General Key Points:

- CKD implies **irreversible** renal failure that remains **stable** for a period of time, but ultimately **progresses**
- Incidence increases with increasing age in dogs and cats
  * Although many things can cause chronic kidney disease, by the time chronic kidney disease is diagnosed the cause(s) is/are not present and not treatable. It can occur as a result of:
    * Congenital renal disease
    * Acquired diseases – hypotension, drugs, toxins, hypotension, infections, cancer
    * Periodontal disease has been linked to renal histologic changes in dogs
    * Feline immunodeficiency virus infection has been linked to renal disease in cats
  * Kidneys are involved with whole body homeostasis; therefore, CKD affects general well-being
- Clinical signs involve primarily
  * Change in **water balance**: polyuria / polydipsia (PU / PD)
  * **Gastrointestinal signs** (vomiting, hyporexia / anorexia, halitosis)
  * Signs of **chronic disease** (weight loss, loss of body condition, unkempt appearance)
- Laboratory evaluation reveals
  * Azotemia
  * Inappropriately dilute urine
  * Hyperphosphatemia
  * Metabolic acidosis
  * ± Hypokalemia
  * ± Non-regenerative anemia
  * ± Bacterial UTI
  * Kidneys are often small and irregular on palpation, abdominal radiography and abdominal ultrasonography; however, some causes of chronic kidney disease are associated with renomegaly (ie neoplasia)
  * ± Systemic arterial hypertension occurs in 65-80% of patients
  * ± Proteinuria (microalbuminuria, macroalbuminuria)
  * Progression of CKD
  * The cause(s) of progression of CKD is not completely known
  * It is likely that in typical situation, CKD results from repeated insults over time that result in sequential loss of nephrons
  * The compensatory response is an increase in single nephron GFR in the surviving nephrons
  * This results in maintenance of total GFR despite loss of functional renal tissue (renal reserve)
  * There is dilation of the afferent arteriole
  * Increase in intraglomerular pressure
  * The result is increase in GFR and renal blood flow
  * There are **trade-offs**, however:
    * Increase in GFR due to increase in renal blood flow and intraglomerular pressure increases likelihood of increased protein loss
    * Increased intraglomerular pressure is transmitted distally
    * There is activation and release of growth factors that promote tubulointerstitial fibrosis and glomerulosclerosis
    * Eventually, these **adaptations** result in loss of further nephrons and the cycle continues
  * Over time, renal reserve is lost as the threshold of nephron mass loss is surpassed resulting in progression of CKD to end stage
International Renal Insufficiency Society (IRIS) Staging

* The International Renal Insufficiency Society (http://www.IRIS-kidney.com) has developed staging system for animals with CKD and treatment based on staging.
  - The staging system is designed for use with dogs and cats with CKD. A diagnosis of CKD is made first and staging is accomplished by evaluating
    - (1) 2 serum **creatinine** values when patient is well hydrated,
    - (2) 2 to 3 urine **UPC** and
    - (3) 2 to 3 **indirect arterial blood pressure** determinations.
      - Indirect arterial blood pressure is determined by 1 of 2 methods
        - **Doppler:** this utilizes ultrasonographic waves that are transmitted by a piezoelectric crystal and is reflected back to the crystal and then converted to audible sound
          - It utilizes the Doppler shift effect – you know the sound an ambulance or race car makes as it approaches and then drives by you (?)
          - Blood in an artery is moving while surrounding tissue is not
          - It is very good for systolic blood pressure, but is not very accurate for measuring diastolic and mean arterial pressure
          - A cuff is placed over the artery proximal to placement of the piezoelectric crystal
          - The crystal is placed on a shaved area over the artery
          - The cuff is inflated above systolic blood pressure so no flow of blood occurs in the artery
          - The cuff is slowly released until blood flow is re-established, which is the systolic blood pressure
          - A sphygmomanometer (gauge) is used to give a numeric value to the systolic pressure
        - **Oscillometric:** this utilizes the principle of movement (oscillations) and the intensity of vascular wall vibration (movement) from the pressure
          - It can determine systolic, diastolic, and mean arterial pressure
          - Although useful, it is less accurate then Doppler
          - A cuff attached to the oscillometric blood pressure instrument is placed over an artery. No clipping is necessary
          - Pressure in the cuff is increased until it exceeds systolic blood pressure and no flow of blood occurs in the artery
          - The instrument slowly releases pressure from the cuff and detects vascular wall vibrations as blood flow is re-established.
            - The first vibration = systolic
            - The most intense vibration = mean
            - The point where vibrations level off = diastolic
  - **Indirect arterial blood pressure is determined over the palmar metacarpal, cranial tibial, or coccygeal arteries**
  - It is important to perform when patient is not stressed; therefore, having the owner hold, use minimal restraint, perform away from people and other patients, and perform prior to sample collection and physical examination
  - **Systemic arterial hypertension may occur in 65-75% of dogs and cats with CKD**
    - CKD is staged by magnitude of renal dysfunction and further modified (sub-staged) by presence or absence of proteinuria and/or hypertension. Proteinuria ONLY refers to renal proteinuria and not pre-renal (e.g. hyperglobulinemia) or post-renal (e.g. urinary tract infection, hematuria, etc), and is based on UPC. Blood pressure determination should be performed several times in order to account for a “white coat” effect using a standard protocol.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Plasma creatinine mg/dl</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dogs: &lt;1.4 Cat: &lt;1.6</td>
<td>Non-azotemic Some other renal abnormality present e.g. inadequate concentrating ability without identifiable non-renal cause; abnormal renal palpation and/or abnormal renal imaging findings; proteinuria of renal origin; abnormal renal biopsy results</td>
</tr>
<tr>
<td>2</td>
<td>Dogs: 1.4 - 2.0</td>
<td>Mild renal azotemia [lower end of the range lies within the reference range for many labs but the insensitivity of creatinine as a screening test means that animals with creatinine values close to the upper limit of normality often have excretory failure] Clinical signs usually mild or absent</td>
</tr>
<tr>
<td>3</td>
<td>Dogs: 2.1 - 5.0</td>
<td>Moderate renal azotaemia Many systemic clinical signs may be present</td>
</tr>
<tr>
<td>4</td>
<td>Dogs: &gt;5.0</td>
<td>Severe renal azotaemia Many extra-renal clinical signs present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UPC value</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>Cats</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>0.2 to 0.5</td>
<td>0.2 to 0.4</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>&gt;0.4</td>
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<table>
<thead>
<tr>
<th>Systolic BP mm Hg</th>
<th>Diastolic BP mm Hg</th>
<th>Adaptation when breed-specific reference range is available *</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>&lt;95</td>
<td>&lt;10 mm Hg above reference range</td>
<td>AP0: Minimal Risk (N)</td>
</tr>
<tr>
<td>150 – 159</td>
<td>95 - 99</td>
<td>10 – 20 mm Hg above reference range</td>
<td>AP1: Low Risk (L)</td>
</tr>
<tr>
<td>160 – 179</td>
<td>100 - 119</td>
<td>20 – 40 mm Hg above reference range</td>
<td>AP2: Moderate Risk (M)</td>
</tr>
<tr>
<td>= 180</td>
<td>= 120</td>
<td>= 40 mm Hg above reference range</td>
<td>AP3: High Risk (H)</td>
</tr>
</tbody>
</table>

- No evidence of end organ damage/complications |
- Evidence of end organ damage/complications |
- Blood pressure not measured |

<table>
<thead>
<tr>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications (nc)</td>
</tr>
<tr>
<td>Complications (c)</td>
</tr>
<tr>
<td>Risk not determined (RND)</td>
</tr>
</tbody>
</table>

**Tests of Renal Function**

- GFR can be estimated using both clearance methods and “spot” or single time point tests.
  - Renal or plasma clearance of an injected substance (e.g., iohexol, creatinine) is most accurate estimate of GFR
  - More sensitive means for detecting early CKD than spot methods of GFR estimation.
  - Determining plasma clearance can be a relatively expensive and time-consuming procedure.
  - Most often performed:
    - To establish a decrease in GFR when clinical parameters (e.g., poorly concentrated urine) create suspicion for CKD but cannot confirm its presence,
    - To determine dosage regimens for therapeutic agents whose excretion is primarily renal in patients with CKD.
- Plasma clearance testing
  - Measuring reduction of an injected substance in the blood over time) can be used to estimate renal clearance and therefore GFR.
    - Most common exogenous substances used in veterinary medicine for estimation of GFR are iohexol and creatinine.
    - Other substances and techniques can be used, such as inulin, radiolabeled markers, and contrast-enhanced computed tomography (CT)
    - A novel fluorescent tracer has been evaluated as a rapid, non-invasive bedside test in dogs.
Ultimately, choice in method used depends on availability of the injected substance and method of measurement as well as the experience.

In some cases, estimation of individual kidney GFR (vs. global GFR) is necessary, as is possible with scintigraphy or CT.

- Iohexol clearance and exogenous creatinine clearance give a measure of total GFR; DTPA (a radiolabelled marker) gives estimate of total as well as individual kidney GFR.
- One of the main limitations with clearance methods is need for serial, precisely timed blood draws.
  - An accurate clearance calculation requires as many as 8 post-injection blood samples over 6 hours or longer, although reasonable estimates can be obtained with limited sampling (i.e., 2 or 3 post-injection samples)
  - Timing of these limited sample collections varies depending on the substance used
  - Some studies have found that calculation of plasma clearance based on a single post-injection sample is strongly correlated with 3-sample techniques, as long as an estimated volume of distribution can be determined
- This is especially important in cats, where multiple collections can prove difficult.
- Another limitation with plasma clearance is the large amount of variability in what is considered to be “normal” in dogs and cats.
  - In one study of 118 healthy dogs, iohexol clearance ranged from 0.95-4.25 mL/min/kg
  - In previously published studies in healthy dogs and cats, the range for various clearance estimates was as wide as 2.45-6.64 mL/min/kg (dogs) and 2.19-3.49 mL/min/kg (cats), although most weighted reference intervals were around 3.4 mL/min/kg (dogs) and 2.5-3.5 mL/min/kg (cats)
- Therefore, it is difficult to define a normal GFR in a particular animal without a baseline for that patient, and it limits ability of plasma clearance to detect early reductions in GFR.
- Week-to-week and month-to-month biological variability must also be considered when monitoring plasma clearance in a particular patient
  - Based on the week-to-week variability of iohexol clearance in a cohort of dogs with mild but stable renal disease, a subsequent measurement must increase or decrease by up to 20% in order to be 95% confident that a true change in clearance has occurred
  - Interestingly, despite using more measurements, each with its own inherent variability, iohexol clearance variability was similar to that for serum creatinine (sCr) in these dogs
- In addition to biological considerations, analytical considerations in plasma clearance calculations are important.
  - When using a limited sampling technique, a correction formula must be applied to correct for the initial distribution phase in order to avoid overestimation of the GFR
- Correction formulas for both dogs and cats are available when using iohexol
- Normalization to body weight, surface area, or extracellular volume has been recommended, but it is not clear which normalization technique should be used in dogs and cats.

**Spot tests**
- Urine specific gravity (USG)
  - USG varies from minute-to-minute and is influenced by hydration and volume status
  - A dilute USG on a spot sample may be normal in patients that have ingested water recently in excess of what is required for hydration
  - Additionally, many non-renal disorders influence USG by altering volume status and/or by inhibiting anti-diuretic hormone function in the distal renal tubule and collecting duct
  - Patients with persistent PU/PD may not have renal disease and other disorders should be ruled out if not azotemic (e.g. hyperadrenocorticism, hypothyroidism, hyperthyroidism, diabetes mellitus, hypercalcemia, hepatic disease, consumption of higher sodium chloride diets, administration of diuretics, supplements, or herbs with diuretic activity, etc).
- Blood urea nitrogen (BUN)
  - Used as biomarker for assessment of renal function
  - More influenced by non-renal factors than serum creatinine – e.g. pre-renal and post-renal
Urea nitrogen is a small molecule that diffuses easily across cell membranes and into and out of tissues
- With dehydration, urea nitrogen is reabsorbed in tubules and less is filtered due to decreased renal blood flow; therefore, it increases more quickly and often to a greater degree than creatinine
- Urea is produced from metabolism of ammonia by hepatic urea cycle; therefore, increased intestinal protein load will result in generation of more ammonia and urea nitrogen
- It should not be used as a sole biomarker for renal function and interpretation of an elevation is not possible without historical and physical examination findings and a urine specific gravity

Serum creatinine (sCr)
- Main endogenous marker currently used for estimating GFR
  - While this molecule meets most of the criteria for an ideal marker of GFR, it has several major limitations, of which the most important in veterinary medicine include breed variations in dogs and decreased production with muscle wasting, as is often the case in animals with CKD.
  - It may overestimate renal function in cachectic, geriatric, and very young patients.
  - Tubular secretion can increase as sCr increases, although this is thought to be minimal in veterinary species as compared with humans.
  - These factors can make monitoring of sCr over time a less reliable indicator of declining GFR.

Early in disease, limitations of sCr in an individual patient are minimal.
- Muscle mass is usually stable in dogs and cats with early renal disease, and tubular secretion due to an increased blood concentration is not a factor.
- Careful monitoring and trending of fasted serum creatinine concentrations can allow for early detection of renal disease manifested by a declining GFR.
- Trending sCr means that serial determinations of sCr are assessed to look for significant increases in a particular patient that are likely to reflect worsening renal function.
- Serum creatinine concentration lends itself to trending quite nicely because it demonstrates very little intra-individual variation in healthy, adult animals, even over several years
- Small increases within the reference interval can reflect significant decreases in GFR in an individual patient, and a reference interval will not be helpful when using sCr to identify the earliest declines in GFR due to kidney disease in most patients.
- When comparing serial measurements of sCr with renal clearance of an exogenous substance, they correlate strongly and subtle increases in sCr can identify a decrease in GFR at a similar point in disease progression (unpublished observations).
- While trending of sCr can be useful in the early detection of renal disease, many patients present to a clinic with no prior bloodwork.
  - In this case, the various factors that can influence sCr need to be considered (e.g., breed, age, muscle mass, diet/fasting status, hydration status) when evaluating a single value.
  - Any concerning values, even within the reference interval, should prompt further evaluation.

When trending sCr, be aware of both its biological and analytical variability.
- Biological variability in an individual patient is best determined by bloodwork performed during routine health checks.
- As long as at least 3 measurements have been obtained, one can calculate the reference change value (RCV) for a patient
This value represents that at which one can be 95% confident that an increase or decrease in the analyte has occurred.

Some reference laboratories are incorporating similar statistical analyses into their reports to allow easy trending of various blood analytes.

If enough previous bloodwork results are not available for a particular patient, another guide that can be used is the RCV determined in a population of dogs with mild (sCr < 2 mg/dl) but stable renal disease.

Total (biological + analytical) variability of sCr determined over a 3-week period in these dogs, and the RCV was 0.2 mg/dl, meaning that an increase in sCr of 0.2 mg/dl would indicate a statistically significant increase in this marker when sCr < 2 mg/dl

- In addition to biological variability, analytical variability is a factor in the assessment of sCr
  - Most reference laboratory instruments have excellent precision in their sCr measurement, having a coefficient of variation < 5%.
  - The difference between sCr measurements in the same sample can be as much as 0.2 mg/dl in mildly azotemic samples using the same instrument and much higher in moderately to markedly azotemic samples or if different instruments are used
  - Many in-clinic instruments have minimal, if any, quality assurance programs in place to ensure optimal performance.
  - Based on both the bias and imprecision found in instruments commonly used in veterinary laboratories, the ASCVP Quality Assurance and Laboratory Standards Committee has set their total allowable error (TEa) guideline for sCr at 20%
    - This means that analytically variability alone could potentially account for an increase or decrease in sCr of ≥ 0.2 mg/dl.
    - It is particularly important that serial determinations of sCr are measured on the same instrument, ideally one that is subjected to a strict quality assurance program.

- Cystatin C
  - Cystatin C is a cysteine protease inhibitor that is produced at a constant level in all nucleated cells.
    - It shares many of the same properties of an ideal marker of GFR as sCr.
    - Non-renal influences appear minimal, although administration of large doses of glucocorticoids, thyroid dysfunction, and some malignancies can increase its production
    - In dogs, cystatin C might be influenced by age, weight, and dietary intake, although several conflicting studies exist
    - The biological variation of cystatin C (inter- and intra-individual variation) is similar to creatinine in healthy dog
    - Its availability in veterinary medicine is still limited, and there has been no verification that the cystatin being measured is truly canine cystatin C (vs. other cystatins).
  - In humans, the majority of studies support that cystatin C is a more sensitive and accurate marker than sCr for detecting early declines in GFR, particularly in those subpopulations in which the limitations of sCr are overtly recognized
    - In dogs, studies have shown cystatin C to be either comparable to or more sensitive than sCr to declines in GFR
    - It might therefore be a reasonable alternative to sCr in detecting decreased GFR due to renal disease.
    - Its value over sCr and the influence of nonrenal factors on its level are still unknown in veterinary medicine.
  - In cats, measurement of cystatin C has recently been determined using both a human-based assay and a feline-specific assay
    - Both of these studies demonstrated high serum and urine cystatin C concentrations in cats with CKD compared with healthy cats.

- Symmetric dimethylarginine (SDMA)
  - SDMA is a small molecule that originates from hydrolysis of methylated proteins.
- This molecule has shown great promise as an endogenous marker of GFR as it appears to be exclusively eliminated by glomerular filtration, and significant extra-renal influences on its production and elimination have not yet been identified
- It is stable in whole blood, serum, and plasma at 4°C and room temperature for up to 7 days, and it is not altered with freezing in serum or plasma
- This molecule has been evaluated in several canine studies.
  - In dogs with rapidly progressing CKD, SDMA correlated strongly with GFR estimated using iohexol clearance
  - Notably, when using reference intervals, SDMA identified a decrease in GFR earlier than sCr, however, when both were trended over time, no major differences in identification of declining GFR were noted
  - These results support that trending of sCr is necessary for sensitive detection of decreasing GFR and that SDMA might be a useful adjunct to sCr in identification of renal disease, particularly given the tendency to classify a dog as azotemic or not based on a reference interval.
  - SDMA is not influenced by muscle mass, but any non-renal change in GFR will impact it. For example, with dehydration there is a decrease in GFR and therefore SDMA will also be influenced.
  - It might prove especially useful in the initial diagnosis of CKD in those patients for which sCr will not provide a reliable estimate of GFR.
- In cats with CKD, SDMA correlates with sCr
  - While preliminary data suggest that SDMA might increase beyond its reference interval before sCr in cats and that a higher SDMA:creatinine ratio might indicate a worse prognosis
  - Similar to dogs, it is not influenced by lean body mass; however, non-renal factors affecting GFR will impact SDMA
  - SDMA changed approximately 17 months earlier than sCr

MANAGEMENT OF CKD
* Goal of management is to minimize excesses and deficits induced by CKD in order to improve quality and quantity of patient’s life
* Summarized using the acronym NEPHRONS

<table>
<thead>
<tr>
<th>N</th>
<th>Nephrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Electrolytes</td>
</tr>
<tr>
<td>P</td>
<td>pH of blood (acid-base status), proteinuria</td>
</tr>
<tr>
<td>H</td>
<td>Hydration status</td>
</tr>
<tr>
<td>R</td>
<td>Retention of wastes</td>
</tr>
<tr>
<td>O</td>
<td>Other renal insults – avoid</td>
</tr>
<tr>
<td>N</td>
<td>Neuroendocrine changes</td>
</tr>
<tr>
<td>S</td>
<td>Serial monitoring</td>
</tr>
</tbody>
</table>

* NUTRITION
* Maintain adequate to optimum body condition and adequate muscle condition (lean body mass)
* Body condition scoring (you will learn in nutrition)
* Want a body condition score of 3/5 or 5/9
* There are formulae to estimate daily caloric requirements (you will learn in nutrition)
* Anorexia and nausea occur commonly with chronic kidney disease. Treatment includes:
  * Minimizing excesses and deficiencies
    * Feeding a highly palatable diet or increasing palatability of diet – add water to dog food, use flavoring agents, warm food to near body temperature
    * Modifying feeding patterns – feed frequent small meals, offer rewards, prevent food aversion
  * Treat uremic gastroenteritis
* Dietary protein induces gastric HCl secretion; therefore, dietary protein restriction is associated with decreasing gastric acid
* Gastrin levels are increased with CKD
* Gastrin stimulates HCl production and secretion by gastric parietal cells
* Results in gastric hyperacidity
* **H2 blockers:** decrease HCl secretion by blocking the histamine-2 receptor on parietal cells of stomach. It is reasonable to put all patients with CKD on these (e.g. Ranitidine, Famotidine)
* **Proton pump inhibitors** interfere with production of HCl by the gastric parietal cells and are more potent antacids than H2 blockers. There is a small study that did not demonstrate a benefit in dogs with CKD.
* **Sucralfate:** a mucosal protectant that forms a “physiologic band-aid” on active ulcers by binding to exposed submucosal collagen in an acidic environment. May also have cytoprotectant effects via PGE2. Additionally, it is a weak antacid and phosphate binder as it contains aluminum hydroxide.
* **Antacid:** are not typically used with CKD although many are available. Usually these are used as phosphate binders.
* **Mirtazapine** (Remeron): a noradrenergic and serotonergic antidepressant. It stimulates appetite and is an anti-emetic. It has been shown effective in cats with CKD
* **Maropitant** (Cerenia): a neurokinin-1 (NK-1) antagonist that is used for motion sickness and is an anti-emetic. It has been shown effective in dogs with CKD
* **Misoprostol** (Cytotec): a prostaglandin E2 analog that increases blood flow to gastric mucosa and increases stir layer on mucosal surface. Not used routinely, but good for prevention of NSAID-induced gastric ulcers
* **Gastrostomy feeding tubes** may be used to facilitate nutritional management as well as used for medication administration and fluid support.
* One theory of progression of CKD involves intraglomerular hypertension in the remaining nephrons. This is beneficial in that it keeps GFR up; however, the intraglomerular hypertension may ultimately result in loss of surviving nephrons and progression.
* Feeding diets containing **omega-3 fatty acids** may be beneficial in dogs
* Omega-3 fatty acids decrease intraglomerular hypertension, maintain GFR, and prolong survival
* An omega-6 to omega-3 fatty acid ratio of 3:1 to 5:1 appears to be a reasonable intake and is present in many renal failure diets
* **Rubenal**
  * An extract of medicinal rhubarb (*Rheum officinale*)
  * Proposed to decrease renal fibrosis
  * In one study of cats of CKD, no benefit was found
* **RenAvast**
  * Proprietary mixture of amino acids and peptides
  * Unproven in a controlled, published study

**ELECTROLYTES**

* **Potassium**
  * **Hypokalemia** may occur especially in cats due to
    * Anorexia
    * Excessive renal and fecal losses
    * Chronic metabolic acidosis (transcellular shift)
    * Activation of renin-angiotensin-aldosterone system (RAAS)
  * Clinical signs of hypokalemia include
    * **Polymyopathy** – classic sign is an animal that cannot lift its head while sitting sternally; however, generalized weakness may occur more commonly
  * **Worsening renal failure**
    * Anorexia
  * Treatment
• Potassium (as potassium chloride) may be added to IV or SQ fluids
• Potassium is often present in renal failure diets as potassium citrate
• Potassium may be supplemented orally using potassium gluconate or potassium citrate
• Potassium citrate provides alkalinization as well as potassium
• May cause GI upset – related to formulation not to drug
• E.G. If problems with liquid – try powder, granules, or tablets
• Serum potassium concentrations should be maintained in middle to upper half of normal range

* Sodium
• Changes in serum sodium concentration occur rarely
• Sodium retention occurs with chronic kidney disease resulting in expansion of extracellular fluid volume and hypertension
• Moderate sodium restriction beneficial
• Decrease fluid retention
• Synergistic with anti-hypertensive medications
• Excessive restriction may activate RAAS promoting urinary potassium excretion
• In one study, high salt intake (1.2%) was associated with increasing azotemia in cats with CKD

* PH OF BLOOD (ACID-BASE STATUS)
* Metabolic acidosis occurs commonly
  • Occurs because of retention of organic acids, decreased renal ability to regenerate and reclaim bicarbonate, decreased ammoniagenesis (ammonia is a buffer and is renally excreted with acid), generation of acids from catabolism,
  • High anion gap metabolic acidosis
    • There is actually no anion gap
    • “the body is not a battery” – negative charged ions (anions) must equal the positive charged ions (cations)
    • Anion gap = (Na+ + K+) – (HCO3- + Cl-)
    • 0 = (unmeasured cations (UC) + Na+ + K+) – (unmeasured anions (UA) + HCO3- + Cl-)
    • UA – UC = (Na+ + K+) – (HCO3- + Cl-)
    • UA are acids; body cannot tolerate much of a change in UC
    • With an increase in unmeasured anions -> decrease in bicarbonate with a subsequent increase in anion gap (high anion gap acidosis)
    • With loss of bicarbonate (base) from body -> decrease in bicarbonate but an increase in chloride to compensate with subsequent normal anion gap (hyperchloremic normal anion gap acidosis)
    • Metabolic acidosis may cause anorexia, hypokalemia, muscle weakness; however, it does not appear to directly influence progression
    • Serum bicarbonate or total carbon dioxide concentration can be used to estimate blood bicarbonate levels
    • Try to maintain a normal concentration

* Treatment
  • Many renal failure diets contain potassium citrate, an alkalinizing agent
  • Because metabolism of dietary protein results in production of organic acids, dietary protein restriction decreases amount of organic acid that must be excreted by kidneys
  • Alkalinizing agents (potassium citrate or sodium bicarbonate):
    • Potassium citrate may be preferred because it provides potassium in addition to its alkalinizing properties
  • Sodium bicarbonate administration results in a large sodium load that may worsen hypertension and fluid retention, but has been used

• Proteinuria
  • Proteinuria is not just a marker of glomerular disease
  • Proteinuria appears to be nephrotoxic
    • Stimulates renal fibrosis and activates inflammation
• Indicated when:
  o CKD IRIS stage 1: UPC > 2.0
  o CKD IRIS stage 2-4: UPC > 0.4 (cats), > 0.5 (dogs)

• Treatment
  o Low protein diet (renal failure diet)
  o ACE-I: decreases intraglomerular pressure
  o Omega-3 fatty acids

* HYDRATION
* Polyuria due to chronic kidney disease is offset by a compensatory polydipsia
* Dehydration occurs if water intake does not equal water loss
* Treatment
  • Oral
    * Clean fresh water should be available at all times
    * Water may be added to food or a canned diet may be fed
    * Flavoring agents, such as broth, may be added to food
  • Intravenous
    * In a dehydrated animal, address 3 parts of fluid therapy
    * Amount needed for rehydration: %dehydrated x BW\text{kg} = litres needed for rehydration
    * Maintenance: for healthy animals: 50-70 ml/kg/day
    * Amount necessary to replace fluid lost as vomitus, diarrhea, or third-spaced fluid
    * Animals with chronic kidney disease, especially cats, may require subcutaneously administered fluids to maintain hydration and prevent dehydration
    * Usually 75-150 ml are administered q12-72hr
    * Use a non-glucose containing electrolyte solution such as lactated Ringer’s solution, Ringer’s solution, etc
    * An implantable device is available for long term subcutaneous fluid administration (GIF-Tube); however, many complications

* RETENTION OF WASTES
* Elimination of wastes particularly nitrogen-containing compounds is an important function of the kidneys
* Reduction of dietary protein seems logical
  • Studies are contradictory whether protein reduction slows progression
  • Dietary protein restriction may be associated with
    * Decreased degree of azotemia
    * Decreased serum phosphorus concentration (meat-based protein is also high in phosphorus)
    * Decreased metabolic acids
    * Decreased gastric acidity (protein digestion occurs in stomach and gastric acid secretion is stimulated, in part, by dietary protein)
  • Two studies, one in cats and one in dogs, of spontaneously occurring renal failure, demonstrated a beneficial effect from feeding a renal failure diet when compared with feeding a maintenance diet
    * Animals lived longer
    * Episodes of uremia were less frequent and time to onset of first episode was longer
    * Owners perceived quality of life was better
    * Renal failure diets differ from maintenance in other ways
  • But, level of dietary protein found in renal failure diets is adequate for maintenance of adult animals is not likely to be associated with protein malnutrition
* Prebiotics: Feeding diets that contain soluble fiber may redistribute a small amount of nitrogen into the gut for elimination thus decreasing the amount required by the kidneys to eliminate (“nitrogen trapping”)
  • Soluble fiber promotes bacterial proliferation in the colon
  • This proliferation requires nitrogen
* The major source of nitrogen is blood urea nitrogen
* Thus, promoting colonic bacterial proliferation may decrease blood urea nitrogen concentration
* The effect is small and studies are lacking to demonstrate an effect on survival or quality of life
* **Probiotics**: involve administering live bacteria. One formulation, Azodyl, is marketed as “enteric dialysis”. In one study of cats with CKD, there was no benefit and administration of Azodyl was not associated with decreasing the degree of azotemia.

**OTHER RENAL INSULTS – AVOID**
* Dehydration may precipitate an acute renal failure episode making the chronic kidney disease worse
* Certain drugs may be directly nephrotoxic or may worsen renal failure
  * Gentamicin
  * Amphotericin
  * Urinary acidifiers
  * Catabolic drugs – glucocorticoids, immunosuppressive drugs
  * Non-steroidal anti-inflammatory drugs
    * May be nephrotoxic if given in high enough dose
    * Are not nephrotoxic when given at recommended dosages, but are a risk factor for renal failure
    * By decreasing production of prostaglandins, vasodilatory prostaglandins may also be decreased
    * If hypotension or hypovolemia occurs, blood flow to renal medulla is compromised due to decreased activity of vasodilatory prostaglandins resulting in ischemia and renal tubular necrosis
* Risk of bacterial urinary tract infection is increased
  * Concentrated urine is a defense against bacterial urinary tract infection
  * Dilute urine occurs with chronic kidney disease
  * Premature apoptosis of white blood cells
  * Clinical signs may be absent because of polyuria
  * May worsen chronic kidney disease
  * Ascending infection from urinary bladder to kidneys
  * May be part of cause of chronic kidney disease
  * Prophylactic antibiotics should be avoided
    * May select for resistant organism
    * Some antibiotics are nephrotoxic
    * Most antibiotics are renally excreted so their kinetics are altered by chronic kidney disease
    * Administration may have side effects – anorexia, vomiting, diarrhea
    * Only use antibiotics if a bacterial infection is documented
    * Because of dilute urine, bacteriuria, pyuria, and hematuria may not be obvious
    * Urine culture of a sample obtained by cystocentesis is best

**NEUROENDOCRINE FUNCTION**
* Renal hyperparathyroidism
  * Occurs, in part, because of phosphorous retention and decreased calcitriol (vitamin D3) metabolism by the failing kidneys
  * Hyperphosphatemia may result in renal mineralization and loss of nephrons
  * Fibrous osteodystrophy (rubber jaw)
  * Hyperphosphatemia is associated with progression of chronic kidney disease and of shortened survival
* **Treatment**
  * Goal is to decrease serum phosphorous concentration to
    * < 4.5 mg/dl with stage 2
    * < 5.0 mg/dl with stage 3
    * < 6.0 mg/dl with stage 3
  * Lower is better.
  * Serum phosphorous concentration may be decreased by:
    * Feeding a low phosphorous diet (renal failure diets)
    * Administering phosphate binders
* Administer with food – the idea is to bind phosphorous within the gastrointestinal tract. Side-effects are anorexia and constipation

* **Aluminum hydroxide**
  * Phosphorous binder as well as antacid
  * Conventional drug of choice
  * Aluminum toxicity extremely rare and occurs with very high dosing

* **Calcium acetate (PhosLo)**
  * Phosphate binder and antacid
  * May induce hypercalcemia
  * No studies in dogs and cats

* **Sevelamer hydrochloride (Renalgel)**
  * Non-calcium containing phosphate binder
  * Minimal side effects in dogs and cats
  * Dose is extrapolated but based on toxicity studies

* **Lanthanum carbonate (Fosrenol)**
  * Non-calcium containing phosphate binder
  * Appears to be well tolerated
  * Dose is extrapolated

* **Chitosan + calcium carbonate (Ipakitine)**
  * Veterinary specific phosphate binder
  * May induce hypercalcemia
  * One study in cats showed decreased phosphorous

* **Vitamin D**
  * Hypovitaminosis D has a role in renal hyperparathyroidism
    * Kidneys metabolize 25-hydroxyvitamin D to the active form 1,25-dihydroxyvitamin D (calcitriol) by enzyme, 1-alpha-hydroxylase
    * Calcitriol decreases parathyroid hormone concentration
    * Although recent study in dogs documented decreased vitamin D3 receptors in parathyroid glands
    * Parathyroid hormone may have a role in clinical signs and of progression of chronic kidney disease, but it is controversial
  * Dietary phosphorous restriction decreases parathyroid hormone levels
  * Oral administration of low doses of calcitriol may decrease parathyroid hormone
  * Serum phosphorous should be normalized before administering calcitriol because of risk of hypercalcemia and increasing calcium x phosphorous solubility product
  * To date, only dogs in stage III or IV IRIS benefit from calcitriol therapy
    * Not been shown to be beneficial in cats at any stage

* **Hypoproliferative anemia**
  * **Normocytic, normochromic non-regenerative anemia** occurs in many animals with chronic kidney disease. May induce progression of disease due to decreased blood flow, stagnation of blood, oxidative stress, decreased oxygen diffusion, and induction of fibrosis
  * Causes of the anemia include
    * Decreased production of erythropoietin
    * Nutritional imbalances because of anorexia
    * Blood loss due to uremic gastroenteritis
  * Treatment includes
    * Maintaining good nutritional status
    * Minimizing gastrointestinal blood loss
    * Stimulating red blood cell production by bone marrow
      * Anabolic steroids have a minimal effect in promoting red blood cell production
        * They may also stimulate appetite
        * They may be associated with hepatopathy
• **Erythropoietin and darbepoetin**
  
  - Recombinant human erythropoietin (rHuEPO) and its synthetic analog darbepoetin have been used successfully in dogs and cats with chronic kidney disease that are severely anemic
    - Many animals receiving rHuEPO feel better even if their anemia does not improve
      - Darbepoetin may be associated with fewer incidence of antibody production and is administered weekly and is the hormone replacement of choice
  - It is indicated when:
    - Packed cell volume is less than 15-20%
  - This is based on using rHuEPO where antibody production occurs commonly
  - Because antibody production does not appear to occur with darbepoetin, consider use when anemia begins to develop
    - Animal does not feel well because of the anemia
      - Because uremic gastroenteritis is common, iron should be supplemented to offset the iron deficiency associated with blood loss
      - Infections should also be treated to minimize iron sequestration
  - Target of treatment is to achieve a **PCV of 35-45%**
    - Once target is reached, the frequency and amount of dosage can be slowly decreased to find lowest amount necessary to control anemia
  - Complications include
    - Irritation at injection site
    - Systemic arterial hypertension
    - Polycythemia
    - Worsening of anemia after initial response
      - Usually associated with antibody production against rHuEPO
        - Occurs in 20-40% of dogs and cats
        - Anti-rHuEPO antibodies may cross-react with native erythropoietin resulting in more severe anemia than initial
        - Discontinuing rHuEPO usually results in improvement of packed cell volume to value at start of rHuEPO treatment
        - This has not been documented with darbopoietin
  - If an animal initially responds to rHuEPO or darbopoietin, but the packed cell volume begins to decline
    - Cross-reacting antibodies may have developed
    - Iron deficiency may be occurring
      - Treat for uremic gastroenteritis
      - Treat any infections
      - Give iron supplementation if not already receiving

• **Systemic arterial hypertension**
  
  - Occurs in 65-75% of dogs and cats with chronic kidney disease
  - Pathogenesis includes activation of RAAS, activation of sympathetic nervous system, increased ADH due to hypovolemia
  - **Risks**
    - **AP0** (sBP < 150 mmHg): minimal risk
    - **AP1** (sBP = 150-159 mmHg): low risk
    - **AP2** (sBP = 160-179 mmHg): moderate risk
    - **AP3** (sBP > 180 mmHg): high risk
  - Results in diseases associated with organs with small vessels
    - **Eyes** – retinal vessel tortuosity, hemorrhage, hyphema, blindness
- **Kidneys** – proteinuria, progression of renal failure
- **Heart** – left ventricular hypertrophy, possible congestive heart failure (left sided)
- **Brain** – ischemic encephalopathy, seizures, death

- Diagnosis is made by measuring arterial blood pressure
- Treatment includes
  - **Goal is sBP < 150 mmHg**
  - **Restricting dietary sodium** – renal failure diets contain less sodium than maintenance diets
  - **Anti-hypertensive drugs**
    - **Calcium channel blockers**
      - Decreases blood pressure by arteriolar vasodilation
      - More effective first line treatment for systemic arterial hypertension in dogs and cats without proteinuria
      - Decreases systolic blood pressure by @ 50 mmHg
      - Dilates glomerular afferent arteriole
      - Appears to have fewer complications than with ACE inhibitors
        - **Hypotension**
        - GI signs
    - **Angiotensin converting enzyme (ACE) inhibitors**
      - Decreases metabolism of angiotensin I to angiotensin II resulting in vasodilation and decreased aldosterone production
      - Systemic arteriolar dilation (via decrease in angiotensin II) and preferentially dilates glomerular efferent arteriole
      - Complications
        - May worsen azotemia – monitor
        - Hyperkalemia
      - Benazepril has been reported to slow progression of chronic kidney disease in cats
        - 1 study of induced chronic kidney disease has been reported
          - GFR values were not different between benazepril and placebo groups
          - The study lasted only 6 months
        - A long term clinical trial failed to show benefit over placebo except in cats with overt proteinuria
          - Decreases systolic blood pressure by @ 10 mmHg
    - **Angiotensin receptor blockers (ARBs)**
      - Inhibit interaction of angiotensin II with receptor
      - Similar effects as ACE-I
        - Decreases systolic blood pressure by @ 10 mmHg
        - Preferential dilation of glomerular efferent arteriole
        - Complications include
          - Worsening of azotemia
          - Hyperkalemia
    - **Aldosterone receptor antagonists**
      - Spironolactone
      - Promotes sodium excretion and very mild diuresis
      - Decreases vascular volume
      - Decreases blood pressure – minimal effect
      - Complications
      - Dehydration
      - Hyperkalemia
      - May work synergistically with ACE-I and ARBs to decrease RAAS activation
    - **Other drugs** are not as effective and are only used if multiple drugs are required to lower systemic arterial blood pressure
      - Beta-blockers (propranolol, atenolol)
Alpha-blockers (prazosin)
Direct arteriolar vasodilators (hydralazine)
Diuretics (furosemide, thiazides, spironolactone)

Renal transplantation
- Renal transplantation can be done
- More effective and higher success in cats vs dogs
- Less than 20% one-year survival in one study; however, in another study, a 50% survival at over 500 days
- Cost is > $10,000 and must adopt donor patient

Intermittent hemodialysis
- Intermittent hemodialysis may be performed in patients with IRIS CKD stage 4 disease
- Requires periodic treatment at hemodialysis facilities
- Interdialytic time is variable and dependent on the patient
- Requires placement of a long term large bore central catheter that is prone to thrombosis and occlusion

Stem cell therapy
- Mesenchymal stem cells (MSCs) have been proposed as a novel treatment option for the management of CKD.
  - MSCs exert potent anti-inflammatory and antifibrotic effects and may therefore indirectly improve renal function by reducing disease-associated inflammation and fibrosis through paracrine effects
  - Demonstrated immunomodulatory effects of MSCs include inhibition of lymphocyte proliferation and cytokine production, suppression of dendritic cell function and suppression of IF-γ production by natural killer cells
  - In vitro studies have demonstrated that MSCs can produce growth factors, cytokines and anti-inflammatory mediators, all of which could help maintain or improve renal function and suppress intra-renal inflammation
  - The ability of MSCs to suppress inflammation appears to be mediated both by secreted factors and by direct contact with inflammatory cells
  - In the majority of studies with experimentally induced CKD in rodents, administration of both adipose-derived and bone marrow-derived MSCs has demonstrated significant renoprotective effects, including reduction of intrarenal inflammatory infiltrate, decreased fibrosis and glomerulosclerosis.
  - Parameters of renal function and clinical health, including weight, creatinine, blood urea nitrogen (BUN), proteinuria, blood pressure and hematocrit have also been demonstrated to improve as a result of MSC therapy
  - Several routes of administration— intraparenchymal, subcapsular, intraperitoneal, intravenous (IV) – have been explored, and all seem to be effective.
  - Efficacy is thought to originate from paracrine effects rather than cell engraftment into the kidney
  - Multiple repeated injections of MSCs appear to be even more effective than single injections
  - As inflammation appears to be present at all stages of CKD in cats, the immunomodulatory actions of MSC are appealing as a potential means of suppressing intrarenal inflammation and subsequent fibrosis.
  - MSC therapy may be an effective new approach to slow the progression of CKD and improve renal function.
- In one randomized clinical trial of cats
  - Six cats received three doses of allogeneic MSC culture without adverse effects.
  - No significant change in serum creatinine, blood urea nitrogen, potassium, phosphorus, GFR by nuclear scintigraphy, UPC or packed cell volume was seen in cats treated with MSCs.
  - Individual changes in GFR were 12%, 8%, 8%, 2%, –13% and –67% in treated cats compared with 16%, 36% and 0% in placebo-treated cats.
- In an abstract presentation a ACVIM in 2014
  - 19 cats (41 TX) & 15 dogs (51 TX)
    - 92 total TX
    - 49 IA (13 cats, 36 dogs), 43 IV (28 cats, 15 dogs)
  - DX: PLN (5), dysplasia (5), K9 CKD (2), Fel CKD (19) with obstruction (12/19), AKI (1)
    - MST
    - Dogs
CKD: > 245 days (2/2 still alive)
PLN: > 227 days (3/5 still alive)
Renal dysplasia: > 198 days (5/5 still alive)

Cats
CKD: > 179 days (12/19 still alive)
Obstructive nephropathy: > 179 days (7/12 still alive)
Those with IRIS CKD stage 3 alone: > 213 days (6/7 still alive)

SERIAL MONITORING
- Chronic kidney disease is progressive and thus a dynamic disease
- Serial monitoring of body condition, body weight, thoracic auscultation, blood pressure, CBC and serum biochemical profile, urinalysis, and urine culture are necessary to adjust treatment
- How often an animal should be examined depends on
- How rapidly the chronic kidney disease is progressing
- Any non-renal influences that affect renal function
- Owner satisfaction and finances

How can medical treatment of chronic kidney disease be improved?
- Early detection and intervention
- Chronic kidney disease is more common in older animals; therefore, geriatric screening blood work may identify animals in early chronic kidney disease
- Minimize or eliminate non-renal influences on renal function
- Individualize treatment
- Avoid over-treatment
- Serial monitoring

Strategies for diagnosis of CKD using creatinine
- Normal ranges can be misleading
- Use IRIS recommendations (cats = 1.6 mg/dl; dogs = 1.4 mg/dl)
- Change of 0.2 mg/dl in a hydrated patient is significant
- Marked reductions in kidney function can be associated with “normal” serum creatinine concentrations
- Serial monitoring

Observations
- At some point, the disease progresses
- Early modification of rate of progression has marked implication
- Early diagnosis of CKD has profound implications
- Educate owners early
  - Changes in water intake, urine volume, food intake, body weight, activity, behavior
  - Decreased body weight and body condition, small or dissymmetrical kidneys, large urinary bladder (polyuria?), hypertension
  - Urinalysis – an extremely important tool

When should diet be changed in an animal with chronic kidney disease?
- Dietary modification can offset many deficiencies and excesses that occur with chronic kidney disease
- Dietary modification includes more than just dietary protein restriction as renal failure diets are more calorically dense, may contain omega-3 fatty acids, may contain soluble fiber, low phosphorous, low sodium, potassium replete, alkalinizing, and water soluble vitamin replete
- I believe diet should be changed when an animal is diagnosed with chronic kidney disease
- Renal failure diets are usually indicated at some point in management of dogs and cats with chronic kidney disease
- Renal failure diets are not associated with deficiencies
- Renal failure diets may be tolerated better if introduced while the animal feels good and is willing to accept a dietary change
- Renal failure diets may decrease uremic episodes and prolong survival
# DRUGS AND DOSAGES MENTIONED IN THESE PROCEEDINGS

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosage for dogs (D) or cats (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2 blocker</td>
<td>Famotidine</td>
<td>D, C: 1-2 mg/kg PO q12h</td>
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<tr>
<td></td>
<td>Ranitidine</td>
<td>D, C: 1-2 mg/kg PO q12h</td>
</tr>
<tr>
<td>Gastroprotectant</td>
<td>Sucralfate</td>
<td>D: 0.5-1 gm PO q8-12h; C: 0.25-0.5 gm PO q8-12h</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>Omeprazole</td>
<td>D, C: 0.7-2 mg/kg PO q12-24hr</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole</td>
<td>D, C: 0.7 mg/kg PO q12-24hr</td>
</tr>
<tr>
<td>Serotonin antagonist</td>
<td>Mirtazapine</td>
<td>D: 15-30 mg PO q24h; C: 1.875-3.75 mg PO q72h- can give q48h with CKD</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>D, C: 1) 0.5 mg/kg IV; then 0.5 mg/kg/hr constant rate infusion 2) 0.1-0.2 mg/kg IV slowly q6-12h prn 3) 0.5-1 mg/kg PO q12-24h</td>
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<tr>
<td></td>
<td>Dolasetron</td>
<td>D, C: 0.6-1 mg/ kg PO, IV q12-24h</td>
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<tr>
<td>NK-1 inhibitor</td>
<td>Maropitant</td>
<td>D, C: 2-4 mg/kg PO q24h</td>
</tr>
<tr>
<td>PGE2 analogue</td>
<td>Misoprostol</td>
<td>D: 2-7.5 mcg/kg PO q8-12hr; C: 5 mcg/kg PO q8hr</td>
</tr>
<tr>
<td>Medicine rhubarb</td>
<td>Rubenal</td>
<td>D: &lt; 3kg: 37.5 mg; 3-6kg: 150 mg; 6-12kg: 150 mg; 13-25kg: 300mg; 26-45kg: 600mg; &gt;45kg: 900 mg PO q12h C: &lt;2kg: 37.5mg; &gt;3kg: 75mg PO q12h</td>
</tr>
<tr>
<td>Amino acids / peptides</td>
<td>RenAvast</td>
<td>C: 1 capsule with food</td>
</tr>
<tr>
<td>Potassium</td>
<td>Potassium citrate</td>
<td>D, C: initial: 75 mg/kg PO q12h</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Azodyl</td>
<td>D, C: &lt; 2.5kg: 1 capsule PO q24h; 2.5-4.5 kg: 1 capsule PO q12h; &gt;4.5kg: 2 capsules PO in AM and 1 capsule PO in PM with food</td>
</tr>
<tr>
<td></td>
<td>Visbiome</td>
<td>D, C: 1/10 packet per 4.5kg PO q24h with food</td>
</tr>
<tr>
<td>Phosphate binder</td>
<td>Aluminum hydroxide</td>
<td>D, C: 15-45 mg/kg PO q12h with food</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>D, C: 60-90 mg/kg PO q12h with food</td>
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<tr>
<td>Sevelamer hydrochloride</td>
<td>D, C: 400-1600 mg PO q12h with food</td>
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<tr>
<td>Lanthanum carbonate</td>
<td>D: 5-20 mg/kg PO q12h C: 1 ml (1 pump) PO q12h (Renalzin)</td>
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</tr>
<tr>
<td>Chitosan + calcium carbonate</td>
<td>D: 1 g/kg PO q12h                                  3-5kg: 1 scoop; 10kg: 2 scoops; 15kg: 3 scoops; 20kg: 4 scoops PO q12h (Ipakitine)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Erythropoietin</td>
<td>D, C: initial:2-2.5 ng/kg PO q24h; maximum: 5 ng/kg PO q24h</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>D, C: 100 ug/kg SQ 3X/week initially</td>
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<tr>
<td>Darbepoetin</td>
<td>D, C: 1.5-1.0 ug/kg SQ 1X/week initially</td>
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<tr>
<td>Calcium channel blocker</td>
<td>Amlodipine</td>
<td>D: 0.1-0.4 mg/kg PO q24h; C: 0.625-1.25 mg PO q24h</td>
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<tr>
<td>ACE-I</td>
<td>Enalapril</td>
<td>D, C: 0.25 mg/kg PO q12h initially</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Benazepril</td>
<td>D, C: 0.25 mg/kg PO q12h initially</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Losartan</td>
<td>D, C: 1 mg/kg PO q12h ($8//mo for 25lb dog)</td>
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<tr>
<td></td>
<td>Azilsartan</td>
<td>D: 0.1-1.0 mg/kg PO q12h ($140/mo for 25lb dog)</td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>D: 5 mg/kg q12-24h ($115/mo for 25lb dog)</td>
</tr>
<tr>
<td></td>
<td>Telmisartan</td>
<td>D, C: 5-10 mg/kg PO q24h ($40/mo for 25lb dog)</td>
</tr>
<tr>
<td></td>
<td>Valsartan</td>
<td>D: 80-160 mg PO q24h ($60-100/mo for 25lb dog)</td>
</tr>
<tr>
<td>Aldosterone receptor blocker</td>
<td>Spironolactone</td>
<td>D, C: 1-4 mg/kg PO q12h-24h</td>
</tr>
</tbody>
</table>