

## MANAGING THE UREMIC CRISIS

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- “Uremic crisis” is a constellation of severe clinical signs and laboratory abnormalities resulting from retention of nitrogenous wastes (azotemia) due to inadequate renal function.
- The exact cause for azotemia (pre-renal, intrinsic renal, or post renal are broad categories of azotemia) is often not known with certainty at the time of diagnosis.
- Therapy and further diagnostics should be run simultaneously.
- Sudden loss of renal function may result from acute intrinsic renal failure, acute pre-renal, obstructive uropathy, urinary leakage into the abdomen (uoperitoneum), or from decompensation of chronic renal failure (CRF).

### IS IT RENAL?

- The first step => determine if the azotemia is pre-renal, intrinsic (renal) or post-renal.
  - **Pre-renal azotemia** => *dehydration or decrease in effective circulating volume*, whereas
    - Urine SG > 1.030 in dogs or > 1.040 in cats
    - Identify the primary non-renal problem while preventing the conversion of pre-renal to primary-renal azotemia from ischemia
  - **Post-renal azotemia** => *obstruction or rupture of the urinary tract*.
    - **Obstruction** => *distended bladder +unfruitful efforts to urinate*.
      - Ureteral obstruction can dramatically worsen azotemia in cats with ongoing intrinsic CRF
      - Chronic partial obstruction strongly resembles chronic intrinsic renal failure.
    - **Rupture of the urinary tract** => *uroabdomen*.
- Correct dehydration and rule-out obstruction/rupture

### IS IT ACUTE OR CHRONIC?

- The second step => differentiate acute from chronic intrinsic renal failure
  - Acute intrinsic renal failure is a potentially reversible disease
  - Chronic intrinsic renal failure is not. Patients with chronic intrinsic renal failure may manifest one or more of the following signs:
    - Long standing history of polyuria and polydipsia
    - Weight loss
    - Anemia
    - Small size kidneys (by palpation, radiography or ultrasonography)
    - Decreased bone radiopacity on radiographs
    - Lack of one or more of the above signs does not rule out chronic renal failure.
    - Kidney biopsy is sometimes necessary to differentiate between acute and chronic renal failure.
  - Chronic pre-renal azotemia can exist in some patients, especially those with hypoadrenocorticism.

### PHASES OF ACUTE RENAL FAILURE

- **Induction Phase**
  - From renal injury to renal lesion before cell death occurs
    - Can last hours to days and is often not recognized

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- Intervention during this phase remove the insult and perfusing the kidneys can stop further damage and allow recovery before development of overt renal failure
- **Maintenance Phase**
  - Renal cell death has occurred and renal failure is established
    - Uremic crisis
    - Can last several days to several weeks
  - Cellular swelling and tubular debris often result in oliguria
  - Intervention at this stage will not reverse the process or shorten the recovery, although it may help to prevent further cell death
  - This is usually the phase at which veterinary intervention is sought and a diagnosis is made
- **Recovery Phase**
  - Gradual improvement of renal function after the maintenance phase
    - Needs sufficient nephrons with viable epithelial cells and intact basement membranes
    - Extreme polyuria often develops
      - Polyuria does not ensure that the animal will recover sufficient GFR to recover from renal failure
    - GFR improves
    - Recovery can be partial and result in chronic renal failure, or it may be nearly complete and result in adequate or even normal renal function

#### WHY IS THIS PATIENT SUDDENLY WORSE?

- Acute renal failure
- Decompensation of chronic renal failure (“acute-on-chronic”)
  - Superimposition of dehydration
  - Urinary tract infection
  - Ureteral stones (especially in cats)

#### HOW DO I TREAT?

- **Rehydrate:** The first step is to correct dehydration within 6 to 8 hours using physiologic crystalloid solutions, as continuing renal hypoperfusion could be detrimental.
- **Induce diuresis:** Polyuric patient are easier to manage.
- **Fix the fixable:** Curable causes of intrinsic renal failure (e.g. bacterial infection associated with pyelonephritis, acute nephritis due to leptospirosis) should be pursued and treated.
- **Manage the unfixable:** Complications (e.g. vomiting and anorexia, hyperphosphatemia, hypertension, anemia, malnutrition, etc) should also be treated.
  - Acute prerenal failure is readily treatable following volume replacement. Acute post-renal failure due to rupture or complete obstruction is usually treatable if recognized early.

#### REHYDRATION

- *Correction of dehydration is the first and most important step in dealing with a uremic crisis.*
  - The uremic crisis is short-lived in cases with pre-renal azotemia following fluid therapy
  - Fluid therapy during uremic crises from primary renal disease usually is successful at least until a definitive diagnosis and prognosis can be made
  - Fluid therapy in **obstruction** .....
  - Large doses of fluids are usually necessary in order to reestablish normal hydration.

- Correct dehydration relatively rapidly, over 4 to 6 hours if possible
  - Help protect a potentially injured kidney from further damage due to renal ischemia.
  - Estimate dehydration volume needs as
  - % dehydration x weight (kg) = liters of replacement fluid volume or start at 100 to 150 ml/kg/day.
  - For patients in a state of vascular collapse, administer shock volume of fluids (0.9% sodium chloride, Lactated Ringer's, Normosol, or Plasmalyte; 70 ml/kg/hr for cats and 90 ml/kg/hr for dogs) until adequately resuscitated.
- Determine whether the patient is polyuric or oliguric.
  - Evaluation of urine volume is made by an assessment of historical and physical findings, or measured urine output through an indwelling urinary catheter.
  - Place an indwelling urinary catheter if there is any concern about the magnitude of urinary output, at least for the first 24 to 48 hours. It is imperative to determine whether the patient is oligo-anuric or not following efforts to rehydrate the patient
  - Normal urine volume production for dogs and cats is 1.0 to 2.0 mL/kg/h,
  - Should be at least 2.0 to 5.0 ml/kg/hr while on fluids following rehydration.
- Polyuric patients may need extra amounts of fluids to compensate to the ongoing kidney losses
- Oliguric patients must be monitored for retention of water and electrolytes.
- Evaluate clinical signs and body weight periodically.
  - Polyuric patients (or that became polyuric after rehydration)
    - If not gaining weight => larger amounts of fluids.
    - Larger doses of fluids are maintained to facilitate excretion of catabolites through the kidneys ("flushing the kidneys").
      - Until creatinine stabilizes at lower concentrations and the pre-renal component is successfully corrected.
      - Fluid therapy can then be tapered off over several days until the patient is discharged from the hospital.
  - Oliguric patients
    - Drastically curtailed infusion of fluid volume needs to be prescribed in those with inadequate urine volume production, otherwise overhydration will result.

#### CAN THIS PATIENT URINATE?

- If after rehydration the patient remains oliguric
  - Attempt to induce diuresis
    - The goal of intensive diuresis is to increase the turnover of body water, electrolyte, and metabolic waste products.
    - Diuresis may result in loss of substances responsible for many of the signs of uremia that accumulated in the uremic environment.
    - An increase in urine volume should not be equated with improved renal function, as glomerular filtration rate can remain unchanged at time of reduced tubular solute and water resorption.
    - In some cases, it is not possible to increase urine flow.

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- After a normally hydrated body weight has been established as a baseline, this weight should be kept constant throughout the administration of the osmotic diuretics.
  - Progressive weight loss during attempts at diuresis may indicate dehydration
    - Some decrease in body weight is expected in patients that do not take in sufficient calories
    - Estimated as 0.1 to 0.3 kg/1000 kcal of energy need per day.
  - Progressive weight gain indicates overhydration
- Inducing diuresis
  - Volume expansion => IV fluid load of a volume 3% to 5% of body weight to unmask undetected mild dehydration.
    - This much dehydration may be missed easily owing to the inaccuracy of clinical estimations of dehydration.
  - Diuretics => if the additional volume expansion does not result in diuresis.
    - *Rehydration **must** be completed before administration of diuretics.*
    - Mannitol (20 to 25 %)
      - Initial dose is 0.25 to 0.50 g/kg of body weight IV over 3 to 5 minutes.
      - Diuresis occurs within 20 to 30 minutes.
      - To maintain diuresis, mannitol is given IV at 40 to 60 mg/kg/h (1 ml/kg/h of a 5% solution). Mannitol may also be diluted in lactated Ringer's solution to supply necessary fluids.
      - A total mannitol dose of 2 g/kg/day should not be exceeded.
      - Mannitol should NOT be given to patients that are overhydrated as the small molecules of mannitol will equilibrate in edematous places potentiating the problem.
      - Mannitol may be superior to other diuretics
        - Works along all aspects of the nephron following filtration
        - May reduce renal edema from its hypertonic effects
        - May decrease intrarenal renin release
        - Can act as a free radical scavenger that may be important in some forms of acute intrinsic renal failure.
    - Furosemide
      - May promote diuresis when mannitol has failed to do so. This drug also may be used initially.
      - Dose of 2 to 4 mg/kg IV.
      - Diuresis occurs within 5 to 15 minutes that may last as long as two hours.
      - If diuresis does not occur within 30 minutes, the dose can be doubled.

- Furosemide can be used every eight hours to maintain diuresis.
- Alternatively, a continuous rate infusion of 0.1 mg/kg/hr can be given. High doses of furosemide may be ototoxic.
- Is contraindicated in patients with acute intrinsic renal failure associated with aminoglycoside toxicity based on work in experimental dogs.
- Dopamine (**NO LONGER RECOMMENDED**)
  - May be successful in promoting diuresis when other treatments have failed (at very low doses: 0.2 to 2 µg/kg/min).
    - Risk of renal ischemia even at such low doses
- If intensive diuresis fails
  - Dialysis
    - Patients with acute intrinsic renal failure which have not responded to initial medical therapy
      - Severe life-threatening overhydration
      - Refractory hyperkalemia
      - Severe non-responsive acidosis are indications to consider dialysis
      - Severe persistent oliguria or anuria which persists despite aggressive medical treatment
    - Peritoneal dialysis
    - Continuous renal replacement therapy
    - Hemodialysis
  - Non-dialytic management
    - In patients that remain oliguric, meticulous attention must be directed to the volume and type of fluid administered in order to avoid iatrogenic overhydration and hyponatremia.
    - Direct measurement of urine output helps to optimize the patient's prescription for replacement fluid volume.
      - Without this system, there is a tendency to overestimate the actual fluid needs. Patients with oliguric renal failure are almost always anorexic.
      - Therefore, metabolic water production is decreased and water requirement are diminished. Insensible losses are estimated to be between 12 to 20 ml/Kg/day in anorexic patients.
      - Sensible losses are equal to the urine output.
      - Contemporary losses may also be occurring due to vomiting or diarrhea.
      - Each 6 hours, an oliguric patient receives approximately:
        - 3 to 5 ml/kg (insensible loss) + the amount of urine produced in the preceding 6 hours (sensible losses).
        - The goal is to maintain stable body weight.
        - The ideal fluid
          - Low sodium and chloride; no potassium (e.g., 0.45% saline, 2.5% dextrose in 0.45% saline).

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## FIXING THE FIXABLE

- Infections
  - Can cause renal failure or complicate a pre-existing renal disease
  - Leading cause of mortality in humans with acute renal failure.
  - Infections should be aggressively pursued and treated.
    - Urinary cultures should be obtained in all patients with renal failure.
    - If infection is present or likely, non-nephrotoxic antibiotics should be initiated.
  - Think LEPTO
    - If there is a chance => penicillins
- Stones
  - Should only be managed aggressively in patients that are obstructed. In all other patients with renal failure, stabilization of the patient should precede surgery or other definitive of treatment for the urolithiasis.

## MANAGING THE UNFIXABLE

- Vomiting and Anorexia
  - Vomiting may result from stimulation of the chemoreceptor trigger zone by circulating uremic toxins, or from gastrointestinal ulceration.
  - Gastric hyperacidity, which is often encountered in uremia, should be reduced.
    - H2-blockers (ranitidine 2 to 4 mg/kg BID; famotidine 1 mg/kg BID initially, then SID)
    - Central control of vomiting may be helpful when H2 blockers alone are not successful (e.g.; metoclopramide 0.2 to 0.4 mg/kg TID to QID, maropitant 1mg/kg q24h).
    - Gastrointestinal coating agents for ulcerations may be helpful (sucralfate 1 tablet/25 kg TID to QID).
  - Severe uremic oral ulcers, stomatitis, and tongue-tip necrosis may contribute to anorexia.
    - Topical lidocaine, glycerine and hydrogen peroxide mouthwash are helpful.
- Electrolyte Disorders
  - **Hyperkalemia** is an uncommon, but life-threatening complication in patients with newly diagnosed oliguric intrinsic renal failure.
    - Rare in pre-renal failure except in patients with hypoadrenocorticism
    - Develops in AIRF in patients with very low GFR and in those with the most severe forms of oliguria.
    - Develops in those with acute urethral obstruction after 48 hours
    - Tends to be a late finding in those with uroperitoneum.
    - Treatment: see notes on Disorders of Sodium and Potassium.
      - Glucose and insulin are more predictable than bicarbonate or glucose alone in lowering potassium in human patients with renal failure.
  - **Metabolic acidosis** may complicate renal failure.
    - Patients with pH below 7.1 should be treated with sodium bicarbonate.
      - Initial dosage of 2 mEq/kg is used.
      - Sodium bicarbonate is then used at the dose needed to maintain pH from 7.1 to 7.2.
        - Sodium bicarbonate may associated with the development of hypernatremia.

- Sodium bicarbonate may also decrease ionized calcium
      - Infusion of alkali should be immediately discontinued if signs of muscle twitching or excitability develop during the infusion.
  - **Hyperphosphatemia** increases mortality in patients during the uremic crisis.
    - Use of intestinal phosphorus binders should be started as soon as the patient stops vomiting.
    - Because most patients have hyperphosphatemia during the crisis, calcium containing binders should be avoided to decrease the risk of tissue calcium deposition.
      - Aluminum salts (aluminum hydroxide gel, aluminum carbonate gel)
      - 10 to 30 mg/kg q8h
- **Anemia**
  - Transfusion with compatible packed red blood cells should be provided to all patients with moderate to severe anemia (PCV < 25% in dogs, < 20% in cats)
  - Treatment with erythropoietin can be considered in patients with severe anemia and chronic renal failure after release from the hospital.
- **Management of Blood Pressure**
  - Both hypertension and hypotension must be identified and promptly treated.
    - Ongoing hypotension provides opportunity for ongoing development of new renal lesions (acute tubular necrosis) due to renal ischemia from which the already diseased kidney cannot protect itself.
      - Maintain hydration !!!!
    - Systemic hypertension of variable severity occurs commonly in dogs and cats with chronic renal failure and may be encountered in AIRF patients following fluid treatment especially those that remain oliguric.
      - Hypertension may not be present at the time of diagnosis
        - Dehydration may mask hypertension
        - Some ARF patients develop hypertension after being sick for several days
    - Patients with systolic blood pressure > 160 mm Hg should be treated.
      - See notes on Hypertension for treatment
- **Nutritional Support**
  - The aim of nutritional therapy is
    - Reduce protein catabolism, which serves as a source of
      - Nitrogenous solutes
      - Phosphorus
      - Potassium
      - Hydrogen ions
    - Promote anabolism.
    - Oral intake of food should be encouraged in patients who are not vomiting,
    - Low-quantity, high-quality protein diets for chronic renal failure patients are preferred.
      - Be careful because some patients may associate diets fed in the hospital with an adverse experience and never again eat that food.
      - It may not be wise to offer the same diet the patient will be required to eat chronically, once released from the hospital.

- Nasogastric or gastric feeding may be indicated in anorexic patients that are not vomiting
  - Nasogastric tube feeding should be considered early on after hydration has been completed and antiemetics are effective.
  - Liquid diets that provide about 1 Kcal/ml can be infused through the NG tube over the day to initially provide basal caloric needs.
- Total parenteral nutrition is also an option.

#### WHAT IS THE PROGNOSIS?

- Pre-renal failure
  - Excellent in nearly all cases if the cause can be corrected.
  - Exceptions include those in which the condition was not quickly recognized and treatment delayed – in such instances there is a transition from acute prerenal to acute intrinsic renal failure.
- Acute intrinsic renal failure
  - Guarded to poor prognosis whenever the animal is in the maintenance phase with severe uremic signs.
  - Over half of dogs with acute intrinsic renal failure die or are euthanized due to inadequate recovery of renal function. Of the remaining, there is about equal chance to regain normal renal function or to survive as a chronic renal failure patient
  - Those with persistent oliguria or anuria have a grave prognosis without dialysis treatment.
  - Dogs with intrinsic acute renal failure and high level azotemia ( $> 10.0$  serum creatinine) after rehydration have fewer chances for survival.
  - Development of overhydration during treatment, especially that associated with pulmonary edema is a poor prognostic factor
  - Maintenance of a normal to increased volume of urine production in conjunction with declining BUN, creatinine, and phosphorus are good indicators of possible recovery
    - Recovery from acute primary renal failure may take from 1 to 3 weeks, or may not be possible
- Decompensation of chronic renal failure (acute on chronic)
  - Have a better short-term prognosis especially if most of the deleterious effect is sudden imposition of pre-renal on top of the chronic renal failure
  - If an element of acute tubular necrosis has been superimposed on the chronic renal failure, the degree of azotemia may not drop back completely to the previous levels of elevation in which case the prognosis is guarded.
  - Diuresis may decrease the BUN disproportionately to any decline in serum creatinine. This decrease in BUN may be associated with feeling better and an inclination to eat more. If so, the prognosis for return to life as a compensated chronic renal failure patient can be fair; otherwise it can be poor to grave
  - At least 3 to 5 days of therapy is provided before a prognosis can be developed.
- Acute post renal failure
  - Due to urethral obstruction
    - Prognosis for recovery is usually excellent
  - Due to rupture of the bladder
    - Very good following repair.
  - Due to ureteral stones in cats
    - Guarded to poor because of the underlying chronic renal failure and surgical difficulty of removing the stones.

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