ACUTE RENAL FAILURE: PREVENTION, DIAGNOSIS AND MANAGEMENT

Scott A. Brown, VMD, PhD, DACVIM
University of Georgia

I. Pathophysiology
   A. In dogs and cats, acute renal failure is primarily due to acute tubular damage.
      1. This results in necrosis and sloughing of tubular cells into the tubular lumen, causing tubular obstruction, and in loss of tight junctions between tubular cells leading to tubular fluid leaking out of tubule and into renal interstitial space.
      2. Renal arteriolar vasoconstriction is another component of acute renal failure. This leads to decreased GFR and renal ischemia with secondary tubular damage.
      3. As a result of acute renal injury, GFR is decreased and tubular function is abnormal.
   B. Since nephrons rapidly become dysfunctional, there is no time for compensation.
      1. Although fewer nephrons may be dysfunctional than in chronic disease, the signs are as severe. Animals with acute renal failure usually appear more ill at a given level of azotemia than animals with chronic renal failure.
      2. Because of the potential for repair and compensation, animals with acute disease have the potential to recover (depending on the severity of injury).
      3. Two to three months are required for maximal compensation and repair to occur.

II. Common Causes
   A. Toxins (Acute Nephrosis)
      1. Ethylene glycol -
         a. most common cause of acute renal failure in small animals; requires only small amounts
         b. generally oliguric in type due to tubular obstruction with crystals and renal tubular cell injury
         c. first signs - CNS (ataxia) plus severe metabolic acidosis; renal failure in 24-48 hours
         d. Presumptive diagnosis based on history of CNS signs (ataxia) plus severe acidemia plus markedly increased anion gap plus renal failure; serum calcium may be decreased; on ultrasonography kidneys are mildly, symmetrically enlarged and markedly hyperechoic
         e. confirm diagnosis by finding large numbers of oxalate crystals in urine or in renal biopsy specimen or by a blood test for ethylene glycol in first 24-48 hours
      2. Aminoglycoside antibiotics (all except streptomycin)
         a. too common a cause of nephrotoxicity; remember the motto "above all else, try to do no harm"
         b. Proximal tubular toxins - cause mild proteinuria, isosthenuria, occasionally glucosuria, cylinduria
         c. progressive course if administration continues: starts as polyuric, non-azotemic, then to polyuric azotemic, then polyuric, uremic, and terminally oliguric, uremic
         d. risk factors
- fever, dehydration, old age, pre-existing renal disease, hypokalemia, overdosage, sepsis, some cephalosporins, other or prior aminoglycosides, furosemide, frequency of administration
e. median onset of toxicity - 9 days (range 5-17)
f. maximal toxicity does not occur until at least 4 days after drug is stopped
g. recommended monitoring - daily urinalysis; if wait until BUN increases, it is too late - gentamycin blood levels can be monitored in some hospitals

3. Other Drugs - For example, amphotericin B, NSAIDs
4. Hemoglobin or myoglobin: hemoglobinuria, myoglobinuria only impair renal function in the presence of hypotension, dehydration or acidosis; when these are present, tubules can become obstructed by hemoglobin or myoglobin casts; in small animals, myoglobinuria is primarily a problem in racing greyhounds
5. Plant toxicities – Lilly toxicity in cats is the best described in small animals
6. Food toxicities – Raisins and grapes in dogs; chocolate in dogs

B. Prolonged ischemia (decreased perfusion): for example, during anesthesia or shock
C. Infectious - acute nephritis: for example, leptospirosis, bacterial sepsis, Rocky Mt. Spotted Fever
1. Leptospirosis is one of the most common primary causes of acute renal failure in dogs. Cats are resistant to leptospirosis. Humans are susceptible to infection and so infected, untreated dog’s urine is a public health risk.
2. The serovars of leptospirosis most associated with acute renal failure in dogs in Georgia are grippotyphosa and pomona, which are not included in the bivalent vaccine. Unfortunately, vaccination against one serovar does not protect against other serovars. Fort Dodge currently makes a vaccine with four serovars: icterohemorrhagiae, canicola, grippotyphosa, pomona.
3. Clinical signs are those of uremia (vomiting, anorexia). There may be abdominal or muscle pain and occasionally muscle fasciculations. Only 50% of cases are febrile, despite this being an infectious disease.
3. If diagnosed early, this is the most reversible cause of acute renal failure, responding to antibiotic therapy (penicillins, ampicillin) and fluid support. This is why many clinicians treat all canine cases of acute renal failure of unknown cause with intravenous ampicillin.
4. Diagnosis is based on a 4 fold rise in titer over a 2 week period, or identification of the organism in the urine or on a renal biopsy specimen; a single titer of $\geq 1:800$ establishes a presumptive diagnosis.

D. Infarction - e.g. associated with embolic shower from bacterial endocarditis or disseminated intravascular coagulation (DIC) of any cause, such as in heat stroke;
E. The one acute glomerulopathy is a vasculitis seen in racing greyhounds (renal vascular glomerulopathy) associated with the feeding of raw or undercooked meat (due to toxin associated with E. coli).

III. Stages of acute Renal Failure: most begin as uremic because of severity of the injury, but some causes (such as aminoglycoside toxicity) begin as polyuric and progress over days to uremic.

IV. Signs which suggest that the renal injury is acute
A.  History:  acute onset with no previous problems related to the urinary system; exposure to a toxin?; exposure to lakes/streams/marshes/puddles? (leptospirosis in dogs)

B.  Physical Findings
   1. Kidney size (palpation): symmetrical, normal or mildly enlarged in size.
   2. Renal pain - due to swelling and stretching of renal capsule (uncommonly recognized)

C.  Clinicopathologic Evaluation
   1. Hematology
      a. Leukocytosis - Uncommon even in inflammatory renal disease with the following exceptions:
         1. Acute pyelonephritis (acute bacterial injection of the renal pelvis and adjacent renal tissue)
         2. In association with a systemic inflammatory disease, such as bacterial endocarditis
         3. Thrombocytopenia: seen with Rocky Mountain Spotted Fever; 50% of cases of leptospirosis; DIC.
   2. Blood Chemistry: changes characteristic of primary renal failure but none specific to acuteness
   3. Urinalysis
      a. May see increased number of casts: numbers are not accurately indicative of the severity or reversibility of the problem; large #’s suggest active, acute disease while small #’s associated with either acute or chronic disease.
      b. Specific gravity is 1.008-1.029 (neither concentrated nor hypothenuric), similar to chronic kidney diseases.
      c. Acute infarction can result in hematuria.
      d. Acute bacterial pyelonephritis causes pyuria, bacteriuria.
      e. Proximal tubular injury may result in glucosuria (with normal blood glucose) and mild proteinuria.
      f. May see large numbers of calcium oxalate crystals with ethylene glycol toxicity.
   D.  Radiography - in acute renal failure the kidneys are symmetrical, either normal in size or mildly enlarged.
   E.  Ultrasonography - echogenicity may be normal to increased; kidneys with ethylene glycol toxicity are very hyperechoic; kidneys in dogs with acute leptospirosis often have mild US changes, even though severely azotemic
   F.  Histopathologic Evaluation - Varies with etiology; may be used to differentiate acute from chronic renal failure and to identify the cause of acute renal failure.

V.  Prognosis - From complete recovery to death, dependent on degree of injury; in general, better than in chronic disease since potential for repair and compensation; time required for recovery: days to months. Chronic renal failure may develop if renal injury not resolvable.

VI.  Prevention
   A. Evaluate renal function by measuring BUN/serum creatinine/urinalysis before major surgical procedures in all animals with a history of PU/PD (this should be a
standard question before any anesthetic episode) and in all older dogs and cats (> 5 years)
B. Rapidly correct pre and post renal azotemia.
C. If poor renal function present, use adequate fluid therapy before, during, and after any anesthetic episode; if renal failure is known to exist and appropriate fluid therapy is given, mild to moderate renal failure is not a contraindication for anesthesia.

VII. General Principles of Treatment
A. Do diagnostic lab work, particularly the UA, before treatment instituted; time usually available for hx, p.e., lab work before treatment necessary in renal failure.
B. Clinical signs of uremia not due to renal disease itself but due to fluid, acid-base, and electrolyte abnormalities, retention of metabolic wastes; basis of tx - keep patient alive until kidney can re-establish homeostasis compatible with life - can be expensive and prolonged - why establishing reversibility, acute or chronic nature, so important to client.

VIII. Specific therapy for renal failure
A. Limited to eliminating precipitating cause if identifiable to prevent further renal damage; especially important in acute renal failure; for example, Leptospirosis, drug toxicity, and heat stroke
B. Renal lesions already present must heal or be compensated; currently no therapy for renal tubules or glomeruli specifically (although research continues in this area)

IX. General Principles of Supportive Therapy
A. Avoid giving anything unnecessarily - drugs eliminated by kidney can accumulate; adjust interval between doses according to route of excretion and toxicity of the drug.
1. Drugs metabolized by the liver require little change in dosage - chloramphenicol, macrolides, short-acting barbiturates.
2. With some drugs, higher than normal blood levels are relatively nontoxic - penicillin and its derivatives, cephalothin.
3. Avoid nephrotoxic drugs - aminoglycoside antibiotics, NSAIDs
4. Avoid corticosteroids and tetracycline - increase protein catabolism.
5. With other drugs - Adjust dosage or increase interval between doses - check before using any drug whose excretion you do not know.
6. If using a drug for urinary tract infection, be sure the drug will still be effective - reduced renal function may prevent excretion of effective urine concentrations, e.g. sulfonamides, nitrofurantoin.
B. Basic premise - maintenance of fluid, electrolyte, acid-base and caloric balance as much as possible; specific requirements for therapy will depend on severity of renal failure (oliguric uremic, polyuric uremic, azotemic but non-uremic, or only polyuric).
C. Be careful with catheterization of vascular and urinary systems - the patients are immunodeficient due to depressed cell mediated immunity.
D. Monitor animal's physical examination often to determine whether it is improving or worsening; monitor body weight to help determine hydration status/appetite; monitor BUN, creatinine, calcium, phosphorus, acid/base, and electrolytes to evaluate response to and efficacy of therapy

X. Treatment of Oliguric Uremic Renal Failure
A. Remember the R/O for Oliguria
1. Severe Pre-renal insult
2. Urinary Tract Obstruction or Rupture
3. Severe renal failure: acute or chronic
B. Insert an intravenous catheter (jugular vein) and an indwelling urinary catheter; record body weight and respiratory rate and character
C. Correct fluid deficit over a few hours - body weight (kg) x % dehydration.
   1. Fluid of choice is usually lactated Ringer's solution (LRS) or Normosol R;
   2. Monitor for signs of overhydration - increasing body weight, pulmonary edema, increasing central venous pressure, clear nasal discharge, peripheral edema.
   3. Check for urine production.

D. If associated with renal vasoconstriction (certain toxins, anesthesia), can try dopamine (3 microg/kg/min) with or without furosemide; this low dose causes renal arterial vasodilation; if too high a dose or too fast a rate is given, renal arterial vasoconstriction can occur; if the dose is too high, respiratory and heart rate increase; at the appropriate rate and dose, respiratory and heart rates are stable.

E. Try osmotic diuresis with hypertonic dextrose (10%)
   1. Mechanism
      a. Expands cardiac output and extracellular fluid volume and thus increases renal blood flow and glomerular filtration rate.
      b. Increases urine flow through the nephron due to increased intratubular osmolarity.
   2. Technique
      a. Administer mannitol or 10% dextrose (5 ml/kg for 20 mins).
      b. After 20 minutes, check urine flow rate and check for presence of glucose if using dextrose.

F. Natriuretic diuresis - Furosemide IV in increasing doses beginning at 2.2 mg/kg; can increase to 10 mg/kg if no response; diuresis should begin within 15 minutes of an IV dose; will be maximal at 30-45 minutes and persist for 2 hours; often used with dopamine as described in D.
   1. Mechanism - Inhibits tubular reabsorption of Cl; therefore induces urine flow in spite of low GRF and may work in patients unresponsive to osmotic diuretics.
   2. Complications if effective - Hypokalemia, dehydration, hypotension
   3. Often ineffective

G. If unable to induce urine production, must reduce fluid intake to amount needed for maintenance and meet losses (urine, GI tract) or dialysis or euthanasia.
   1. Supply insensible fluid losses - 20 ml/kg/day maximum.
   2. Replace measured urinary losses
   3. Replace losses from vomiting/diarrhea.

H. Peritoneal or hemodialysis: rarely used in general veterinary practice but available in a limited number of referral centers

I. To monitor oliguric patient for improvement:
   1. Urine output
   2. Clinical signs
   3. Degree of azotemia, acidemia
   4. Serum K (if originally increased)

XI. Treatment of Polyuric Uremic Renal Failure
A. Insert intravenous catheter (jugular vein)
B. Correct fluid, acid-base and electrolyte abnormalities with fluid therapy - do this over a few hours rather than the usual 24-48 hours for other causes of dehydration; generally use Lactated Ringers or Normosol R; maximum fluid administration rate is 90 ml/Kg/hr.

C. Anti-emetics - Anti-emetics may be necessary to control vomiting from uremia; H2 blockers often used because of hypergastrinemia associated with renal failure, even though H2 blockers are not direct anti-emetics.

D. Lactated Ringers or Normosol R for Maintenance
   1. Calculate maintenance at 60 ml/kg/day; give throughout the day intravenously if uremic
2. Supplement with 16 mEq/L KCL to bring LRS to a total of 20 mEq/L (4 mEq/L in LRS)

E. Management of hypokalemia
1. If patient is polyuric (producing > 2.2 ml/kg/hr) and is on osmotic diuresis, will become hypokalemic if not supplemented; can supplement by
   a. Oral elixirs 1-3mEq/Kg/day if not vomiting.
   b. SQ KCl, 40 mEq/L in Lactated Ringers.
   c. IV KCl, 20 mEq/L Lactated Ringers.
   d. Adjust the above doses by monitoring serum K.

2. Try not to exceed 0.5mEq K/Kg/hour intravenously

3. Hypokalemia is frequent in some cases of renal failure in cats; in fact, muscle weakness may be the principle presenting sign; in these cases, much higher doses of potassium may be needed:

<table>
<thead>
<tr>
<th>Serum Potassium</th>
<th>IV/SQ Supplementation (mEq/250 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0-3.5</td>
<td>5/10</td>
</tr>
<tr>
<td>2.5-3.0</td>
<td>7/14</td>
</tr>
<tr>
<td>2.0-2.5</td>
<td>10/20</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>12/24</td>
</tr>
</tbody>
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G. If patient requires osmotic diuresis for more than 24 hours and cannot (continued vomiting) or will not eat, institute nutritional support. If patient will not eat, but is not vomiting, insert a feeding tube and utilize this to provide sufficient calories. If patient cannot tolerate feeding because of vomiting, parenteral nutrition is required.

H. While patient is on diuresis, must monitor each day and correct dehydration each day - we usually estimate a minimum of 5%.

I. Monitoring therapy - Serial evaluations of BUN, creatinine, electrolytes, patient's clinical status, body weight; adjust therapy as necessary; it is not necessary to reduce BUN or creatinine to normal - just return patient to point of being able to maintain itself; may also need to monitor PCV/TS.

J. When patient stable, discontinue fluid therapy gradually by about 33% per day, continuing to monitor BUN, creatinine, electrolytes, clinical status and body weight.

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