute renal azotemia, is the cause an infection?</td>
<td>Urine culture, Specific disease testing</td>
<td>Antibiotics if pyelonephritis suspected, Antibiotics in a dog if leptospirosis not ruled out or another specific cause is not identified</td>
</tr>
<tr>
<td>What are the consequences of renal failure in this patient?</td>
<td>Volume status, Blood pressure, Perfusion parameters, Body weight, Appetite, Urine output, Serum chemistry profile, Blood gas/lactate, Complete blood count, Urinalysis</td>
<td>Fluid therapy, Pressor support, Antihypertensive medications, Address electrolyte abnormalities, Address acid-base status, Provide nutritional support</td>
</tr>
</tbody>
</table>
**KIDNEY DISEASE**

Kidney disease may be defined as structural or functional abnormalities in 1 or both kidneys.\(^3\) Thus, a clinically insignificant renal cyst and catastrophic acute renal failure (ARF) caused by ethylene glycol intoxication are both examples of kidney disease. Disease of 1 or both kidneys may be detected by laboratory testing (including blood and urine tests), histopathologic examination of tissue, or imaging studies such as radiographs or ultrasonography. The severity of renal disease and the implications for therapy and prognosis can vary between patients. Many of the terms used to describe kidney disease are confusing or poorly defined. One example is the term renal insufficiency. This may be interpreted to mean loss of renal concentrating ability in the absence of azotemia; it may be used to signify mild azotemia, or it may imply loss of renal reserve or an inability to compensate for further loss of renal function.

Poorly defined terms have led to attempts to standardize the language and terminology of kidney disease. The use of consistent definitions should allow clearer communication and recording of clinical findings, and also more meaningful comparisons between research studies.

**Chronic Kidney Disease: Definition and Staging**

The international renal interest society (IRIS; [www.iris-kidney.com](http://www.iris-kidney.com)) has proposed that the term chronic kidney disease (CKD) be used in preference to chronic renal failure. In this context, chronic implies the presence of kidney damage for at least 3 months.\(^3\) This time course is typically inferred from historical findings or from the results of repeated laboratory tests that show persistent azotemia or abnormalities on urinalysis. Historical findings in chronic renal failure may include polyuria/polydipsia, weight loss, decreased appetite, and lethargy. The chronicity of the disease process may be supported by the presence of a nonregenerative anemia, or by the appearance of the kidneys or radiographs or ultrasound examination.

CKD may be defined as:

1. Kidney damage present for at least 3 months, with or without a decrease in GFR, or
2. A reduction in GFR by more than 50% below normal, present for at least 3 months.\(^3\)

CKD is then staged from the fasting creatinine value assessed on at least 2 occasions in the stable patient, which implies that a CKD stage is not usually assigned at the initial time diagnosis of kidney disease, and, more importantly, a CKD stage should not be applied to a patient that is not clinically stable. **Table 2** summarizes the IRIS stages of CKD in dogs and cats. This system allows for primary staging based on serum creatinine values. Additional substages are then assigned depending on the level of proteinuria present and the patient’s blood pressure.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine Value (mg/dL)</th>
<th>Azotemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dogs</td>
<td>Cats</td>
</tr>
<tr>
<td>1</td>
<td>&lt;1.4</td>
<td>&lt;1.6</td>
</tr>
<tr>
<td>2</td>
<td>1.4–2.0</td>
<td>1.6–2.8</td>
</tr>
<tr>
<td>3</td>
<td>2.1–5.0</td>
<td>2.9–5.0</td>
</tr>
<tr>
<td>4</td>
<td>≥5.0</td>
<td>≥5.0</td>
</tr>
</tbody>
</table>
ARF and Acute Kidney Injury

Many definitions of ARF can be found in the veterinary literature, such as:

- The sudden inability of the kidneys to regulate water and solute balance.\(^\text{10}\)
- Rapid deterioration of renal function resulting in the accumulation of nitrogenous wastes such as urea and creatinine.\(^\text{10}\)
- An abrupt and prolonged decline in glomerular filtration resulting in the accumulation of nitrogenous wastes.\(^\text{11}\)

The elements that these definitions have in common are that renal failure occurs in a short time period, and that there is a consequent loss of renal function. Some of these definitions also state, or imply, that BUN and/or creatinine are increased beyond the reference range in ARF. What is less clear from these definitions is the nature of the other renal functions that are affected, the methods by which these functions are assessed, and the amount of deviation from normal that is considered significant. The terms sudden, rapid, abrupt, and prolonged are also not clearly defined.

In human medicine, the term acute kidney injury (AKI) is gradually replacing ARF.\(^\text{12–14}\) and classification schemes are used to define the severity and outcome of AKI in people. One example of such a scheme is a multilevel classification system\(^\text{15–17}\) that defines 3 levels of severity of AKI: risk (R), injury (I), and failure (F) based on objective measurement of serum creatinine and/or GFR, and urine output. The criteria also allow for 2 levels of outcome of AKI: loss of function (L) and end-stage renal disease (E). This system is known as the RIFLE classification scheme, and it is summarized in Table 3. By replacing the term ARF with AKI, proponents of the RIFLE classification system have suggested that the entire spectrum of acute changes in renal function is included in the definition. The use of the classification system provides a more uniform definition of AKI, and this should facilitate a more uniform approach to diagnosis, therapy, and prognosis. It should also assist in the design and interpretation of studies of AKI in clinical patients.\(^\text{13}\)

Classification schemes for AKI have not yet been broadly adopted in veterinary medicine, although a scoring system has been proposed to facilitate prediction of the outcome of hemodialysis in dogs with AKI.\(^\text{18}\) Examination of Table 3 reveals at least 2 significant reasons why this scheme would be difficult to apply to veterinary

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIFLE classification scheme for AKI in human patients</strong></td>
</tr>
<tr>
<td><strong>Severity Category</strong></td>
</tr>
<tr>
<td>R (risk)</td>
</tr>
<tr>
<td>I (injury)</td>
</tr>
<tr>
<td>F (failure)</td>
</tr>
<tr>
<td><strong>Outcome Category</strong></td>
</tr>
<tr>
<td>L (loss)</td>
</tr>
<tr>
<td>E (end-stage kidney disease)</td>
</tr>
</tbody>
</table>

Abbreviations: GFR, glomerular filtration rate; UO, urine output.

patients: baseline creatinine values are rarely known, and urine output is not routinely measured. The term AKI is also not consistently applied in veterinary patients. Most clinicians are more comfortable with the term ARF. Because strict definitions have yet to be agreed on in veterinary medicine, AKI and ARF are used interchangeably in this article.

PATHOPHYSIOLOGY OF ARF

ARF is frequently described in 4 stages: initiation, extension, maintenance, and recovery. It is not always possible to distinguish clinically between these phases. The initiation phase begins with the renal insult and continues until there is a detectable change in renal function. Intervention during this phase may prevent progression. In the extension phase, the initial renal insult is amplified by ongoing renal inflammation and hypoxia. In the maintenance phase, there is little normal tubular function, GFR is decreased, and a critical amount of irreversible damage has occurred. In the recovery phase, the renal tissue regenerates and repairs. In patients that survive ARF, this phase is often identified by the development of a significant polyuria. During this phase it is important to avoid any further renal insults.

Both ischemic renal damage and nephrotoxins lead to pathologic changes in the kidney known as acute tubular necrosis. Although still widely used, this term is inaccurate, because necrosis of tubular cells is not a consistent finding. A full description of the cellular and molecular events underlying acute tubular necrosis is beyond the scope of this article. However, an appreciation for the changes that occur can help the clinician understand the rationale behind the common therapeutic interventions that are indicated in the prevention and management of ARF.

When the pressure in the renal artery decreases to below the autoregulatory range, constriction of the afferent arteriole reduces glomerular filtration pressure and GFR (leading to prerenal azotemia). Blood flow also decreases in the postglomerular capillaries and, as this worsens, ischemia leads to renal tubular damage. Oxygen depletion in the renal tubular cells leads to cytoskeletal disruption, with resultant sloughing of intact cells and cellular debris into the tubular lumen. Cytoskeletal disruption also causes mislocation of the Na/K-ATPase from the basolateral to the apical cell membrane, thus disrupting sodium transport. The ensuing high Na concentration in the tubule causes Tam-Horsfall protein polymerization. The net result of these changes is that the renal tubules become occluded by cellular and protein casts and debris. This occlusion increases intratubular hydrostatic pressure and reduces GFR. Glomerular filtrate also leaks across the denuded tubular walls into the capillaries, further reducing the effective GFR and contributing to azotemia. Other factors involved in the pathophysiology of ARF include intrarenal vasoconstriction, renal medullary hypoxia, and neutrophil chemotaxis with associated release of damaging enzymes and inflammatory mediators.

CAUSES OF ARF

In human medicine, ischemia and nephrotoxin exposure are the most common causes of ARF. Hospital-acquired ARF is a significant problem in human medicine, particularly in the intensive care unit (ICU), and it is frequently multifactorial. Considering both hospital-acquired and community-acquired causes of ARF in humans, approximately 50% of cases are caused by ischemia, 35% are caused by toxins, 10% are attributed to interstitial nephritis, and 5% to acute glomerulonephritis. In contrast with the wealth of data regarding causes of ARF in human patients, there are few studies that document the relative frequency of the causes of ARF in dogs and
cats. Table 4 summarizes the causes of ARF in dogs and cats. In a retrospective study of ARF in 99 dogs presented to a large referral hospital, 33 patients were diagnosed with an isolated ischemic event, the most common of which was pancreatitis (9 cases), 21 dogs were exposed to a single nephrotoxicant (including 12 cases of ethylene glycol toxicosis), 4 dogs had an infectious cause (leptospirosis or pyelonephritis), and 18 dogs had multiple disorders. Of the dogs with multiple disorders, 10 dogs had disseminated intravascular coagulation (DIC) in conjunction with another disease and 5 dogs had pancreatitis in conjunction with another disease. In 22 of the dogs in this case series, no cause for the ARF could be identified.

A recently published case series documented the causes of naturally-acquired ARF in 32 cats. Nephrotoxicosis was the most common cause, accounting for 18 cases (56%). Nine of these were caused by lily ingestion. Four cats had experienced ischemic events, including 2 patients that underwent general anesthesia. The remaining 10 cats had suspected pyelonephritis or ARF of unknown cause.

Community-acquired ARF

In human medicine, prerenal causes account for about 70% of cases of community-acquired ARF. Common causes include excessive fluid losses caused by gastrointestinal disease, inadequate fluid intake, heart failure, and use of diuretics.

In the canine case series summarized earlier, it is not clear how many dogs had community-acquired ARF and how many had hospital-acquired ARF. It is possible that some of the ischemic events occurred in hospitalized patients before referral. Nonetheless, this case series suggests that most cases of community-acquired ARF in dogs likely result from ischemia or nephrotoxicant exposure, or are of unknown cause. In contrast, the feline case series indicates that nephrotoxicants are the most common cause of ARF in cats, although this is based on a small number of cases.

Hospital-acquired ARF

Hospital-acquired ARF in humans is often the result of multiple renal insults, with frequent contributions from hypovolemia, sepsis, and nephrotoxic medications. A multicenter study of almost 30,000 human patients in ICUs revealed that the 5 most common causes of ARF were sepsis, major surgery, low cardiac output, hypovolemia, and medications. There is only 1 published study documenting the causes of hospital-acquired ARF in dogs, and there are no studies involving cats. In the study on dogs, a retrospective case series identified hospital-acquired ARF in 29 dogs. The most common inciting causes identified were nephrotoxicosis in 21 dogs (72%), advanced age (≥7 years) in 20 dogs (69%), chronic heart disease (12 dogs; 41%) and preexisting renal disease (9 dogs; 31%). The most common nephrotoxicants were aminoglycoside antibiotics, cardiac medications, and cisplatin. The overall mortality in this case series was high at 62%. Older dogs appeared to be at greater risk of developing hospital-acquired ARF, and were more likely to subsequently die. Although small, this case series is important because it highlights that some of the inciting causes of hospital-acquired ARF are within the control of the veterinarian. Aging is inevitable, but medications can be chosen and used with care.

A recent multicenter retrospective case series examined organ dysfunction in dogs with sepsis caused by gastrointestinal tract lesions. The study revealed that multiple organ dysfunction syndrome can be identified in these patients, and that organ dysfunction increased the odds of death. Renal dysfunction, as well as respiratory, cardiovascular, or coagulation disorders, was found to independently increase the odds of death. Thus prevention of hospital-acquired ARF is likely to improve patient survival.
Table 4
Selected causes of ARF in small animals

<table>
<thead>
<tr>
<th>Prerenal and Postrenal Causes</th>
<th>Endogenous Nephrotoxins</th>
<th>Exogenous Nephrotoxins: Drugs and Medical Interventions</th>
<th>Exogenous Nephrotoxins: Environmental</th>
<th>Infectious, Inflammatory, Neoplastic, and Miscellaneous Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>Myoglobin</td>
<td>Aminoglycosides</td>
<td>Ethylene glycol</td>
<td>Leptospirosis (D)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Hemoglobin</td>
<td>Cephalosporins</td>
<td>Lilies (C)</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Hypercalcemia</td>
<td>Tetracyclines</td>
<td>Grapes, raisins, currants (D)</td>
<td>Lyme disease (D)</td>
</tr>
<tr>
<td>MODS</td>
<td></td>
<td>Other antibiotics</td>
<td>Melamine/cyanuric acid</td>
<td>Rocky Mountain spotted fever (D)</td>
</tr>
<tr>
<td>Decreased cardiac output</td>
<td></td>
<td>Amphotericin B</td>
<td>Snake venom</td>
<td>Ehrlichiosis (D)</td>
</tr>
<tr>
<td>Renal artery disease</td>
<td></td>
<td>Thiacetarsamide</td>
<td>Heavy metals</td>
<td>Other systemic bacterial infections</td>
</tr>
<tr>
<td>Other causes of ischemia</td>
<td></td>
<td>Cisplatin</td>
<td>Chlorinated hydrocarbons</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Urethral obstruction</td>
<td></td>
<td>Doxorubicin</td>
<td></td>
<td>Amyloidosis</td>
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<tr>
<td>Ureteral obstruction</td>
<td></td>
<td>Vincristine</td>
<td></td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td></td>
<td></td>
<td>Other cytotoxic drugs</td>
<td></td>
<td>Vasculitis</td>
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<tr>
<td></td>
<td></td>
<td>Cyclosporine</td>
<td></td>
<td>Transplant rejection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAIDs</td>
<td></td>
<td>Lymphosarcoma</td>
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<tr>
<td></td>
<td></td>
<td>Diuretics</td>
<td></td>
<td>Other neoplasia</td>
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<tr>
<td></td>
<td></td>
<td>ACE inhibitors</td>
<td></td>
<td>Trauma</td>
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<tr>
<td></td>
<td></td>
<td>Methylened blue</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Radiocontrast agents</td>
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</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; C, cats; D, dogs; MODS, multiple organ dysfunction syndrome; NSAID, nonsteroidal antiinflammatory drug.
NORMOTENSIVE ISCHEMIC ARF

As noted earlier, ischemia is one of the most common causes of ARF in humans, and, in many of these patients, there is an obvious inciting cause, such as sepsis, surgery, heart disease, or hypovolemia. However, in some cases, systemic hypotension is not detected, and ischemia seems to result from increased renal susceptibility to modest reductions in perfusion pressure. This condition is called normotensive ischemic ARF and is associated with conditions in which autoregulation is impaired. The healthy kidney is able to maintain GFR in the face of systemic hypotension by decreasing afferent arteriolar resistance. This mechanism may be ineffective in patients with atherosclerosis, hypertension, or chronic renal failure, because of structural narrowing of the arterioles. Failure to decrease afferent arteriolar resistance is also the mechanism by which nonsteroidal antiinflammatory drugs (NSAIDs) can lead to ARF, because these drugs inhibit the synthesis of renal vasodilatory prostaglandins. Other causes of increased afferent arteriolar resistance include sepsis, hypercalcemia, and radiocontrast agents. When renal perfusion pressure decreases, GFR is also maintained by constriction of the efferent arteriole. In patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, this protective mechanism is diminished, and moderate decreases in renal perfusion may lead to ARF. Hypertension, chronic renal failure, and sepsis may all occur in critically ill small animals, and these patients may also be receiving NSAIDs or ACE inhibitors. Thus, it is reasonable to assume that normotensive ischemic ARF may also occur in dogs and cats.

PREVENTION OF HOSPITAL-ACQUIRED ARF

Several steps are necessary to minimize the risk of ARF in hospitalized patients. These steps can be summarized as follows:

**Awareness of Risk Factors for ARF**

Risk factors for ARF in small animal patients are presented in Table 5. Some of these factors are beyond the control of the clinician (examples include preexisting renal disease and age), which emphasizes how important it is to be aware of the risk factors that are within the control of the clinician, so that they may be minimized or avoided. In addition, risk factors are likely to be additive. For example, the use of an aminoglycoside antibiotic in a normovolemic young animal is likely to be associated with a lower risk of nephrotoxicity than the use of that same drug in an elderly patient that is volume-depleted because of chronic vomiting. In this example, an alternate antibiotic should be used, and, if this is not possible, the aminoglycoside should be used in conjunction with therapeutic drug monitoring and should not be administered until all volume and electrolyte deficits have been addressed.

**Management of Risk Factors for ARF**

Crystalloid and colloid fluid therapy should be used in critically ill patients to prevent or treat volume and hydration deficits and maintain renal perfusion. Patients undergoing general anesthesia should receive fluid therapy. Intravenous fluids can be used to reduce the risk associated with other necessary procedures. For example, use of crystalloid fluid therapy may reduce the risk of ARF caused by contrast-induced nephropathy. Fluids can also be used to correct electrolyte and acid-base disorders. Blood pressure monitoring is essential in critically ill patients, and pressors should be used if necessary. Hypertension should also be corrected because this is directly damaging to the kidneys, as well as other end-organs such as the heart and central
Early Detection of ARF

In human medicine, serum creatinine levels are compared with baseline values, and urine output is measured to classify AKI, particularly when this develops in the ICU. The RIFLE system uses these elements for classification (see Table 3). Veterinary patients may already be critically ill when initially hospitalized, and a true baseline creatinine value is therefore not available. However, daily monitoring of creatinine values in hospitalized patients may reveal trends that suggest declining renal function. Serum creatinine is a readily available test and it continues to be the primary tool used for assessment of renal function. Despite this, it is important to recognize that a single creatinine value can be an insensitive tool. A doubling of serum creatinine correlates with a loss of approximately 50% of GFR, or functional nephron mass. Thus, with constant production, an increase in serum creatinine from 0.6 to 1.2 mg/dL represents a 50% decrease in GFR, although both values are within the reference range.

Measurement of urine output is sensitive to renal hemodynamics, and changes in urine output may precede changes in serum creatinine values. In human medicine,
low urine output has a high positive predictive value for the development of ARF. However, good urine output does not rule out renal dysfunction, thus the negative predictive value is low.\textsuperscript{16} Quantitation of urine output in small animal patients is most likely to occur in patients with a diagnosis of ARF, and in patients that are non-ambulatory and have a urinary catheter placed for ease of management. Consideration should be given to the monitoring of urine output in other critically ill patients that may be at risk for development of ARF.

Results of urinalysis and urine sediment examination can provide evidence of renal disease before significant changes in serum creatinine or urine output are observed. Examples include the presence of casts, pyuria, or bacteruria, and the presence of glycosuria in the absence of hyperglycemia.\textsuperscript{28} For example, casts in the urine may signal aminoglycoside nephrotoxicity before there are changes in the serum creatinine.\textsuperscript{29}

In addition to the standard urinalysis, measurement of urine electrolytes can provide further information about renal function. For example, fractional excretion of Na can be used to help distinguish between prerenal azotemia and intrinsic ARF in azotemic patients, although the distinction may not always be definitive in clinical patients.\textsuperscript{30} Urinary Na and chloride levels may also be useful for detecting significant renal damage after suspected NSAID toxicity, and for monitoring for the development of aminoglycoside toxicity,\textsuperscript{30} and in both of these situations, a value should be obtained on admission to the hospital or before administration of the potential nephrotoxin. Serial measurements may then detect renal damage.

Detection and measurement of enzymuria (enzymes in the urine) has also been used for early detection of renal injury.\textsuperscript{31} These are typically molecules that are too large to be filtered at the glomerulus, and therefore their appearance in the urine may indicate leakage from damaged tubular cells. For example, $\gamma$-glutamyltransferase (GGT) and N-acetyl-$\beta$-$d$-glucosaminidase (NAG) both originate in proximal tubule cells, and measurement of their levels, sometimes expressed as a urine enzyme/creatinine ratio, has been used as a marker for aminoglycoside-induced renal damage.\textsuperscript{29,32–34} These measurements are most useful when a baseline value is obtained before the use of aminoglycosides.\textsuperscript{28,31} Other urinary markers that are being increasingly studied in dogs include C-reactive protein (CRP), immunoglobulin G (IgG), thromboxane B$_2$ (TXB$_2$), and retinol binding protein (RBP).\textsuperscript{35,36} Both CRP and IgG are markers for glomerular damage, whereas RBP is a marker for proximal tubular damage, and TXB$_2$ levels may reflect intrarenal hemodynamics. Some of these markers have been used in experimental models of canine ARF,\textsuperscript{37} but there is little information available regarding their clinical use in critically ill veterinary patients at risk for development of AKI.

**MANAGEMENT OF ARF**

When ARF is suspected or diagnosed, the following stepwise approach is suggested:

1. Obtain a detailed history.
   - Determine whether the patient has been exposed to any potential nephrotoxicants, or has recently experienced anesthesia, surgery, or any other illness.
   - Document all current and recently administered medications, including supplements and nutraceuticals.

2. Obtain baseline physical examination data.
   - Assess volume, hydration, and perfusion parameters. Record temperature, pulse/heart rate, respiratory rate, arterial blood pressure, and body weight.
3. Obtain venous access.
   A jugular catheter or peripherally inserted central catheter (PICC) is recommended, which allows measurement of central venous pressure (CVP), and a multiple lumen catheter facilitates repeated blood sampling for monitoring purposes. Record initial CVP, packed cell volume (PCV), and total solids (TS). Note: if the patient is likely to be referred for renal replacement therapy, the jugular veins should be preserved for that purpose.

4. Obtain baseline laboratory data.
   Complete blood count, serum biochemistry profile, venous blood gas, and complete urinalysis should be performed. Urine should be saved for culture.

5. Correct fluid and volume deficits.
   Calculate volume required for rehydration using body weight (in kilograms) times estimated dehydration (%), which gives fluid deficit in liters. The deficit should be corrected in 4 to 24 hours, depending on the patient’s clinical status and ability to handle a fluid load. A buffered balanced electrolyte solution should be used initially, such as lactated Ringer’s solution or Normosol. Consider colloidal support, if indicated.

6. Place a urinary catheter.
   A urinary catheter with a closed collection system facilitates measurement of urine output. A urinary catheter is also important if leptospirosis is suspected, because it limits environmental exposure to potentially infectious urine. If placement of a urinary catheter is not possible, small dogs can be encouraged to urinate on absorbent pads that can be weighed to assess urine output, and cats can be provided with litter boxes containing nonabsorbent litter.

7. Treat the treatable and test for the testable.
   Stop any potentially nephrotoxic medications. Submit urine for aerobic culture. Perform testing for leptospirosis in all dogs with ARF. Test for ethylene glycol, if indicated.
   Obtain abdominal radiographs and ultrasound to rule out postrenal azotemia, once the patient is stable. Administer antibiotics if leptospirosis is not ruled out in a dog and if pyelonephritis is suspected in a dog or cat. Consider antidotes for ethylene glycol ingestion as soon as possible, if there is a possibility of exposure.

8. Determine urine output.
   Once the fluid deficit has been corrected, urine output (UOP) should be quantified and expressed as milliliters per kilogram body weight per hour. Determine whether patient is polyuric (UOP>2 mL/kg/h), oliguric (UOP<1 mL/kg/h), or anuric (UOP = 0 mL/kg/h).

9. Correct anuria or oliguria.
   If the patient is not overhydrated, an additional fluid load equal to 2% to 5% of body weight may be administered over 4 to 6 hours. If there is no increase in UOP, several other interventions should be considered, alone or in combination:
   A. Administer mannitol as a bolus, followed by constant rate infusion (CRI). This step is contraindicated in patients that are volume overloaded. 
   B. Administer furosemide as a bolus, followed by CRI. This step is often used in combination with dopamine.
   C. Administer dopamine by CRI, with blood pressure and electrocardiogram (ECG) monitoring.
D. Consider diltiazem in dogs, given by CRI.  
E. Consider fenoldopam in cats, given by CRI.

Note that the use of dopamine and furosemide, alone or in combination, has little support in the human literature.  

There are few studies in the veterinary literature that address the value of these interventions in veterinary patients with anuric or oliguric renal failure. It is clear that conversion to a polyuric state allows ongoing fluid support and management of the patient with ARF, whereas failure to resolve anuria or oliguria necessitates the provision of continuous renal replacement therapy, peritoneal dialysis, or hemodialysis.


For the polyuric patient, the fluid recipe should be calculated using the ins-and-outs method, and thus measurement of urine output is necessary. Urine output should be measured over a period of 2 to 6 hours, and the hourly output calculated. This hourly rate is added to insensible losses to give the total hourly rate of crystalloid fluids. Insensible losses are usually assumed to be 20 mL/kg/24 h. Additional losses such as vomiting or diarrhea should be measured or estimated, and added to the patient’s fluid needs. The fluid requirement should be recalculated at least 4 times daily, and the accurate measurement of urine output is essential in the polyuric patient because the volume of urine produced can be unpredictable and high. The use of shortcuts such as twice maintenance or 3-times maintenance is discouraged. Failure to account for polyuria in these patients rapidly leads to a worsening fluid deficit with associated worsening of renal perfusion. The patient is driving the urine output, and the clinician must respond to this with administration of appropriate fluid volumes.

11. Monitor the patient:

A. Hydration status and body weight (at least twice daily)
B. CVP
C. Systemic blood pressure and perfusion parameters
D. Urine output
E. PCV/TS
F. Electrolytes
G. Acid-base parameters
H. Creatinine, BUN, and phosphorus.

12. Provide adequate nutrition.

Manage nausea and vomiting and address possible uremic gastritis. Use enteral nutrition whenever possible, using feeding tubes if necessary. If enteral nutrition is not tolerated, parenteral nutrition should be provided. Volumes administered enterally or parenterally should be accounted for in the fluid therapy recipe.

13. Address the consequences of renal failure.

Use phosphate binders for hyperphosphatemia to mitigate development of renal secondary hyperparathyroidism. Treat hypertension and address anemia.

14. Renal replacement therapy.

This should be considered for patients that remain anuric or oliguric, for patients with fluid overload or refractory electrolyte/acid-base abnormalities, and for patients with severe uremia that is not responsive to medical management. Options for renal replacement therapy include continuous renal replacement therapy, intermittent hemodialysis, and peritoneal dialysis.  

These
options are available in few locations, and therefore clinicians should famil-
larize themselves with the options that are available in their practice area,
and be prepared to discuss these interventions with clients at an early stage.

SUMMARY

Many risk factors for AKI are likely to be present in critically ill patients. Factors to
consider include age, preexisting disease, concurrent medical therapy, electrolyte
and fluid imbalances, and exposure to potential nephrotoxicants. Many risk factors
are correctable or manageable, and these should be addressed whenever possible.
In human patients in the ICU, the 5 most common causes of ARF are sepsis, major
surgery, low cardiac output, hypovolemia, and medications. It is reasonable to
assume that these are also important causes in veterinary medicine. Measurement
of serum creatinine is an insensitive tool for the detection of AKI, and therefore clini-
cians should consider assessment of other parameters such as urine output, urinal-
ysis, and urine chemistry results.

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