

## Acute Renal Failure

Rebecca Kirby, DVM, DACVIM, DACVECC  
Animal Emergency Center  
Glendale, Wisconsin

Emergency clinicians can play a significant role by identifying acute renal failure (ARF) early in the course of the disease process, preventing iatrogenic renal injury and potentially reversing the course of ARF. In the intensive care unit (ICU), sepsis, hypotension, administration of potentially renal toxic drugs, and alterations in coagulation warrant close patient assessment for the onset of ARF and aggressive methods for offsetting its occurrence. In humans in the ICU, mortality from ARF is high, up to 80%, and is generally part of multiple organ failure.

Acute renal failure (ARF) is the sudden loss of the ability of the kidneys to remove waste and to regulate fluid and electrolyte concentrations. There are no standard definitions of ARF in literature, but, in humans, the diagnosis generally includes a 50% increase in serum creatinine or a creatinine level greater than 2 mg/dl. In 2004, the Acute Dialysis Quality Initiative (ADQI) group published the RIFLE classification of ARF, based on changes from the human patient's baseline values of either serum creatinine level or glomerular filtration rate (GFR), and/or urine output (UO).

The RIFLE classification of ARF is as follows:

<b>Classification</b>	<b>Creatinine</b>	<b>GFR</b>	<b>Urine output</b>
<b>Risk</b>	Increase x1.5	decrease 25%,	<0.5 mL/kg/h 6h
<b>Injury</b>	Increase x 2.0	decrease 50%	<0.5 mL/kg/h 12h
<b>Failure</b>	Increase x 3.0 or level > 4 mg/dl	decrease 75%	<0.3 mL/kg/h 24h anuria for 12 hours
<b>Loss</b>	Persistent ARF, complete loss of kidney function > 4 wk		
<b>End-stage disease</b>	Loss of kidney function > 3 month		

The driving force for glomerular filtration is the pressure gradient from the glomerulus to Bowman's space and is dependent on renal blood flow (RBF). Renal blood flow is a result of arterial blood pressure and renal vascular resistance, which is a result of the combined resistance of renal afferent and efferent arterioles. Important neurohumoral mechanisms autoregulate tone of afferent and efferent arterioles, with the rennin-angiotensin-aldosterone system one of most important. Reductions in RBF represent a common pathologic pathway for decreasing GFR and initiating ARF. Three main mechanisms for alterations in RBF or GFR associated with ARF are: pre-renal, renal or post-renal.

Prerenal failure is defined by conditions with normal tubular and glomerular function and no cellular injury. GFR is depressed by compromised renal perfusion and is reversible with correction of the causative factors such as volume deficiency, drug administration (eg. non-steroidal anti-inflammatory drugs (NSAIDs)) or congestive heart failure. It is characterized by bland urine sediment and fractional excretion of sodium (FENa+) < 1%. Aggressive restoration and maintenance of patient tissue perfusion in the ER and ICU, and careful dose adjustment and monitoring of renal function when giving potentially nephrotoxic drugs, can contribute to making ARF a rare complication in hospitalized patients.

Post-renal failure is the result of bilateral obstruction of urine flow and reported as an uncommon cause of ARF in the human ICU. Post-obstructive renal failure initially

causes an increase in tubular pressure, decreasing the filtration driving force. This pressure gradient soon equalizes, and maintenance of a depressed GFR is then dependent upon renal afferent vasoconstriction. Patient evaluation for post-renal causes involves ultrasonography of the urinary outflow tract and urethral catheterization.

Renal failure is associated with anatomic injury to the nephron affecting one or more of the following, glomerulus, tubules, interstitium, or vasculature, and is associated with release of renal afferent vasoconstrictors. In the human ICU, acute tubular necrosis ATN is most common form which includes both tubular and vascular injury. This must be differentiated from pre-renal causes by evaluation of the urine sediment which may have tubular or granular casts, as well as a urine fractional excretion of sodium [ $FE_{(Na^+)} > 1\%$ ]. Acute tubular necrosis can be associated with pre-renal causes as well as nephrotoxic agents such as antibiotics, heavy metals, solvents, contrast agents, or crystals.

Patients with chronic renal failure also may present with superimposed ARF.

Renal origin ARF is further classified as oliguric or non-oliguric depending upon urine output. The definition of oliguria is urine output less than 200 to 500 ml/24 hr in humans. Acute Dialysis Quality Initiative adopted definition of less than 0.3 ml/kg/h for at least 24 hours in humans. Oliguria is defined as  $< 0.5$  ml/kg/hr in the dog and cat in the veterinary literature. Of human ICU patients that develop ARF, 69% are oliguric (2) with oliguria carrying a higher risk of death than non-oliguria.

Urine output is a function of GFR, tubular secretion and tubular resorption. Oliguria is most commonly a marker of either reduced GFR or mechanical obstruction to urine flow. When associated with decreased GFR, oliguria can be either pre-renal or renal in origin. A reduction in RBF, and therefore GFR, can occur due to absolute intravascular volume deficits, vasodilation, vascular structural changes, significant vasoconstriction, renal vascular outflow obstruction, and acute tubular necrosis.

Oliguria can also be a result of mechanical obstruction to urine flow (post-renal causes). Problems such as ureteral, urethral and bladder neck obstruction, or occlusion of a urinary catheter should be ruled out.

### **Patient Evaluation**

A detailed history can help elucidate possible underlying etiologies of ARF. Evidence of trauma, hemorrhage, and/or shock warrants careful evaluation and monitoring of renal parameters. Age, reproductive status, and breed can direct diagnostic efforts towards congenital, hereditary or anatomical disorders. Vaccination history, exposure to other animals and information of living environment can suggest infectious problems such as leptospirosis or FIP. Concurrent diseases such as infections, diabetes mellitus, hyperadrenocorticism, congestive heart failure, and gastrointestinal or peritoneal pathology can affect perfusion and RBF. A thorough investigation must be made regarding exposure to toxins, such as ethylene glycol, and drug administration or ingestion (e.g. vasodilators, vasoconstrictors, aminoglycosides).

Physical examination may reveal abnormalities that are contributing to the onset and maintenance of ARF or physical changes that have occurred as a result of ARF. Careful evaluation of perfusion parameters (heart rate, pulse quality, and capillary refill time) and of hydration parameters (skin turgor, corneal moisture) is essential. Poor perfusion and dehydration can contribute to pre-renal and renal ARF by reducing RBF. Acute oliguria can lead to volume overload, especially if aggressive fluid therapy has been initiated without recognition of the renal compromise. Signs of volume overload can include any of the following: subcutaneous edema, conjunctival edema, pleural and abdominal effusion, and pulmonary edema.

Thoracic auscultation can reveal arrhythmias and pulmonary or pleural fluid. Careful abdominal palpation can reveal intra-abdominal fluid or pressure which can affect blood volume and/or RBF. Organ enlargement or distension warrants evaluation for vascular occlusion or neoplasia which can affect the kidneys. The kidneys should be palpated for evidence of bilateral enlargement or pain, suggestive of a bilateral acute

process such as toxin or infection. Irregular kidneys are ore compatible with infiltrative disease, cysts, hematomas or fibrosis. Asymmetry between kidneys may be related to post-renal obstruction in one kidney or ureter, unilateral thrombosis or infiltration, cyst or fibrosis of one kidney.

Laboratory work should include complete CBC, biochemical profile, coagulation profile and urinalysis. Venous blood gases will help assess acid-base status. A search is made for underlying etiologies as well as consequences of ARF. Common findings with ARF include evaluation of serum creatinine and blood urea nitrogen, hyper or hyponatremia, hyperkalemia and metabolic acidosis. Hyperphosphatemia and hyperkalemia seen with ARF are a reflection of seriously compromised GFR or post-renal rupture or obstruction. Platelet function may be impaired secondary to the systemic toxins of renal failure, necessitating a buccal bleeding time for assessment if platelet count is normal and bleeding is noted. Other tests to submit to determine etiology include: titers for *Leptospiriosis* species, PCR for feline infectious peritonitis, feline leukemia and feline immunodeficiency virus tests, heartworm test, and ethylene glycol test.

Knowledge of the animal's baseline serum creatinine is very important, with a change in serum creatinine commonly reflecting changes in GFR. The rate of change in serum creatinine is an important variable in estimating GFR. It is reported in humans that stable changes in serum creatinine correlate with changes in GFR by the following relationships:

- Creatinine 1.0 mg/dL – Normal GFR
- Creatinine 2.0 mg/dL – 50% reduction in GFR
- Creatinine 4.0 mg/dL – 70–85% reduction in GFR
- Creatinine 8.0 mg/dL – 90–95% reduction in GFR

In humans, small changes with low baseline levels of creatinine are important clinically much more than large changes with high basal creatinine. However, significant decline in GFR can occur in the normal range of creatinine. It should be noted that certain diseases and medications can interfere with the correlation of serum creatinine with GFR. Trimethoprim and cimetidine cause decreased creatinine secretion and a falsely elevated creatinine with no change in GFR. Acute glomerulonephritis causes increased tubular secretion of creatinine, falsely depressing the rise in serum creatinine when ARF occurs in acute glomerulonephritis.

Evaluation of the urine specific gravity will provide a reflection of the concentrating ability of the kidneys. Fluid therapy and diuretic administration can cause medullary washout and a reduction in the concentrating ability of the kidneys unrelated to ARF. In addition, animals with peracute renal failure may have concentrated urine during the initial onset of the pathology. Urine glucose without elevation in serum glucose suggests proximal tubular cell dysfunction and/or injury. The presence of renal tubular cell casts or coarse granular casts indicates intrarenal damage. White blood cell casts are seen with pyelonephritis and red blood cell casts with glomerular disease.

Physicians evaluate urine electrolytes to distinguish pre-renal from renal azotemia in humans. Guidelines reported are:

	Pre-renal	renal
Osmolality (u)	>500	<400
Na+(u)	<20	>40
[urea]/[creatinine] (s)	>0.1	<0.05
creat (u)/creat(s)	>40	<20
osmo(u)/osmo(s)	>1.5	>1
FE <sub>(Na+)</sub>	<1	>2
FE <sub>(urea)</sub>	<25	>25

$$FE(Na^+) = Na^+(u) \times [creat(s)/Na^+(s)] \times [creat(u) \times 100]$$

FENa<sup>+</sup> is unreliable if the patient is on diuretics or natriuretic agents (including dopamine and mannitol). The interpretation of results may also be confounded by endogenous osmolar substances (glucose or urea).

Renal ultrasonography is the test of choice to evaluate the outflow tract and eliminates the need for potentially renal toxic radiocontrast studies. Evaluation of the kidneys, ureters, bladder, bladder neck, and urethra is necessary. Initial results may be equivocal in dehydrated animals, requiring a follow-up evaluation to detect change as the animal is hydrated. Prostatic or other organs or masses compressing on the outflow tract should be identified.

### **Treatment**

It is important to ensure that there is adequate renal perfusion and correct hypotension. A quick assessment of intravascular volume and cardiac function is necessary. With ARF, patient may have excess total body water and salt, and yet have intravascular volume depletion. It is important to provide adequate volume replacement prior to using any vasoactive agents. The heart rate and blood pressure may be affected by many treatment variables in the ICU and may not reflect volume status. More accurate assessment of preload with central venous pressure is helpful. Often a fluid bolus is given as a "fluid challenge" to determine changes in heart rate, blood pressure, and central venous pressure as a result of intravascular volume expansion. The use of hetastarch in addition to crystalloids will minimize the amount of crystalloid required, minimizing interstitial fluid extravasation if there is capillary leakage or hypoalbuminemia. The response to a single fluid challenge or even multiple fluid challenges may not detect obvious changes in measured parameters when there is substantial intravascular volume depletion.

Following the Rule of 20 (Table 1) for the monitoring of ICU patients is essential for early recognition of complications and providing the best conditions for healing. Monitoring and supporting albumin, coagulation, oxygenation, ventilation, gastrointestinal function, analgesia and nutrition should be a major aspect of therapy. It is important to avoid nephrotoxic drugs. Any drugs that require renal excretion may need an adjustment in dose.

The use of diuretics to increase urine flow has been advocated with little or no evidence to support their benefit. Converting oliguric renal failure to non-oliguric was found associated with no reduction in the need for renal replacement therapy (RRT) or mortality. The PICARD study (1989 through 1995) had a large cohort of critically ill human patients with ARF and determined that diuretic use was associated with an increased risk of death or non-recovery of renal function. Current recommendations in human literature restrict the use of diuretics to the treatment of volume overload, and even then caution is advised.

Low dose (< 5 µg/kg/min) dopamine has also been advocated to increase urine output and GFR based on the action on dopamine-1 receptors. A comprehensive meta-analysis (14) of research and human data showed that dopamine did not prevent the onset of ARF or decrease mortality nor the need for dialysis. By increasing solute delivery to the distal tubule, dopamine agonists actually worsen medullary oxygen balance. A study of vasopressin in septic shock demonstrated that a 4-hour infusion improved the urine output and creatinine clearance. More information is necessary before a recommendation is made.

Indications for RRT have traditionally been volume overload, hyperkalemia, acidosis, symptoms of uremia such as encephalopathy and pericarditis, and azotemia. Current human literature regarding RRT suggests that early initiation improves survival. Indications for RRT in ICU for ARF include: non-obstructive oliguria; severe acidemia; hyperkalemia (>6.5 mEq/L), uremia (encephalopathy, pericarditis, neuropathy, myopathy), severe dysnatremia (Na<sup>+</sup> >160 or <115) regardless of urine output; hyperthermia; clinically significant organ edema (especially lung); and drug overdose with dialyzable toxin. (Bellomo, Crit Care 2000,4:339-345). Daily dialysis was found

associated with less hypotension, sepsis, GI bleeding, and respiratory failure as well as a significant decrease in mortality. Peritoneal dialysis is a form of RRT and can be performed in most veterinary ICUs. The procedure is outlined in Table 2.

Hallmark of metabolic alterations of ARF in humans is the activation of protein catabolism and the release of amino acids from skeletal muscle. Also there is insulin resistance which leads to hyperglycemia from hepatic gluconeogenesis fueled by protein catabolism. Enteral feeding has become the standard form of nutritional support in critically ill patients since it helps to maintain gastrointestinal function and decrease infectious complication. In the past, protein restriction was employed in ARF, but current thought is that it is likely to be detrimental. It is possible to control nitrogen balance and uremia associated with dietary protein with RRT. Better to err on the side of slight underfeeding than over feeding.

Once RBF is restored, the remaining functional nephrons increase their filtration and eventually hypertrophy. GFR recovery is dependent upon the size of this remnant nephron pool. If the number of remaining nephrons is below some critical value, continued hyperfiltration results in progressive glomerular sclerosis, eventually leading to increased nephron loss. A vicious cycle ensues with continued nephron loss causing more hyperfiltration until complete renal failure results. This has been termed the *hyperfiltration theory* of renal failure and explains the scenario in which progressive renal failure is frequently observed after apparent recovery from ARF.

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Table 1. Rule of 20 check list .

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- Fluid balance
  - Oncotic pull, albumin
  - Glucose
  - Electrolytes
  - Oxygenation/ventilation
  - Level of consciousness/mentation
  - Blood pressure
  - Heart rate/rhythm/contractility
  - Body temperature
  - Coagulation
  - Red blood cells/hemoglobin
  - Renal function
  - Immune status/antibiotic dosages/WBCs
  - GI motility and mucosal integrity
  - Drug dosages and metabolism
  - Nutrition
  - Pain control
  - Nursing care/temperature control
  - Wound care/bandage change
  - Tender loving care
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Table 2. Procedure for Peritoneal Dialysis

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1. Place peritoneal dialysis catheter (toward pelvic inlet) aseptically, secure and apply sterile dressing and bandage.
2. Select 1.5%, 2% or 4.0% dextrose peritoneal dialysis solution and warm to body temperature prior to infusion. A water circulating heating blanket wrapped around the dialysate fluid bag can be used.
3. Add 500 units heparin/2000 ml dialysate, using aseptic procedure.
4. Attach infusion line and collection bag to dialysate and dialysis catheter. Wrap each connection with povidone-iodine soaked sterile gauze.
5. Infuse 10–20 ml/kg warm dialysate into the peritoneal space by gravity flow.
6. Allow infused dialysate to remain in contact with peritoneal surfaces for 45 minutes (dwell time). Record amount infused.
7. Allow 15 minutes for drainage by gravity. Drain as much fluid out as possible. Record amount recovered.
8. Continuous dialysis (infuse and drain dialysate every hour) for removal of exogenous toxins such as ethylene glycol or endogenous toxins in an unstable patient.
9. Administer systemic broad spectrum bacteriocidal antibiotics. Dosage may require adjustment during dialysis.
10. Monitor the patient PCV, TS for hydration; serum Na, K, creatinine, osmolality; urine for protein, casts, cells, glucose, bacteria; WBC count and differential for left shift; and dialysate for WBCs and bacteria.

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