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Nature of Progression – A Unifying Hypothesis

CRF is clinically characterized in dogs and cats by the development of variably progressive irreversible intrarenal lesions and loss of renal functions. Progressive loss of various renal functions seems inevitable in most patients with advanced stages of chronic renal disease. Progression will occur if the underlying renal insult cannot be treated (e.g. glomerulosclerosis due to an unidentified antigen, amyloidosis) but can also progress at times when the cause of the initial injury has been removed. The "inexorable progression of chronic renal failure" only occurs however after substantial loss of renal mass has already occurred regardless of the original inciting injury. A variety of interventions (diet and drugs) can slow the progression of the renal diseases, improve the quality of life for the patient, and/or extend the quantity of life.

"Super-nephrons" that result from hypertrophy of renal function and increased glomerular volume in remaining viable nephrons may result in their eventual demise. Hemodynamic adaptations in remnant nephrons cause increased single nephron GFR, glomerular plasma flow, and increased transglomerular capillary hydraulic pressure that are initially adaptive to maintain filtration and maintain renal function at higher levels that would be otherwise. Ongoing intraglomerular hypertension and increased glomerular volume eventually harm glomeruli. Tubular hyperperfusion, hyperammoniagenesis, renal mineralization, secondary hyperparathyroidism, systemic arterial hypertension, intrarenal coagulation, and immune mechanisms may also contribute to chronic progressive renal injury. It is not possible to predict the rate of this progression in experimental or clinical animals.

Compensatory increases (so called adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in some instances as shown in this figure.
Kidney failure leads to a dysregulation of glomerular hypertension that can benefit from reductions in transglomerular forces. An additional potential benefit from ACE-inhibition is improved control of systemic blood pressure. This may be because the kidney is an important organ for the production of angiotensin II. ACE-inhibition reduces glomerular capillary hydraulic pressure by decreasing postglomerular arteriolar resistance. Proteinuria is decreased secondary to decreased glomerular capillary hydraulic pressure and potentially by its effects on glomerular permeability.

Vasoconstriction of the efferent arteriole at a time of no change in the afferent arteriole increases intraglomerular capillary pressure. Progression of renal disease in remnant nephrons can be prevented with this effect. Angiotensin-II plays a pathophysiologic role in proteinuria and the progression of renal disease. It may play a role in the progression of non-proteinuric renal diseases too.

Converting enzyme inhibitors and angiotensin receptor blockers should become a standard of care. Intermittent rather than daily dosing treatment protocols are likely to become the standard of care since less hypercalcemia occurs during this protocol. Treatment of dogs and cats with serum creatinine concentrations in the lower to mid range for normal serum phosphorus provides additional benefits in control of PTH.

Calcitriol treatments help to decrease PTH or prevent its increase in those with renal secondary hyperparathyroidism. This occurs mostly by genomic effects to block PTH synthesis in the parathyroid cell as well as increased number of cells due to parathyroid hyperplasia leads to increased circulating PTH. A calcitriol deficit in uremic patients is the most important factor in the development of renal secondary hyperparathyroidism. The majority of clinical patients with early CRF and creatinine concentrations between 2 and 2.5 mg/dL will have hyperparathyroidism effectively controlled with calcitriol. Serum calcitriol concentrations are desirable but do not guarantee that PTH is normal. Phosphorus binding agents should be given with meals or within 2 hours of feeding to maximize their binding of dietary phosphorus.

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**Beneficial effect must be balanced against their potential to worsen azotemia since glomerular pressure provides the driving force for GFR in the “super-azotemia”.**

In a 6 month study of dogs with modest azotemia and moderate to severe proteinuria, enalapril treatment (0.5 mg/kg PO q4h) reduced proteinuria (as assessed by urine protein/creatinine ratio), decreased blood pressure, and slowed progression of renal disease in dogs with biopsy-proven glomerulonephritis compared to treatment with placebo. Results from this study provided enough clinical evidence to make the ACE-inhibitor standard of care for protein-losing nephropathy. Currently, enalapril and benazepril are considered candidates for anti-hypertensive therapy. First agent anti-hypertensive therapy using ACE-Inhibitors (ACE-1; enalapril, benazepril), calcium channel blockers (amiodipine), beta adrenergic antagonists (atenolol, propranolol), or alpha-1 adrenergic antagonist (prazosin) may lower blood pressure. Diuretics and dietary salt restriction are not effective treatment for severe hypertension.

**Hypertension**

It is essential that dogs and cats be in a quiet environment before and during blood pressure measurements. Cats especially are prone to “white coat artefact” making it difficult to determine if a given cat is truly hypertensive. Multiple measurements are taken until there is less than 10% variation amongst them – average of these 5 measurements is reported as the blood pressure for that animal.

The prevalence of systemic hypertension in dogs and cats with CRF ranges from approximately 30 to 75% of affected patients when determined by indirect methods; the prevalence of hypertension is a major risk factor for the progression of CRF in people and cats. Recent evidence suggests that it is also true for dogs and cats with CRF. Perfusion pressure in renally normal during CRF is increased (vasodilatation of different arterioles due to the super-nephron phenomenon), and the fear is that increased systemic blood pressure will be transmitted to the glomerular vascular beds causing further damage. It is likely that high systemic blood pressure is transmitted to the glomerular vesicles, which promotes further injury.

A clinical study of dogs with CRF showed that dogs with systemic hypertension at the time of diagnosis progressively lost renal function at greater rates than dogs with intermediate or lower blood pressure. More dogs with initial blood pressure greater than 160 mm Hg developed renal failure. In this study, the addition of antihypertensive treatments in 10 of 11 dogs. Those in the high blood pressure group had 3 times an increased risk for uremic crisis than dogs in lower pressure groups and had much greater risk for renal related death. CRF as assessed by urinary protein to creatinine ratio was higher in cats with dog hypertension (Jacob 2003). The correlation of unregulated arterial blood pressure to the progression of CRF has not been established. Cats that have systemic hypertension from a variety of causes have been shown to have increased blood pressure.

Patients with systolic blood pressure readings consistently above 170 mm Hg or with abnormally high blood pressure readings that also have fundic lesions consistent with hypertensive retinopathy on ophthalmoscopy, arterial tortuosity, retinal detachment are considered candidates for anti-hypertensive therapy. Therapy may be started in symptomatic cats with PCV values < 20% if clinical signs of anemia are present and the anemia of CRF, use of rhEPO is associated with antibody formation in up to 50% of treated dogs and cats after 1 to 3 months of treatment. The resulting anemia can be more severe than that present before treatment because the induced antibodies can cross-react with the animal's native EPO. The canine EPO gene has been isolated, and recombinant canine EPO can now be used to stimulate erythropoiesis in normal dogs and in those with naturally occurring CRF. It is not as effective when used in dogs that have developed red cell aplasia from previous treatment with rhEPO. Feline recombinant EPO also has been produced, but unfortunately unexplained red cell aplasia developed in some treated cats. Other adverse effects have been observed during administration of rhEPO to dogs and cats and include vomiting, seizures, hypertension, uveitis, and hypersensitivity–like mucocutaneous reaction.

**Selected References**

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Table 1. Serum creatinine concentrations for assignment of IRIS stage of CKD in dogs and cats

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine concentration (mg/dl)</th>
<th>Serum creatinine concentration (µmol/l)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 1.4 (dog) &lt; 1.6 (cat)</td>
<td>&lt; 125 (dog) &lt; 140 (cat)</td>
<td>Nonazotemic. Often discovered fortuitously during routine examination. May have evidence of decreased urinary concentrating ability or proteinuria. Usually no obvious clinical signs. May be polyuric.</td>
</tr>
<tr>
<td>2</td>
<td>1.4-2.0 (dog) 1.6-2.5 (cat)</td>
<td>125-175 (dog) 140-240 (cat)</td>
<td>Mildly azotemic. Decreased urinary concentrating capacity. May have proteinuria. Clinical signs minimal. May have polyuria and polydipsia.</td>
</tr>
<tr>
<td>3</td>
<td>2.1-3.0 (dog) 2.9-5.0 (cat)</td>
<td>180-430 (dog) 200-430 (cat)</td>
<td>Moderate azotemia. Decreased urinary concentrating capacity. May have proteinuria. Many systemic clinical signs may be present.</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 3.0 (dog) &gt; 5.0 (cat)</td>
<td>&gt; 440 (dog) &gt; 440 (cat)</td>
<td>Severe azotemia. Decreased urinary concentrating capacity, proteinuria. Systemic clinical signs present and may be severe.</td>
</tr>
</tbody>
</table>

Table 2. Proteinuria (assessed by urine protein/creatinine ratio) for assignment of IRIS sub-stage of CKD in dogs and cats

<table>
<thead>
<tr>
<th>Proteinuria (urine protein/creatinine ratio)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2 (dogs) &lt; 0.2 (cats)</td>
<td>Nonproteinuric</td>
</tr>
<tr>
<td>0.2-4.5 (dogs) 0.2-4.0 (cats)</td>
<td>Borderline proteinuric</td>
</tr>
<tr>
<td>&gt; 0.5 (dogs) &gt; 0.4 (cats)</td>
<td>Proteinuric</td>
</tr>
</tbody>
</table>

Table 3. Systemic blood pressure for assignment of IRIS sub-stage of CKD in dogs and cats

<table>
<thead>
<tr>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Nick level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>&lt; 60</td>
<td>Minimal</td>
</tr>
<tr>
<td>150-175</td>
<td>60-90</td>
<td>Low</td>
</tr>
<tr>
<td>160-175</td>
<td>100-113</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 180</td>
<td>&gt; 120</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 4. Options of possible treatments for compensated chronic renal failure

First Level of Treatment
- Change to renal therapeutic diet – reduction in dietary protein in case of muscle wasting – commercially available or homemade – wet foods better than dry if possible
- Fresh water available at all times
- Medical or peritoneal dialysis – use of continuous or intermittent peritoneal dialysis
- Intestinal phosphate binders to reduce serum phosphorus – aim for mid-normal range, aluminum or calcium-based binders used most often
- Treat severe hyperkalemia now (> 6.0 mm Hg systolic) – get below 6.0 mm Hg soon
- Treat urinary or systemic infection
- Avoid anesthesia or exposure to nephrotoxic agents when possible
- Intravenous fluids if not maintaining hydration
- Add in metoclopramide or other antiemetics to reduce vomiting and nausea if needed
- Potassium supplementation if hypokalemia is overt or borderline
- Optimize phosphate restriction (diet or binders) based on PTH or serum P – consider dose or class change for phosphate binders
- Further blood pressure control – minimal aim to < 165 mm Hg, optimal < 145 mm Hg
- Provide perioperative renal protection with IV fluids for several hours before, during, and following anesthetic and surgical procedures
- Androgenic steroids for DOGS ONLY when poor body condition persists – monitor liver parameters

Second Level of Treatment
- Provide ACE-inhibition and antiproteinuric effects, independent of normal systemic blood pressures
- Blood pressure control optimized for renal patient – multiple drug therapy or dose escalation as needed to maintain systolic blood pressure at < 145 mm Hg
- Calcium – daily or intermittent dosing protocol to control PTH and prevent gastrointestinal hypercalcemia – base doses on serum calcium and PTH
- Arterial placement when patient will not consume adequate nutrition and body condition is poor
- EPO if patient approaches transfusion dependency – not for minor anemia

Third Level of Treatment
- Provide ACE-inhibition and antiproteinuric effects, independent of normal systemic blood pressures
- Blood pressure control optimized for renal patient – multiple drug therapy or dose escalation as needed to maintain systolic blood pressure at < 145 mm Hg
- Calcium – daily or intermittent dosing protocol to control PTH and prevent gastrointestinal hypercalcemia – base doses on serum calcium and PTH
- Arterial placement when patient will not consume adequate nutrition and body condition is poor
- EPO if patient approaches transfusion dependency – not for minor anemia

Fourth Level of Treatment
- Renal transplantation – considered for select cases
- Chronic dialysis – only for the extremely wealthy

Emerging or Unproven Treatments
- Acriol – to reduce azotemia following feline urolithic disease
- Spironolactone – anti-adrenergic remodeling and further anti-proteinuric effects
- Cinnarizine – calciumimetics to lower PTH, calcium, and phosphates
- Hemofen (Carrabé et al. 1986) – non-selective sorbent to remove uremic toxins from intestinal juice
- Lipid Inhibitor – Chelation and calcium carbonate phosphate binders
- Naloxone – Lartram carbonate phosphate binders
- Darbropet – Stimulate new red blood cell production, may have less antibody production than EPO
<table>
<thead>
<tr>
<th>Nutritional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight</td>
</tr>
<tr>
<td>Body Condition Score</td>
</tr>
<tr>
<td>Muscle Condition Score</td>
</tr>
<tr>
<td>Serum Phosphorus</td>
</tr>
<tr>
<td>Total Protein</td>
</tr>
<tr>
<td>BUN</td>
</tr>
<tr>
<td>Cholesterol</td>
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<table>
<thead>
<tr>
<th>Serum Calcium Control</th>
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</thead>
<tbody>
<tr>
<td>Poor, acceptable, excellent, worse, stable, improving</td>
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</table>

<table>
<thead>
<tr>
<th>Blood gas (preferred), HCO3$^-$ on profile</th>
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<tbody>
<tr>
<td>Poor, acceptable, excellent, worse, stable, improving</td>
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<table>
<thead>
<tr>
<th>CVD Progression Control</th>
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<tr>
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Figure 1: Development of Renal Secondary Hyperparathyroidism - calcitriol trade-off hypothesis
Figure 2. Effect of orally administered phosphate binder to bind phosphate within the intestinal lumen preventing its absorption across the intestinal tract. Some binders undergo absorption across the intestine and others do not.
Figure 3 - ACE-Inhibition Provides Glomerular Afterload Reduction. High pressures of the supernephron (left panel) are created by dilatation of the afferent arteriole. In the right panel, intraglomerular pressure has been restored to normal during treatment with ACE-inhibition. ACE-inhibitors reduce the effect of angiotensin-II to cause intrarenal vasoconstriction but the effect is greater on the efferent arteriole which lowers resistance to outflow from the glomerular beds.