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THE CRITICALIST’S APPROACH TO TREATING ACUTE RENAL FAILURE – A PATHOPHYSIOLOGICAL APPROACH

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INTRODUCTION

Azotemia refers to a state where there is an increase in non-protein associated nitrogen in the blood. Both increases in urea and creatinine are commonly assessed when determining if a patient is azotemic. This is different then in urea and creatinine are commonly assessed when determining if a patient is azotemic. This is different then

Azotemia does not have to be a primary kidney disorder. It may be:

• Pre-renal, caused by
• Dehydration
• ↓ perfusion
• Renal
• Post renal, caused by a urinary obstruction or a ruptured renal pelvis, ureter, bladder or urethra.

Acute renal failure (ARF) is characterized by a rapid onset of renal insufficiency, reduction in glomerular filtration rate (GFR) and renal plasma flow. It results in an acute uremic syndrome with potential severe hematomal and systemic effects. In some patients this syndrome is accompanied by insufficient quantities of urination (oliguria or anuria), although this is not pathognomonic, and likely true for less than half of the patients seen. The excretory failure is identified by rapid (hours to days) increases in BUN, serum creatinine and phosphate, and variable hyperkalemia and metabolic acidosis. Urine concentration capability is impaired. Acute renal failure is a tenuously reversible state, which must be treated aggressively. Failure to initiate therapy may result in irreversible parenchymal damage and death.

Stages of acute renal failure

Three stages are classically described in ischemic renal failure although not always clinically evident.

1. The initial phase lasts from the onset of the ischemic insult until the development of azotemia and oliguria if it develops. This is the stage where the kidney is damaged and is characterized by acute cell injury leading to decreasing urine concentration capability, sloughing of casts and cellular debris and finally azotemia. If aggressive therapy is implemented in this stage there may be a complete and rapid return to normal function.

2. The maintenance phase is characterized by increasing azotemia loss of concentrating ability and in some cases oliguria, along with increasing percentages of cell death. Intervention in this phase may result in complete resolution and return to normal function although the improvement will take longer than in the previous phase. Without treatment this phase will end in death if the damage is extensive enough.

3. The recovery phase includes recovery of the vascular blood supply but still with tubular dysfunction resulting in diuresis and polyuria. Our therapeutic goal is to convert our patients in the maintenance phase to the recovery stage and allow time for renal healing. This phase can last many days. The degree of return of function depends on the severity of the tubular injury sustained in the prior two phases.

THE PATHOPHYSIOLOGY OF ACUTE RENAL FAILURE

In general acute renal injury results from either toxic exposure or ischemic insult. Both may result in primary vascular (hemodynamic) or tubular renal damage. Several mechanisms are thought to be involved in each case of renal insult. There are 6 major sites of impairment:

- Afferent arteriole vasoconstriction disrupts glomerular flow. This frequently happens as a result of decreased systemic blood pressure, hypovolemia and dehydration
- Mesangial cell contraction causes a reduction in glomerular filtration surface area. This is commonly a result of ischemia, humoral agents or toxins.
- Vasodilation of the efferent arteriole causes decreased glomerular capillary pressure and GFR. This is most commonly a result of pharmacological blocking of the production angiotensin II with an ACE inhibitor.
- Reduced tubular reabsorption of NaCl causes excessive Na delivery to the distal tubule (macula densa) and causing tubular glomerular feedback and increased afferent vasoconstriction.
- Damage to the tubular epithelial cells disrupts the integrity of the tubular lining and may result in tubular backleak, reducing excretory capacity and the effective GFR.
- Tubular damage can also cause tubular flow obstruction by sloughing cellular casts and debris, reducing GFR by reducing glomerular filtration gradient.
- The intracellular results of ischemia are ATP depletion, increased intracellular calcium concentrations, increased free radical production causing cellular dysfunction and if severe cell death.

Recognizing patients at risk for developing acute renal failure is a crucial role of the clinician. Many cases of acute renal failure are preventable and occur in the hospital setting or in a patient receiving veterinary care.

These are just some of the potential risk factors for acute renal failure:

PRE-EXISTING DISEASES
- Renal insufficiency
- Pancreatitis
- Hepatic insufficiency
- Diabetes mellitus
- Heart disease
- Trauma

Clinical Conditions
- Volume depletion
- Electrolyte abnormalities (Na+, Ca2+, K+)
- Hypoalbuminemia
- Hyper or hypotension
- Fever
- Sepsis
- Anesthesia
- Surgery
- Radio contrast media
- NSAIDs
- Nephrotoxic drugs
Intrinsic Renal Disease (partial list)
- Infectious
- FIP, pyelonephritis, sepsis...
- Glomerular disease
- SLE
- Vascular (thrombotic)
- Urinary outflow obstruction
- Urethral obstruction
- Ureteral obstruction
- Toxic – huge list
- Ethylene glycol, cisplatin, amphotericin B
- Pigmenturia
- Neoplasia
- Lymphoma
- Adenocarcinoma
- Hypercalcemia

Clinical Presentation
The clinical presentation of patients with acute renal failure varies based on the cause, severity, previous therapy and associated diseases predisposing to the renal injury. Consistent and characteristic signs of ARF include the sudden onset and rapidly progressive development of listlessness, depression, anorexia, vomiting and diarrhea. Oliguria (<0.27 ml/kg/hr) and anuria may or may not be present, more commonly occurring in ischemic than nephrotoxic disease. Obtaining a thorough history especially of any possible exposure to nephrotoxins or medications is crucial for accurate diagnosis and therapy.

Physical examination commonly demonstrates dehydration (prior excessive fluid therapy makes overhydration a common presentation at referral centers), hypothermia, oral ulceration, “uremic breath,” scleral injection, tachycardia or bradycardia, tachypnea, abdominal pain, rarely seizures and enlarged and painful kidneys on abdominal palpation. Melena resulting from GI bleeding is a common finding on rectal palpation.

Because of the abrupt onset of uremia, patients are often of good body condition, good hair coats and normally pink or injected mucous membranes when compared to the general poor condition of chronic renal failure patients on presentation. When the acute disease comes “on top” of a chronic condition the presentation becomes quite confusing.

LABORATORY EVALUATION
The initial data base should include a CBC, biochemical profile (including HCO3- or TCO2 or central venous blood gas), urinalysis (if urine is obtainable) and urine culture.

CBC
The hemogram is generally non-specific. A non-regenerative anemia would be more suggestive of underlying chronic renal disease, or other chronic disease, although can occur with acute GI bleeding as well. Hypovolemia and dehydration may induce hemoconcentration and increased serum proteins, potentially masking pre-existing anemias. Therefore, the PCV should be reassessed once rehydration has been achieved.

CHEMISTRY PANEL
Azotemia is the biochemical hallmark of renal failure. It is common for the azotemia to be marked in cases of acute renal failure (BUN above 100mg/dl and creatinine above 6mg/dl), although it is not possible to definitively distinguish pre, renal, and post renal azotemia based on the degree of azotemia.

Serum phosphate is regulated primarily via urinary excretion and tubular reabsorption and is heavily dependent on glomerular filtration. In acute renal changes increases in serum phosphate concentrations are often times marked, more than with the same degree of azotemia in chronic disease. This is a valuable tool in our battle to differentiate acute from chronic renal disease.

Additional electrolyte abnormalities include hyperkalemia. This can be severe in oliguric or anuric renal failure and is exacerbated by concurrent acidosis. This is a life threatening condition and necessitates rapid therapeutic measures when present. Hypocalcemia is also a common finding in acute renal failure, it too can be life threatening, although is usually not. The hypocalcemia results mainly from the acute rise in serum phosphorus without time for secondary hyperparathyroidism to develop. Treatment may be warranted in severe cases or if clinical signs of hypocalcemia are evident. The acidosis typically seen with acute renal failure is primary metabolic in origin and results mainly from decreased renal bicarbonate production and reabsorption, vomiting, diarrhea and a respiratory component may induce a mixed acid-base disturbance that requires careful blood gas analysis.

Increases in additional values in the chemistry panel may be increased as well, if they are dependent on GFR. Pancreatic enzymes amylase, lipase and TLI (trypsin like immunoreactivity) are all typically elevated. Although ARF and pancreatitis can occur concurrently it is important to remember this fact and not to suspect that every case of renal insufficiency also has biochemical evidence of pancreatitis.

URINALYSIS
Obtaining urine for analysis prior to initiation of fluid therapy is extremely valuable in differentiating acute renal failure from pre-renal azotemia. If there is no urine at that time it should be obtained as soon as possible after initiation of therapy. Concentrated urine (>1.025) is consistent with pre-renal disease, whereas azotemia in the presence of non concentrated urine is suggestive of at least some degree of renal insufficiency, drug therapy (diuretics) or concurrent disease (hyperadrenocorticism, diabetes insipidus, etc....). Proteinuria and glucosuria (indicative of tubular damage) are commonly seen in ARF. The sediment is frequently “active”, containing RBCs, WBCs, epithelial cells, and casts – reflecting active tubular damage. An abundance of oxalate crystals, bacteriuria may predict the cause of the renal disease.

IMAGING
On routine radiographs kidney size can be assessed although masses and cysts may not be differentiated from renal parenchyma. Ultrasound evaluation is superior for the evaluation of renal parenchyma and is indicated in acute renal disease. Kidneys are generally normal to enlarged and may be hyperechoic in certain disease states (ethylene glycol toxicity for example). Uroliths and signs of urinary obstruction may be seen in radiographic or ultrasonographic evaluations. Ultrasound also is necessary for percutaneous renal aspirates or biopsies in most dogs but is not usually necessary in cats. Additional studies such as contrast radiography, computer tomography and nuclear scintigraphy are useful in some cases.
OLIGURIA (<0.3ML/KG/HR) & ANURIA

Oliguria or anuria are present in up to 50% of ARF cases seen at veterinary centers. Before making this clinical assumption one must try and rule out pre-renal causes of oliguria (as long as a normal animal is dehydrated urine output should be minimal) as well as post renal causes such as obstruction or tear in the urinary system. (DO NOT act upon oliguria until rehydration has been established!)

When oliguria is present it is devastating and life threatening as it does not allow for conservative medical management via diuresis and electrolyte therapies. The solute retention increases the uremia, hyperkalemia results as well as worsening acidosis and death. Inappropriate attempts at diuresis cause life threatening overhydration. If oliguria or anuria are present in a hydrated animal despite fluid therapy in a patient with ARF every attempt must be made to re-establish adequate urine production. If this is not achieved then there is no chance of improvement with continued conservative medical therapy.

Additional consequences of ARF

Neurological complications have been associated with:

- Uremic encephalopathy
- Weakness, lethargy
- Seizures
- Hypertension
- Drugs (H2 blockers?)

- Bleeding disorders
- Platelet dysfunction
- Vasculitis (Lepto..)
- DIC

- GI disorders
- Uremic ulcers
- Vomiting
- Hypergastrinemia

- Electrolyte imbalances
- Hyperkalemia
- Hyperphosphatemia
- Increased Phosphorous X calcium product
- Hypocalcemia
- Severe metabolic acidosis

Prevention, prevention, prevention!!!

Many cases of ARF occur in the clinic or in animals under ongoing veterinary care!

Think about ARF as likely complication in CRF, surgery, trauma, heatstroke, sepsis, hypervolemia, pancreatitis, any severe systemic disease! Prevent ARF today!!!

- Avoid nephrotoxins
- Managing hypovolemia
- Maintaining blood pressure
- Use reno-protective agents – mannitol or Lasix and dopamine in animals predisposed to ARF or doing any surgery on a patient predisposed.
- Monitor hydration and urine production during surgery or in any sick animal.

Acute Renal Failure – Management

Prior to therapy try to differentiate pre-renal/renal/post-renal azotemia

- Obtain blood for PCV, BUN, creatinine (a full CBC and chemistry panel when possible)
- Obtain urine for specific gravity and ideally a full urinalysis and culture
- Physical examination and good palpation of the urinary bladder to try and rule out post renal disease

STEPS TO TAKE –

- Achieve rehydration, adequate colloid oncotic pressure.
- Correct electrolyte imbalances:
  - Hypocalcemia
  - Hyperkalemia
  - Hypo/hypernatremia
- Correct metabolic acidosis
- Give a lot of bicarb!

Assess blood pressure and begin to correct severe hypertension. Hypertension is common with acute and chronic renal disease. Systolic pressure should be lowered to no more than 160mmHg. Drugs in common use today include:
Amlodipine
Hydralazine
ACE inhibitors (Enalapril, Benazepril)

After Rehydration and mild volume expansion!!! Document urine production
And then - treat oliguria/anuria Do not assess urine production prior to rehydration!

Mannitol – Mannitol can be given as an initial bolus (0.5-1g/kg over 20 minutes) and then as a constant rate infusion (1-2mg/kg/min). It causes an osmotic diuresis, vascular volume expansion and increased GFR. It also has antioxidant properties.

Lasix (furosemide) and dopamine can be use alone or together. A synergistic affect has been documented in dogs with concurrent use.

Our goals at this point are to maintain GFR and renal blood flow (RBF) as well as to flush out debris obstructing the tubules and likely causing the acute oliguria/anuria. Besides massive amounts of fluids, it is not clear what the best way of achieving those goals is in dogs and cats. We have recently shown in healthy cats that in addition to high rates of fluids mannitol increases GFR and RBF whereas a combination of lasix and dopamine and most effective in increasing urine output.

When possible - treat underlying disease
Antidote (ethylene glycol)
Antibiotics (pyelonephritis, leptospirosis)

Treat GI manifestations
Metoclopramide
H2 blocker

If oliguria/anuria cannot be converted to polyuria
Do not overhydrate!!!!!
Consider peritoneal/pleural/hemodialysis