FOR THE MANAGEMENT OF RENAL FAILURE IN CATS AND DOGS
Chronic renal failure (CRF) is characterised by the presence of irreversible structural lesions, and is generally considered, at least in clinical cases, to be progressive which ultimately result in the death. Therapy is thus aimed at ameliorating the clinical signs and systemic complications associated CRF, and slowing the progressive decline of renal function. CRF is a frequent cause of death in cats and particularly geriatric cats and in dogs.

1. Initial lesions

The initial lesion causes reduction in the nephron population. It may be caused by toxic or infectious agents. In most instances it remain unnoticed until CRF has been diagnosed.

<table>
<thead>
<tr>
<th>MAIN LESIONS CAUSING CRF</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital in origin</td>
<td>Glomerulopathy</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Interstitial nephropathy</td>
</tr>
<tr>
<td>Polykistosis</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Dysplasia</td>
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</tbody>
</table>

2. Clinical symptoms

Clinical symptoms are usually noticed when the kidneys have lost 70% of their initial mass. Uraemia is the clinical state towards which all generalised renal diseases converge. The symptoms are attributed to the numerous uraemic toxins. Most of them emanate from the catabolism of proteins.

<table>
<thead>
<tr>
<th>LIST OF THE MAJOR URAEMIC TOXINS</th>
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<tbody>
<tr>
<td>Urea</td>
<td>Phenols</td>
</tr>
<tr>
<td>Creatinine</td>
<td>“Middle molecules”</td>
</tr>
<tr>
<td>PTH</td>
<td>Hormons</td>
</tr>
<tr>
<td>Indoles</td>
<td>Skatols</td>
</tr>
<tr>
<td>Amines acids</td>
<td>Aliphatic amines</td>
</tr>
<tr>
<td>Guanidine compounds</td>
<td></td>
</tr>
</tbody>
</table>

The clinical symptoms are not pathognomonic and are different in dogs and in cats. Complementary biochemical analysis is needed to assess the exact diagnosis. Anorexia and digestive problems are frequent in cats: it makes changing their diet more difficult.

<table>
<thead>
<tr>
<th>MOST FREquent CRF SYMPTOMS (RANKED BY DECREASING FREQUENCY)</th>
<th>IN CATS</th>
<th>IN DOGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td></td>
<td>Polyuria – polydypsia</td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Polyuria – polydypsia</td>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Prognosis

Animals with CRF often survive for many months or years with a good quality of life. The diagnosis is more difficult in dogs because the symptoms occur later. Compensatory mechanisms of the body maintain a state of biochemical homeostasis despite significant renal dysfunction. As renal failure progresses, the animals are forced to live in a narrowed state of physiologic activity. A uraemic crisis may be suddenly precipitated by decreased intake of nutrients or water, development of concomitant diseases or administration of certain drugs.

**PROGRESSION OF CRF: ROLE OF THE COMPENSATORY MECHANISMS**

Chronic renal failure is an inherently progressive disease. Its progression either results from continuing renal damage induced by the nephropathy or from mechanisms independent of the initiating lesion and responsible for the spontaneous self perpetuation of the disease.

![Diagram of Chronic Renal Failure Progression]

(according to D.J. Polzin and C.A. Osborne)

**MECHANISMS OF COMPENSATORY ADAPTATION**

- **Hyperfiltration model:** compensatory hyperfiltration and intraglomerular hypertension occur initially as adaptive responses to reduction in nephrons but eventually leads to progressive proteinuria, glomerular sclerosis and loss of functional nephrons.

- **Nephrocalcinosis** causes tubulo-interstitial injury characterised by tubular atrophy and dilation, interstitial fibrosis and interstitial inflammation. Excess PTH, caused by hyperphosphataemia, promotes too great flux of calcium into these cells, thus activating enzymes that destroy phospholipids, proteins, and nucleic acids. These effects result in cell dysfunction and death.
CRF: Prolongation of life expectancy in cats and dogs

Management of compensatory mechanisms

Improving the health status and slowing down the progression of the disease is an important goal of treatment of CRF.

Reduction of phosphataemia: the corner stone of CRF treatment.

Reducing phosphataemia has been shown to prolong life expectancy in cats and dogs whatever the stage of the disease.

Reduction of protein intake: proven ineffective on survival time

Dietary protein restriction has been reported to have no effect on survival time. (1), (4), (5). The benefits of low protein diets seen in cases of advanced CRF (ie animals with moderate to severe azotemia and showing clinical signs of uraemia such as anorexia, weight loss, vomiting, diarrhoea and constipation) are non-renal. Low protein diets benefit the patients condition (they will feel better) but do not prevent the progression of renal lesions or halt the decline in renal function.

Reduction of glomerular hypertension: limited to the most severe cases

Vasodilators which specifically target the efferent arteries of the glomerulus should help in decreasing intraglomurular hypertension thus limiting glomerular sclerosis.

Some preliminary results indicate they are probably effective in the most severs cases (Urine Protein to Creatine ration >0.8).

1. Reduction of phosphataemia in dogs

Dogs fed with low phosphorus diets show better glomerular filtration rate. They also enjoy a significant prolonged survival. Protein has no effect.

(Finco and coll. 1992)
2. Reduction of phosphataemia in cats

The life expectancy of cats with borderline naturally occurring CRF is 2.5 times longer when they are fed with phosphate restricted diets in combination, with phosphate binders.

![Graph showing evolution of phosphataemia and plasma PTH](image)

* p<0.01 vs NPD Group
** p<0.002 vs initial diagnosis

The Kaplan-Meier survival curves show a highly significant difference between the 2 groups (p=0.0036)


Ipakitine is a combination of calcium carbonate + chitosan (cellulose fibre). They are synergistic in preventing the absorption of substances which exacerbate renal failure. Calcium phosphate-binding agents, when administered with meals substantially decrease intestinal absorption of phosphates.

Ipakitine is a bland off white powder with no discernable taste. It is mixed in to food at meal time. It is a very small dose (1 g/5 kg body weight) important for long term administration to cats with CRF.

1. Calcium carbonate: the phosphate eliminator agent

- Calcium carbonate belongs to the short list of substances commonly used in human medicine to bind phosphate in patients with CRF:

<table>
<thead>
<tr>
<th>Intestinal phosphorus binding agents</th>
<th>Approximate daily Recommended dose</th>
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</thead>
<tbody>
<tr>
<td>Aluminium hydroxide</td>
<td>30 to 90mg/kg/day</td>
</tr>
<tr>
<td>Aluminium carbonate</td>
<td>30 to 90mg/kg/day</td>
</tr>
<tr>
<td>Aluminium oxide</td>
<td>30 to 90mg/kg/day</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>90 to 150mg/kg/day</td>
</tr>
</tbody>
</table>

- Calcium carbonate is considered safe without long term side effects at the prescribed dose. On the other hand Aluminum salts are reported to accumulate in bones and brain which may be deleterious when used in long term treatment.

2. Chitosan: a naturally derived polysaccharide; similar to plant cellulose

- Chitosan is a polysaccharide derived from chitan which is extracted from the shells of crabs. It is a naturally occurring substance chemically similar to the plant fibre cellulose.

- Shown to reduce blood urea and creatinine levels in laboratory animals and humans.
- Prolongs the phosphate –binding properties of calcium in the gastro – intestinal tract.
- Binds and blocks absorption of uraemic toxins.
Ipakitine was the subject of a comparative study at the Veterinary University of Vienna in 2003 (6). It was aimed at assessing Ipakitine efficacy in reducing phosphataemia and uraemia. It involved both healthy young cats and cats with early stage naturally occurring chronic renal failure.

1. **Ipakitine reduces phosphorus blood concentration**

**IPAKITINE LOWERS PHOSPHORUS ABSORPTION IN NORMAL CATS**

![Graph showing apparent digestibility of phosphates with and without Ipakitine.]

* significant difference  p < 0.05 (Wagner and coll. 2004)

**IPAKITINE LOWERS PHOSPHATAEMIA IN CATS WITH CRF**

![Graph showing Ipakitine action upon phosphatemia with and without Ipakitine.]

* significant difference  p < 0.05 (Wagner and coll. 2004)

In cats with CRF, Ipakitine decreases the serum phosphorus concentration from 1.7 mmol/l (above the normal range) to 1.1 mmol/l (within the normal range).
Ipakitine, a proven efficacy in reducing uraemia in cats

2. Ipakitine reduces uraemia in cats with CRF

![Graph showing Ipakitine action upon uraemia]

* significant difference  \( p < 0.05 \) (Wagner and coll. 2004)

3. Ipakitine: lack of side effects

All other biological parameters (TP, AST, ALT, WBC, RBC, Hk, MCV, MCH, MCHC) remained at a normal level and especially blood calcium concentration which did not change during the 35 days of the trial.

When to prescribe Ipakitine?

1. Early symptoms of CHF: initiate prophylactic treatment

Reducing plasma phosphorus blood concentration is now considered as the primary goal in CRF treatment. It should take place even before the reduction of protein intake.

2. Moderate symptoms of CRF: pragmatic treatment, an alternative to renal diets

Once azoatemia has been diagnosed, it is advised to lower the protein intake in order to relieve clinical symptoms. Nevertheless, anorexia is a very common clinical symptom for CRF and the main one for cats. In many cases it is very difficult or even impossible to make the cat change its usual diet towards a less palatable renal diet.

- ‘Ipakitine – a palatable powder for mixing with food, a change of the diet may not required at this stage of CRF.’

- Clinical studies indicate Ipakitine reduces phosphataemia and uraemia

Ipakitine is a practical treatment option that enables the veterinarian to address to the main objectives of the treatment of CRF: an increase in survival time and improved health status of the patient.

3. Moderate to severe chronic renal failure: essential treatment to support renal diets

At this point in the evolution of CRF, renal diets will not limit the level of phosphataemia. Phosphate – binders are indicated block dietary phosphate uptake from the gastrointestinal tract.

Ipakitine is a veterinary phosphate-binder which has been researched and developed for cats and dogs. Efficacy, palatability and safety have been the cornerstones of the product’s development.

Ipakitine may be used in combinations with ACEi’s which are indicated in the later stage of CRF.
Summary: Ipakitine is a palatable, cost effective phosphate-binder for management of CRF in cats and dogs

1. Chronic renal failure
   - An important life threatening disease of cats and dogs
   - A degenerative, progressive disease which requires regular monitoring and treatment.
   - Clinical symptoms become evident when there is a significant loss of the kidney’s mass. The symptoms differ in cats and dogs.
   - Compliance with prescribed and dispensed treatments important for optimum clinical outcome.
   - Early and aggressive treatment improves longevity of the patient.

2. Increasing life expectancy in pets with CRF
   - Reducing phosphataemia is the corner stone for the treatment of CRF. It has been clinically proven in dogs and in cats.

   **In Cats**
   
   ![Mean cats survival graph](image)
   (Elliott and coll. 2000)

   **In Dogs**
   
   ![Survival time graph](image)
   (Finco and coll. 1992)

   - Protein reduction has no effect on survival time.
   - Use of vasodilators should be limited to the most severe cases.
3. Ipakitine mode of action

- Calcium carbonate is proven as a phosphate-binder, in human medicine with little or no toxicity or side effects.
- Chitosan binds phosphates and various uraemic toxins.

4. Ipakitine palatability

- A high level of acceptance and palatability has been demonstrated. Published clinical studies confirm Ipakitine effectively binds and blocks absorption of dietary phosphates.

5. Ipakitine efficacy

- Ipakitine has shown its potential in decreasing both phosphataemia and urea in cats with CRF.

6. Ipakitine use

- Ipakitine can be used in all stages of CRF.

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* significant difference  \( p < 0.05 \)  
(Wagner and coll. 2004)
Ipakitine composition
Fine white powder made of:
- Calcium carbonate .................................................. 10%
- Chitosan (=crab shell extracts) ................................. 8%
- Lactose ................................................................. 82%

Ipakitine dose rate
1g for 5kg body weight, twice a day, preferably combined with feed.

Ipakitine presentations
- 50g packs with a 1g measure
- 150g packs with a 1g measure
- 300g packs with a 2.5g measure