Acute Renal Failure

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Acute renal failure (ARF) is characterized by the rapid loss (over hours to several days) of nephron function, resulting in azotemia and fluid, electrolyte, and acid–base abnormalities. Although obstruction to urine flow or rupture of the urinary tract can cause renal failure that occurs within a short time (postrenal failure), this article covers only ARF due to intrinsic disease of the renal parenchyma.

Clinically, ARF is divided into three stages. The first (initiation) occurs during and immediately following the insult to the kidneys, when pathologic damage to the kidneys is occurring. This phase usually lasts less than 48 hours, during which time clinical and laboratory abnormalities may not be apparent. The second stage (maintenance) is characterized by azotemia and/or uremia and may last for days to weeks. Oliguria (<0.5 ml urine/kg body weight/hr) or anuria (no urine production) may occur during the maintenance stage. A number of theories have been proposed for the pathogenesis of this oliguria or anuria, although the exact mechanism is not clear. The third stage is recovery, during which time azotemia improves and renal tubules undergo repair. Marked polyuria may occur during this stage as a result of partial restoration of renal tubular function and osmotic diuresis of accumulated solutes. Renal function may return to normal, or the animal may be left with residual renal dysfunction. Nonazotemic renal failure can occur and is characterized by abnormalities similar to those seen during the polyuric recovery phase of ARF.

ARF in dogs and cats can have many causes (see box on page 4), and identification of the cause is important. Although supportive therapy is similar, prognosis and outcome vary with the cause.

Diagnostic Criteria

Historical Information
Gender/Age/Breed Predisposition
• None.

Owner Observations
Acute onset (hours to several days) of clinical signs, which may vary depending on the cause of ARF:
• Depression, lethargy, weakness.
• Anorexia, vomiting, diarrhea.
• Change in urine production:
  — Usually decreased.
  — Increased urine production (polydipsia/polyuria) is much less common and tends to be of short duration.
• Ataxia, seizures.

Other Historical Considerations/Predispositions
• Exposure or potential exposure to toxic substances, including drugs (see box on page 4).
• Seasonal and environmental conditions conducive to exposure to infectious diseases.
• Recent or concurrent severe illness that could result in ischemia, sepsis, and/or multiple organ dysfunction syndrome.

Also in this issue:

10 Anemia as a Manifestation of Malignancy
Physical Examination Findings

- Normal body condition.
- Bilaterally normal to enlarged kidneys that may be painful when palpated; however, normal renal palpation does not rule out ARF.
- Signs of dehydration:
  - Decreased skin turgor.
  - Dry or tacky mucous membranes.
- Signs of hypovolemia:
  - Slow capillary refill time.
  - Tachycardia.
  - Weak pulses.
  - Hypothermia.
- Depression, lethargy, weakness.
- “Uremic” breath.
- Oral ulceration and/or necrosis of the tongue.

Laboratory Findings

- Elevated blood urea nitrogen (BUN; normal, 10–25 mg/dl) and serum creatinine (normal, 1.0–2.0 mg/dl) concentrations.
- Dilute urine (specific gravity [SG] < 1.030 in dogs and < 1.035 in cats) concurrent with azotemia. Some animals with less severe renal injury lose the ability to concentrate urine but do not become azotemic.
- Normal to elevated serum potassium concentration (normal, 3.5–5.5 mEq/L).
- Metabolic acidosis.
- Hyperphosphatemia (normal, 3.0–6.3 mg/dl).
- Hypocalcemia (normal total calcium, 9.5–11.5 mg/dl; normal ionized calcium, 1.17–1.38 mmol/L).
  - Usually mild to moderate.
  - May be severe in association with marked hyperphosphatemia or in animals with ethylene glycol intoxication.
- Hematocrit may be normal to elevated, consistent with dehydration.
- Leukogram may reflect the underlying disease causing ARF (e.g., leukocytosis with pyelonephritis).
- Coagulation profile may reflect the underlying disease causing ARF (e.g., thrombocytopenia with leptospirosis).

Other Diagnostic Findings

Radiography

- Normal to enlarged kidneys.
- Absence of radiopaque uroliths.

Ultrasonography

- Normal to enlarged kidneys.
- May show increased echogenicity and loss of corticomедullary distinction.

KEY TO COSTS

$ indicates relative costs of any diagnostic and treatment regimens listed.
$ costs under $250
$$ costs between $250 and $500
$$ costs between $500 and $1,000
$$$$ costs over $1,000
A hyperechoic band at the corticomedullary junction has been seen with ethylene glycol toxicity and other causes of ARF; however, it has also been seen in normal dogs and cats, and therefore its significance is unknown.

Other $$-$$$ Tests to rule out specific causes of ARF may be performed, depending on such factors as the patient’s species (dog or cat), geographic location, season, and potential for exposure.

• Ethylene glycol poisoning:
  — Serum level.
  — Severe metabolic acidosis (normal arterial blood pH, 7.36–7.44) with increased anion gap (anion gap = [serum Na + K] – [serum bicarbonate + Cl]; normal, 12–25 mEq/L).
  — Increased serum osmolar gap (osmolar gap = measured serum osmolality – calculated serum osmolality; normal, <10).
• Normal measured serum osmolality: 280–310 mOsm/kg.
• Calculated serum osmolality = \(1.86 \times (Na + K) + [Glucose + 18] + [BUN + 2.8] + 9\).
• Serology for leptospirosis.
• Urine or renal tissue culture and sensitivity for pyelonephritis.
• Arterial blood pressure measurement:
  — Decreased if animal is severely dehydrated or in patients with concurrent systemic disease, such as sepsis.
  — Increased, especially after IV fluid administration.
• Renal histopathology: Renal biopsy ($$) is indicated if the results will change prognosis or therapy, but potential benefits should be weighed against associated risks (anesthesia, hemorrhage). Biopsy is the gold standard for diagnosis of acute lesions.

Summary of Diagnostic Criteria
• Renal biopsy consistent with acute pathology.
• Positive diagnostic test for a known cause of ARF.
• Azotemia and concurrent dilute urine.
• Lack of historical, physical, or laboratory evidence of chronic disease.
• Acute onset.
• Exposure or potential exposure to toxin(s) or environmental exposure to infectious disease(s).

Diagnostic Differentials
Prerenal Azotemia $$-$$$ • Concentrated urine (dogs, SG > 1.030; cats, SG > 1.035) in conjunction with azotemia.

Postrenal Azotemia $$-$$
Obstruction
• Urethral:
  — Historical and/or physical examination findings of stranguria, dysuria, hematuria, and inability to urinate.
  — Inability to pass a urinary catheter.
  — Radiographic or ultrasonographic evidence of obstructing urolithiasis or tissue masses.
• Ureteral urolithiasis:
  — Appears to be occurring with increasing frequency, especially in cats; therefore, all cats with ARF should be evaluated for ureteral urolithiasis.
  — Radiographic or ultrasonographic evidence of obstructing urolithiasis.

Rupture of a Portion of the Urine Collecting System
• History or possibility of trauma.
• Ultrasonography or contrast radiography to identify location of rupture.

Chronic Renal Failure $$-$$
• Epidemiology: If the animal is young, familial renal disease should be considered if it has been reported in the breed in question.
• History: Signs of several weeks’ duration or longer:
  — Polydipsia/polyuria.
  — Weight loss.
  — Decreased appetite.
  — Vomiting.
  — Animals with chronic disease may experience acute exacerbations of clinical signs of renal failure or even oliguria or anuria.
• Physical examination:
  — Poor body condition.
  — Pale mucous membranes.
  — Small kidneys on palpation.
  — Rarely, “rubber jaw” (flexible mandible) due to renal secondary hyperparathyroidism.
• Laboratory data:
  — Normocytic, normochromic anemia.
  — Hypoalbuminemia in animals with protein-losing nephropathies.
• Imaging: Small, irregular kidneys.
• Histopathology: Confirmation of chronic disease.

Hypoadrenocorticism $$
• Corticotropin stimulation test.
COMMON CAUSES OF ACUTE RENAL FAILURE IN DOGS AND CATS

Ischemia
Infarction
Toxins
- Ethylene glycol
- Heavy metals
- Organic compounds
Drugs
- Aminoglycoside antibiotics
- Amphotericin B
- Cisplatin
- NSAIDs
- Radiographic contrast agents
- Grapes or raisins
- Hemoglobinuria/myoglobinuria
- Lily plant
- Envenomation (e.g., snake, bee, wasp, bull ant)

Infectious diseases
- Pyelonephritis
- Leptospirosis

Hypercalcemia
- Calciferol-containing rodenticides
- Human dermatologic preparations containing vitamin D analogs
- Paraneoplastic syndrome (e.g., associated with lymphoma or apocrine gland adenocarcinoma of the anal sac)

Hyperviscosity
- Hypoglobulinemia
- Polycythemia

Multiple organ dysfunction syndrome

Sepsis
Acute pancreatitis

$^a$Reported only in dogs.
$^b$Reported only in cats.

TREATMENT RECOMMENDATIONS

Initial Treatment

The dose of drugs that are excreted primarily in urine needs to be reduced in proportion to the degree of azotemia. These drugs are noted with an asterisk (*). The following measures are indicated in most patients:

- Intravenous fluid therapy is the mainstay of therapy in most patients (see box on page 5): Placement of a jugular catheter ($) allows monitoring of central venous pressure, which can be beneficial in adjusting fluid therapy. However, if hemodialysis is a therapeutic option, the jugular veins should be preserved for placement of a hemodialysis catheter and peripheral IV catheters should be used instead for initial fluid therapy.

  - Hyperkalemia should be corrected if present (see box on page 5).
  - Placement of an indwelling urinary catheter to monitor urine output should be considered, but potential benefit should be weighed against the risk of inducing an ascending urinary tract infection.

Specific Treatment of Underlying Cause (If Identified or Strongly Suspected)

Ethylene Glycol Intoxication

- Emesis should be induced if ingestion of ethylene glycol occurred within 3 hours of presentation and the animal is not obtunded.
- Antidote should be administered if the patient is not yet azotemic.
  - Ethanol 20%: 5.5 ml/kg IV q4h for five treatments, then q6h for four treatments.
  - Ethanol 30%: 1.3 ml/kg IV bolus, then 0.42 ml/kg/hr IV for 48 hours.
  - 4-Methylpyrazole (dogs only): 20 mg/kg IV then 15 mg/kg IV at 12 and 24 hours, then 5 mg/kg IV at 36 hours.
  
  OR
  - Ethanol 30%: 1.3 ml/kg IV bolus, then 0.42 ml/kg/hr IV for 48 hours.
  - 4-Methylpyrazole (dogs only): 20 mg/kg IV then 15 mg/kg IV at 12 and 24 hours, then 5 mg/kg IV at 36 hours.
  
  OR
  - 4-Methylpyrazole (dogs only): 20 mg/kg IV then 15 mg/kg IV at 12 and 24 hours, then 5 mg/kg IV at 36 hours.

- Diuresis should be induced with IV fluids.

Leptospirosis

- In endemic areas, leptospirosis should be considered as a differential diagnosis in all dogs with renal failure of unknown cause; treatment should be instituted immediately.
- Initial antibiotic therapy for 2 weeks to eliminate leptospiremia:
  - Penicillin*: 25,000–40,000 U/kg IV, SC, or IM bid.
  - Ampicillin*: 22 mg/kg IV or SC tid.
  - Amoxicillin*: 22 mg/kg PO bid.
  - Doxycycline: 5 mg/kg PO or IV bid.
- Subsequent antibiotic therapy for 2 weeks to eliminate renal carrier state:
  - Doxycycline: 5 mg/kg PO or IV bid.
  - Tetracycline*: 22 mg/kg PO tid.
  - Azithromycin: 20 mg/kg PO sid.
FLUID THERAPY AND ELECTROLYTE MANAGEMENT FOR ANIMALS WITH ARF

Intravenous Fluid Therapy

- Type of fluid:
  - Lactated Ringer’s solution (in patients that are not hyperkalemic).
  - Potassium-free fluid (e.g., 0.9% sodium chloride or 0.45% sodium chloride in 2.5% dextrose) in hyperkalemic patients or if serum potassium cannot be immediately measured.

- Fluid volume calculation:
  - Replacement of deficit: \( \text{Deficit} = \text{body weight (kg)} \times 1,000 \text{ ml fluid deficit. Deficit should be replaced over 4–6 hr to correct hypovolemia and improve renal blood flow. (NOTE: This rate replaces fluid deficits more rapidly than is normally recommended, which is indicated in patients with renal failure to restore renal blood flow.) An initial bolus of up to 90 ml/kg may be necessary in animals that are severely volume depleted.}

  - Maintenance: 66 ml/kg/24 hr.

  - Volume to compensate for ongoing losses via the gastrointestinal tract (estimate volume) and/or polyuria (measure urine output).

- Frequent monitoring of volume and hydration status (by clinical assessment and measurement of central venous pressure) and urine production and appropriate adjustment of IV fluids are critical.

Special Considerations for Oliguric or Anuric Patients

- Following replacement of volume deficits, urine flow should rapidly increase to 2–5 ml/kg/hr.

- If urine production is inadequate, the patient’s circulating blood volume should be reassessed.

- Additional IV fluids should be administered if the animal is hypovolemic.

- If the animal has normal to increased circulating volume:
  - The rate of fluid administration should be decreased.

- Drugs that are ineffective in clearing the renal carrier state include chloramphenicol, sulfonamides, and fluoroquinolones.

Pyelonephritis

- Antibiotic therapy should be based on culture and sensitivity testing of urine or renal tissue.

- Antibiotic used should be nonnephrotoxic and primarily excreted by the kidneys.

- Duration of therapy is typically 4 to 8 weeks.

Alternative/Optional Treatments/Therapy

- If oliguria (urine output < 1 mg/kg/hr) or anuria occurs after the animal is adequately hydrated and receiving appropriate fluid therapy, measures should be instituted to try to increase urine output (see box on page 7). It is important to recognize that increased urine output is not necessarily associated with improvement in renal blood flow or glomerular filtration rate. The goal is to permit continued fluid therapy and medical management in the hope that the kidneys will be able to repair the renal damage.

- If the measures discussed in the box on page 7 are not successful in restoring urine output within 6 to 12 hours, the next therapeutic step would be either peritoneal dialysis or hemodialysis; if hemodialysis is not available or the owners are unwilling to pursue it, euthanasia should be considered.

Treatment of Severe Hyperkalemia (>8.0 mEq/L)

- Specific therapy is indicated in patients with severe hyperkalemia; fluids alone may be sufficient in patients with mild to moderate hyperkalemia. The decision whether to administer sodium bicarbonate, dextrose, or insulin and dextrose initially appears to be a clinical judgment that varies among specialists and institutions.

- Sodium bicarbonate: 0.5–2 mEq/kg IV over 15–20 min to effect.

- Insulin and glucose:
  - Regular insulin (2.2 U/kg) added to a 250-ml bag of 2.5% dextrose; administered at 5–10 ml/hr.
  - OR
  - Regular insulin (0.5–1.0 U/kg) and glucose (2 g/U of insulin) added to IV fluids.
  - OR
  - Regular insulin (0.25–0.5 U/kg) and glucose (2 g/U of insulin) diluted to a 5% to 10% solution and given by IV push; followed with 2.5% dextrose in IV fluids.

- Calcium gluconate: 0.5–1.0 ml/kg 10% calcium gluconate IV over 10–15 min in very severe cases; should be avoided in animals with hypercalcemia.

- Recommended dose varies among specialists.
beyond the scope of this article. $$\$$$  
- If the animal improves and enters the recovery phase of ARF, marked polyuria can result in fluid and/or electrolyte deficits. Frequent monitoring (Table 1) and adjustment of fluid volume and type are necessary.

**Supportive Treatment**

Uremia will result in a number of pathophysiologic abnormalities, including vomiting, metabolic acidosis, arterial hypertension, and malnutrition. Therapy to alleviate these abnormalities should be tailored to the needs and response of the individual animal.

**Treatment for Vomiting**

**Gastric Protectants** $\$
- H$_2$ receptor antagonist:
  - Famotidine* (Pepcid, Merck & Co.): 0.5–1 mg/kg PO, SC, IM, or IV sid–bid.
- Proton pump inhibitors:
  - Omeprazole* (Prilosec, Procter & Gamble): 0.7 mg/kg PO sid.
  - Lansoprazole (Prevacid, TAP Pharmaceutical Products): 0.6–1.0 mg/kg IV sid.
  - Pantoprazole* (Protonix, Wyeth Pharmaceuticals): 10–40 mg IV slowly over 15 minutes sid OR 0.7–1 mg/kg IV sid.

**Antiemetics** $\$
- Metoclopramide* (Reglan, Schwarz Pharma or Baxter Healthcare): 0.1–0.5 mg/kg PO, IM, SQ, or IV tid–qid OR 1–2 mg/kg/day CRI.
- Dolasetron* (Anzemet, Sanofi-Aventis): 0.6 mg/kg PO or SQ sid OR drug can be diluted in compatible IV fluid and administered over 15 min sid.
- Ondansetron (Zofran, GlaxoSmithKline): 0.1–0.2 mg/kg SQ tid OR 0.5 mg/kg IV loading dose and then 0.5 mg/kg/hr CRI.
- Chlorpromazine: 0.2–0.5 mg/kg SQ, IM, or IV tid–qid. May cause sedation.

**Treatment of Metabolic Acidosis**
- IV fluid therapy may be sufficient for patients with mild to moderate acidosis; treatment should be considered if blood pH is below 7.2 or serum bicarbonate is less than 14 mEq/L after correcting fluid deficit.
- Calculation of bicarbonate deficit: Body weight (kg) × 0.3 × (24 – measured bicarbonate) = mEq of bicarbonate to replace.
- One-quarter of the total bicarbonate deficit should be given as sodium bicarbonate (IV) in the first 12 hours; the patient should then be reevaluated. Further bicarbonate can be administered if indicated, but a conservative approach should be used.
- Sodium bicarbonate is incompatible with lactated Ringer’s solution.
- Complications of sodium bicarbonate therapy include paradoxical cerebrospinal fluid acidosis, decreased ionized serum calcium, and hypernatremia.
- The total bicarbonate deficit should be replaced over 48 hours, if necessary.

**Treatment of Arterial Hypertension** $\$

Treatment may be limited because the vomiting associated with uremia often precludes oral medication, and most antihypertensive drugs are available only in oral formulations.

**Dogs**
- Amlodipine (Norvasc, Pfizer): 0.1–0.25 mg/kg PO sid–bid.
- Angiotensin-converting enzyme (ACE) inhibitors;
TREATMENT OF OLIGURIA OR ANURIA

1. An indwelling urinary catheter should be placed to monitor urine output.
2. Drugs should be administered to increase urine output. These agents can be administered in different sequence, serially, or in combination, depending on the judgment of the veterinarian. If urine output does not increase within 6–12 hours, dialysis should be considered.

- Diuretic therapy:
  - Furosemide: 2 mg/kg IV bolus; if effective, diuresis usually begins within 15–30 min.
  - Dose should be increased at hourly intervals to 4–6 mg/kg if initial dose does not induce diuresis.
  - In normal dogs, CRI has been shown to be more beneficial than intermittent dosing in increasing urine production: 0.66 mg/kg IV bolus followed by 0.66 mg/kg/hr CRI; some clinicians recommend a dose of 0.5–1.0 mg/kg/hr CRI.

- Osmotic diuresis:
  - Mannitol 20%: 0.5–1 g/kg IV bolus slowly followed by either 1.0–2.0 mg/kg/min CRI or repeat boluses q4–6h at a dose of 0.25–0.5 g/kg.
  - Contraindicated in animals with fluid overload, pulmonary edema, or congestive heart failure.

- Dopamine infusion:
  - At low doses (0.5–3 µg/kg/min), dopamine has been used to stimulate dopamine DA1 receptors, induce smooth muscle relaxation, decrease renal vascular resistance, increase renal blood flow, and induce natriuresis.
  - Controversial; see Checkpoints

3. Treat hyperkalemia (see box on page 5).

ACE inhibitors have been reported to be associated with increases in BUN and creatinine in a small percentage of dogs.
- Enalapril* (Enacard, Merial): 0.25–0.5 mg/kg PO or IV sid–bid.
- Benazepril (Lotensin, Novartis): 0.25–0.5 mg/kg PO sid.

Both an ACE inhibitor and amlodipine can be administered if necessary.

Cats
- Amlodipine: 0.625–1.25 mg PO sid.

Severe Hypertension $*
- Hypertension severe enough to cause clinical consequences may require more aggressive therapy.

Nutritional Support $–$$*
- Parenteral nutrition is indicated initially until the animal is no longer vomiting.
- Enteral nutrition using a feeding tube (nasoesophageal, esophagostomy, or gastrostomy) can be used when the animal is not vomiting and can tolerate sedation or anesthesia necessary for tube placement.

Patient Monitoring
Parameters to be monitored include BUN, serum creatinine, electrolytes, blood gas, hematocrit and total solids, arterial blood pressure, body weight, clinical assessment of hydration, central venous pressure, and urine production. Frequency of monitoring depends on the severity of uremia and stage of ARF (Table 1).

Home Management
- Animals must not be discharged until renal function returns to normal or until they are stable and no longer showing signs of uremia.
- Management recommendations depend on the inciting cause of ARF, if identified, and the degree of resolution of azotemia at the time the patient is discharged from the hospital.
- Future exposure to nephrotoxic substances must be avoided and exposure to infectious agents minimized.

CHECKPOINTS
- The drugs used to stimulate urine production in animals with oliguria or anuria—furosemide, mannitol, and dopamine—may be administered in a different sequence, sequentially, or in combination, depending on the judgment of the veterinarian.

- Dopamine infusion for treatment of oliguria or anuria is controversial. In humans, it is no longer recommended for use in ARF because studies have failed to show any benefit in preventing ARF in at-risk patients or in reducing mortality in patients with established ARF.

- Nitroprusside infusion should be considered, but administration must be performed in an intensive care unit setting with close monitoring.
  - 0.5–1.0 µg/kg/min IV.
  - Dose is increased by 0.5–1 µg/kg/min every 5 min until desired blood pressure is attained.
- Rapid or marked decreases in blood pressure that may affect renal blood flow must be avoided.
Animals should always have free access to fresh drinking water.

Animals with pyelonephritis:
— Antibiotic therapy for a minimum of 4 to 8 weeks.
— Urine culture and sensitivity testing should be conducted 1 to 2 weeks after completion of antibiotic therapy and every 3 to 6 months thereafter.

Animals with residual renal dysfunction should be managed for chronic renal failure; a discussion of these measures is beyond the scope of this article.a

Milestones/Recovery Time Frames
• Recovery from ARF may take days, weeks, or months; it is impossible to predict in any given patient.

Recovery is characterized by decreasing BUN and serum creatinine, normalization of electrolytes and acid–base status, improvement in urine concentrating ability, and resolution of signs of uremia.

Hospitalization and IV fluid therapy is recommended until BUN and serum creatinine levels return to normal or plateau for 3 to 5 days. If the animal is eating, drinking, and maintaining hydration even though it is still azotemic, discharging the patient and allowing the owners to manage it at home should be considered.

Treatment Contraindications
• Administration of nephrotoxic drugs, such as aminoglycoside antibiotics or NSAIDs.
• Excessive fluid administration resulting in overhydration.
• Medication or other treatment that results in hypotension.

aSee Langston C: Chronic renal failure in cats. Standards of Care 8(3):1–8, 2006. Subscribers can access this article online free at www.SOCNewsletter.com.
PROGNOSIS

Favorable Criteria

• The cause of ARF is one that responds well to appropriate therapy (e.g., pyelonephritis, leptospirosis).
• Rapid improvement in azotemia with appropriate therapy.
• Absence of concurrent systemic disease.

Unfavorable Criteria

• Cause of ARF is one that has historically been associated with poor prognosis (e.g., ethylene glycol intoxication).
• Oliguria or anuria.
• Severe azotemia (serum creatinine > 10 mg/dl).
• Lack of improvement or worsening of azotemia with appropriate fluid and supportive therapy.
• Concurrent systemic disease, such as pancreatitis or sepsis.

RECOMMENDED READING