# Chronic Kidney Disease

Functions of the Kidneys

- Excretory Functions
    - Nitrogenous wastes (BUN, Crea), water, potassium, sodium, phosphorus, medications
- Endocrine Functions
    - Erythropoietin, vitamin D (calcitriol)
- Regulatory Functions
    - Fluids, electrolytes, minerals, blood pressure

**Chronic Kidney Disease**

Definition: permanent damage/loss of nephrons

Recruitment of non-perfused nephrons

Once critical mass of nephrons is lost there is hyperperfusion and hyperfiltration of the surviving nephrons. This leads to progressive glomerular hypertension, inflammation, progressive damage, and ultimately CKD. Fibrotic tissue replaced the gel-like interstitium leading to an inability to hold water and a loss of communication between nephron segments and the vasa recta.

**Renal Failure**

Definition: Failure of the kidneys to carry out their normal functions, resulting in accumulation of uremic toxins and dysregulation of fluid, electrolyte, and acid-base balance

**Disease (CKD)**

Any structural of functional abnormality present in the kidneys for ≥3 months

- 3 months should allow for repair and regeneration; this process is typically progressive and exists before azoetmia develops
- >53% of cats over 7 years old have CKD
- Cats are more commonly affected than dogs

**Diagnosis of CKD**

Elevation in creatinine with inappropriate urine concentrations. The urine is often isosthenuric due to the loss of normal concentrating ability. It is crucial to ruleout volume responsive azotemia and consider variation in normal creatinine values. Do NOT just look at the reference ranges, it is all about TRENDS!

~75% of renal function needs to be compromised before elevations of creatinine are outside the reference range. That is why it is crucial to look for trends instead of reference range alterations. Non-azotemic CKD occurs commonly so this is also crucial to keep in mind.

**Creatinine and GFR Variation with Body Size**

Small breed dogs will have a lower creatinine than large breed dogs

Small breed dogs will have a higher GFR than large breed dogs

**Symmetric Dimethylarginine (SDMA)**

Methylated form of arginine released into circulation after protein degradation. This compound is almost exclusively excreted by the kidney and is not affected by the loss of lean muscle mass. It may be more sensitive in detecting CKD because it increases outside of the reference range at 40% nephron loss.

**IRIS Staging System for CKD**

1. Staging is initially based on fasting plasma creatinine assessed on at least two occasions in the stable patient
   *you cannot say a patient has CKD without ruling out all causes of an acute reversible injury!
2. Cases are further substaged based on proteinuria (UP:C) and blood pressure

Causes of acute reversible kidney injuries

- Pyelonephritis
- Ureteral obstruction
- Leptospirosis
- Nephrotoxin

CKD CANNOT be diagnosed simply by finding increased creatinine in a patient, you need to confirm that there is irreversible damage

| Acute Kidney Injury | Chronic Kidney Disease |
|---|---|
| Shorter history of illness | Longer history of illness |
| Normal body condition score without a history of weight loss | Thin BCS *History of weight loss |
| Normal hematocrit | Anemia *Dependent on hydration status |
| Normal to enlarged kidneys which may be painful on palpation | Normal to small, irregular kidneys on palpation |

## Clinical Consequences of Chronic Kidney Disease

**Clinical Signs (can vairy depending on staging)**

- Polyuria and polydipsia
- Gastrointestinal
    - Weight loss due to inappetence/anorexia
    - Catabolic state
    - Malabsorption
    - Vomiting/diarrhea
    - Uremic ulcers (oral and/or gastric)
- Lethargy
- Weakness

**These signs are less clinically significant at stages >2*

**Ensuring Proper Nutrition**

- Many patients with CKD are malnourished making the azotemia appear less severe due to muscle waisting
- Renal diet
    - Low protein
    - Low phosphorus
    - +/- potassium supplementation
    - B-complex vitamins
    - Acid-buffering effects
    - Omega-3 supplementation
    - Fermentable fiber
    - <u>These diets may help improve the patient's quality of life!</u>
- Canned diets
- Soup diets
- Consider balanced home cooked diet
- Educate owners about adequate intake and <u>monitor weight trends</u>
- Appetite stimulant
- Feeding tube
    - Typically life-long
    - Allows for the administration of adequate amounts of appropriate diet
    - Definitive medication administration
    - Fluid administration
    - Patient can still eat on their own
    - Owner education is key because this is a significant time commitment

**Uremic Stomatitis**

- Causes

    - Oral urease producing bacteria
- Treatment
    - Pain management
    - Oral chlorhexidine rinse BID (0.1-0.2%)
    - Maintain oral health

**Uremic Gastropathy**

- Causes
    - Elevated gastrin levels
        - Decreased renal excretion which induces gastric hyperacidity
    - Dystrophic mineralization
        - Elevated Ca x Phos product
- Treatment
    - Proton pump inhibitors
        - Omeprazole
    - Sucralfate

**Vomiting**

- Causes
    - Uremic toxins affect the chemoreceptor trigger zone (CRTZ) and vomiting center
    - Gastritis
    - Gut edema
- Treatments
    - Anti-emetics
        - Ondansetron
        - Cerenia
    - Pain management
    - Prevent fluid overload

**Dehydration**

- Causes
    - Polyuria
        - Inability of kidney to conserve water
        - Polydipsia may not be sufficient to prevent dehydration
    - Patient may be inappetent and not drinking
- Progressive dehydration
- Hypovolemia
    - Decreased GFR
    - Progression of renal disease and clinical signs

## Ensuring Adequate Hydration

Supplemental fluids should ONLY be prescribed to

1. Treat dehydration
2. Prevent dehydration

This is accomplished by…

- Ensuring fresh water sources
- Adding water to the diets
- Hydra Care (Purina)
- Subcutaneous fluids when indicated (usually less than 5% of patients)
- Hospitalization and IV fluids when indicated
    - LRS
    - 0.9% NaCl
        - "high" sodium content
        - May exacerbate hypertension
    - Can lead to pain for the patient with repetitive needle sticks or hospitalization

In every patient fluids should be prescribed thoughtfully and should ONLY be prescribed to prevent or treat hydration!!!

**Anemia**

- Causes normocytic, normochromic, non-regenerative anemia
    - Deficient erythropoietin production (typically stage 3-4 CKD)
    - GI hemorrhage
    - Decreased RBC lifespan because they do not live as long in a uremic environment
    - Increased bleeding tendency
    - Iron deficiency
    - Anemia of chronic inflammation
- Consequences
    - Inappetence
    - Hypoxic damage
        - Progressive kidney damage
- Treatments
    - Ensure adequate iron load
        - Adequate nutrition
        - +/- iron panel
        - Iron dextran injection (10 mg/kg IM q 4-6 weeks or based on iron panel)
    - Blood transfusion (ONLY when indicated)
- Naraquin

    - Oral iron supplementation
- Erythropoietin Stimulating Agents (ESA)
    - Need to rule out and treat other causes of anemia and assess if the patient's profile supports a lack of endogenous erythropoietin
    - Ensure iron loads adequately before starting ESA
    - Darbepoetin (Aranesp)
        - Stimulates erythropoiesis
        - 85% autologous to feline EPO
        - Less likely to cause antibody formation
    - EPOETIN alpha (Epogen)
        - Increased risk for side effects
            - Antibody formation
            - Pure red cell aplasia
            - NOT recommended
- Monitor for..
    - Antibody formation to r-HuEPO
    - Polycythemia
    - Hypertension

Hypoxia-Inducible Factor

- Stimulates erythropoiesis in response to hypoxia
- There is a decreased HIF expression in CKD
- Molidustat
    - Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
    - FDA conditionally approved oral drug for feline CKD-associated anemia in cats
    - HIF-PHIs promote erythropoiesis primarily through increased endogenous EPO production and modulation of iron metabolism
    - May decrease hepcidin levels
        - Enhance iron absorption from the GIT
        - Enhanced iron availability from cells into plasma
    - MOA: increase Hct through increasing iron availability and by increased signals for erythropoiesis

Hepcidin is a key regulator of iron metabolism. It degrades iron transporters and can decrease iron availability for erythropoiesis. It also impairs the release of intestinal iron stores and has been shown to be increased in cats with CKD due to decreased renal clearance, increased uremic inflammation, and iron loading.

**Hypertension**

*Ensure you are getting an accurate measurement!

If hypertension goes untreated there can be major downstream consequences

- Progressive renal damage
    - Glomerular
    - Tubulointerstitial
    - Proteinuria
- Retinal detachment (SBP > 180 mmHg) *Do a fundic exam
- Sustained afterload and L ventricular hypertrophy
- Hypertensive encephalopathy

<u>Treatment</u>

- Moderate sodium intake (minimal effect)
    - SQ fluids vs free water
- Amlodipine
    - Calcium channel blocker
    - Negative inotrope and chronotrope
    - Recheck BP ~1 week after starting therapy
    - TAPER to goal BP (SBP <150 mmHg)
    - May upregulate the renin0angiotensin system (RAAS) which can cause progressive hypertension
- Angiotensin Converting Enzyme Inhibition (ACEi)
    - Enalapril/Benazapril
    - Prevents constriction of EFFERENT arteriole
    - Decreases glomerular hypertension and proteinuria
    - LESS effect on systemic blood pressure if used alone
    - Monitor for progressive azotemia
- Angiotensin Receptor Blockers (ARB)
    - Telmisartan

**Hypokalemia**

- Causes
    - Malnutrition (lack of intake)
    - Increased renal losses
        - Exacerbated by diuretics
    - Malabsorption
- Consequences
    - Weakness

    - Anorexia
    - Progressive renal damage
        - Reduced renal blood flow
        - Alters response to anti-diuretic hormone
            - Progressive polyuria
- Treatment
    - Ensure adequate nutrition
    - Potassium supplementation
        - Potassium gluconate
        - Potassium citrate
        - Adjust/titrate dose based on serum potassium

**Metabolic Acidosis** ***** Recall past formulas: Anion gap $(Na^+ + K^+) - (Cl^- + HCO_3^-)$

- Causes
    - Retained metabolic acids (sulfates, phosphates)
    - Decreased bicarbonate production
- Consequences
    - Disrupts cellular metabolism
    - Increased bone and protein turnover
    - Progressive anorexia
    - Progression of renal disease
- Treatment
    - Goal is to get the serum bicarbonate ~ 20 mmol/l
    - Oral dosing of sodium bicarbonate
        - 30-90 mg/kg/day PO or via E-tube
    - Taper to maintain appropriate levels
    - Hypernatremia is NOT common with oral supplementation
    - IV dosing for sick hospitalized patients
        - BW (kg) x Base Deficit x 0.3 = Bicarbonate dose (mEq)
        - Base deficit = 20 – bicarbonate

**Hyperphosphatemia**

- Causes
    - Phosphorus (P) retention
    - Exacerbated by diet
- Consequences
    - Calcium (Ca) x P product
        - Tissue mineralization (gut, kidney, etc)

    - Renal secondary hyperparathyroidism
        - Changes in PTH occur before elevated serum P
- FGF-23
    - Can be an early indicator of CKD and you should switch the animal to a low P diet
- Achieving serum phosphate goals
    - DIET is key!
    - Phosphate Binders
        - Binds P from diet
        - Ensure prescribed dose is ingested
        - Titrate does to ensure adequate control
- Aluminum Hydroxide (AlOH)
    - Helps form relatively insoluble complexes with P
        - These complexes are excreted in feces
    - Formulations
        - Powder or dried gel
        - Liquid suspensions
        - Chewable tablets
    - Dose
        - 30-90 mg/kg/day divided and mixed into each meal
    - Complications
        - Constipation (rare)
        - Toxicity due to excessive Al levels (rare)
            - Microcytic anemia is early and reversible evidence of toxicity
        - Neurologic consequences: weak, ataxic, encephalopathy
        - Occurs in patients with higher stages of CKD and blood levels do not always correlate with toxicity
    - Lanthanum Carbonate
        - Fosrenol
        - Lanthanum is a rare earth element
        - Binds and complexes with P from food and these complexes are not readily absorbed
        - Formulation
            - Chewable pill
            - Must be crushed
        - Increased cost
    - Calcium salts
        - Calcium carbonate
        - Calcium acetate
        - Calcium citrate

                - Binds P from food and prevents absorption
                - Calcium absorption can exacerbate hypercalcemia
    - Epakitin
        - Calcium-carbonate based P binder
            - Contains chitin
                - Reported to decrease protein digestibility and azotemia
                - Chitin may decrease calcium absorption

**Drug metabolism**

- Keep in mind that drugs with renal excretion may require dosage adjustments
    - Baytril (enrofloxacin)
    - Pepcid (famotidine)

**Enteric dialysis**

- Some uremic toxins are synthesized by the GIT bacteria
- GIT acts as a semi-permeable membrane that absorbs uremic toxins
- Hemodialysis
    - Removes uremic toxins from blood
- Enteric dialysis
    - Removal of uremic toxins or precursors from the gut
    - Non-invasive method
    - Improve quality of life
    - Trademark phase held by Kibow Biotech, Inc.
- Probiotics
    - Live microorganisms when given orally in adequate amounts confer a health benefit
    - Lactobacillus acidophilus and Bifidobacteria spp. commonly used
    - In theory, probiotics may alter uremic toxins and trap them in the GIT for excretion in feces
- Azodyl
    - Encapsulated probiotic
    - Unknown MOA (maybe urea recycling)
        - Proposed MOA: Alter gut PH and recycling of nitrogen by bacteria
- Oral Adsorbents
    - Bind uremic toxins and precursors in GIT
    - Epakitin
    - Sevelamer

**Renal Secondary Hyperparathyroidism**

- Causes

    - Decreased GFR
        - Phosphorus retention (exacerbated by diet)
- Normal renal function
    - PTH causes P levels to decrease and $Ca^{2+}$ levels to increase
        - Calcitriol (with normal kidneys
            - Normalizes calcium levels
            - Enhances intestinal Ca and P uptake
            - Inhibits PTH synthesis and release
- Calcitriol and CKD
    - With higher stages of CKD
        - Activation of vitamin D by the kidneys
        - Calcitriol
            - Elevated PTH levels to maintain ionized calcium but decrease calcitriol
            - PTH levels increase leading to renal secondary hyperparathyroidism
- Clinical signs
    - Inappetence
    - Soft tissue mineralization
    - Fibrous osteodystrophy
        - Primarily in growing dogs (calcium is being pulled from the bones)
    - Bone marrow suppression
    - Urolithiasis
    - Neuropathy
- Calcitriol benefit in canine CKD
    - In a small study, dogs given a low dose of calcitriol were seen to have a longer survival time than the placebo group
    - Calcitriol administration appeared to
        - Decrease progression of CKD
        - Increase survival time
    - Similar benefit was not observed in cats
    - Phosphorous levels NEED to be controlled BEFORE administration of calcitriol
    - More studies are needed before the use of calcitriol can be recommended as standard of care

**Hyperkalemia**

- Usually only presents in HIGH STAGE CKD in well-nutritioned patients
- Decreased renal excretion
- Exacerbated by
    - Feeding

    - Metabolic acidemia
    - Angiotensin-converting enzyme inhibitors
- Therapeutic diet
    - Low potassium
    - Commercial renal diet
    - Home-cooked diet
- Increased potassium removal
    - Potassium binders (GUT)
        - Sodium polystyrene (SPS)
        - Prevents potassium excretion
        - KIONEX: Exchanges sodium for other gut cations
        - More efficient with low potassium diets
        - Can cause constipation, do NOT use with AlOH
        - Can also cause hypernatremia and exacerbation of hypertension
        - Can cause severe colonic necrosis when mixed with sorbitol in human reports as well as with sorbitol-free kayxalate enema
        - Less sever upper GIT damage
    - LOW dose furosemide (KIDNEYS)
        - Induces kaliuresis without large increase in urine output
        - 0.25-0.5 mg/kg PO q24h
        - For use in stable patients
        - Monitor hydration status and prevent dehydration
        - Consider supplemental water administration
- Control factors that exacerbate hyperkalemia
    - ACEi
    - Metabolic acidosis
        - Shifting of potassium intracellularly
        - Sodium bicarbonate
    - Potassium citrate
- Feeding adequate amounts
    - RARELY need potassium supplementation
    - Often need home-cooked diet in LATE CKD stages
    - Severely compromised renal excretion
- Sodium bicarbonate
    - Shifts potassium intracellularly
    - Most useful in patients with metabolic acidosis NOT due to lactic acid!
    - IV for rapid correction, oral to maintain bicarbonate levels