I. CKD– how to find it ASAP!

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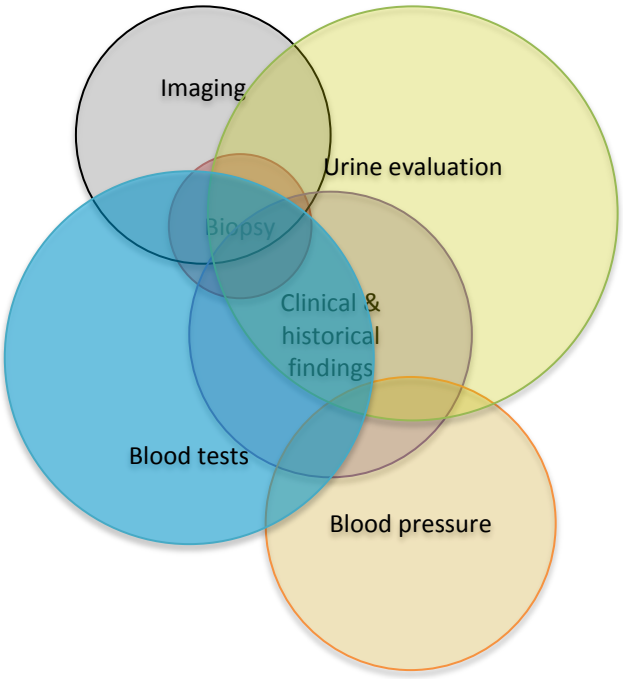
Chronic Kidney Disease, or CKD, is the modern definition that encompasses chronic renal failure (CRF), chronic renal insufficiency (CRI) and "Interstitial Nephritis" that has progressed to the point of no return.

Many patients present to the private veterinarian in an advanced state of CKD, which is a huge shame, because early intervention brings about longer survival times. However, the diagnosis of renal disease is complex, as no one test is totally effective. In fact, because of the massive reserve capacity of the kidneys, early diagnosis is incredibly hard. A diagnosis of CKD is often made by combining the results of several different modalities:



The relationships and importance of different tests varies between patients as well. We'll get into the importance of each modality in a bit, but the most critical factors that will determine the success or failure of your clinic and staff in the EARLY diagnosis and SUCCESSFUL management of CKD are:

1) Creating client awareness at every visit;
2) Starting senior pet monitoring schemes and publicising them;
3) Acting on early disease by recognising and communicating its importance;

Creating awareness means you need to have a real heart-to-heart discussion with all members of your team – from reception to nurses, and all vets. Everyone must be shown the evidence that early

diagnosis means better outcomes – and if you are not trying to achieve better health outcomes for your patients, then what exactly are you there for?

1) Better outcomes (longer survival once diagnosed + better quality of life during this period) comes from earlier diagnosis.
2) Early diagnosis comes from frequent and appropriate testing of at-risk patients;
3) Appropriate testing means identifying the:
    a. at-risk population; and
    b. the available, meaningful and affordable tests;
4) Knowing the results of these investigations;
5) Acting on these results; and
6) Monitoring the response to any intervention using the same tests and modifying or maintain your actions accordingly

Earlier diagnosis = Better Outcomes

Instinctively, this makes sense, but what evidence is there for this?

Firstly, let's discuss the importance of age. Increased age is a risk factor for the development of CKD in cats.[1, 2]

Identifying at-risk patients

The mortality rate due to CKD is greater in cats over 9 years old, than in younger animals. Therefore, testing for CKD or the conditions that lead to CKD, such as hyperthyroidism or hypertension, should begin no later than 9 years old (we use 7 years in my hospital). In one study, 30.5% of aged, apparently healthy cats became azotaemic within 12 months of being observed in the study. Only blood creatinine and proteinuria at presentation were predictive of cats being at risk of developing azotaemia within this period.[3] Aging itself is not the cause of azotaemia, which may, in fact, represent a form of compensatory response.

Hypertension is also considered to be a potential risk factor for the development of CKD in cats, although the evidence is equivocal, and HT is also not "caused" by aging.[2] Nonetheless, hypertension can aggravate existing CKD and HCM and complicate their management. Consider also the *indirect* effects of HT for example, retinal detachment. The sudden onset blindness caused by retinal detachment can cause inappetance in a cat with stable CKD, precipitating dehydration and full blown renal crisis.

These are but two examples, so my question to you is: *what are you doing about it, and what are you looking for?*

There is enormous debate about the frequency of vaccination of adult pets. I have my own opinions, but these are based on the fact that, in KwaZulu-Natal (where I practice in South Africa), only 3.9% of pets are vaccinated against rabies, whilst 94% of all South African rabies incidents occur in this province. So let's just accept that I have a good argument for annual vaccination, life long. In the decidedly first-world, vets may be switching to core/non-core vaccination strategies. The big challenge for practitioners is then to convince clients for the need to continue ANNUAL HEALTH

CHECKS. I find my clients understand the importance better when I use the human example of annual mammograms/pap smears/PSA tests/Cholesterol/blood pressure etc etc. A 7-year-old cat is pretty much equivalent to a 40-year-old human and her body functions change accordingly.

Thus, ANY cat of 7+ years, and particularly cats of 11+ (when hyperthyroidism begins to increase in incidence) is an AT RISK patient.

My suggestion is to put together a reduced-cost, standard practice protocol for SENIOR HEALTH CHECKS. If you have an in-practice blood machine, this will help. If not, seriously consider it. A simple, robust machine like the IDEXX VetTest 8008 shouldn't set you back much and will pay itself off – not least in convenience (rapid results). A good, high definition oscillometric blood pressure machine like the machine from S+B Medvet is an excellent investment as well. Of course, you need a microscope and centrifuge (which IDEXX give you with the VetTest).

A suggested senior profile is:[4]

1. (The clinical evaluation – if at the time of vaccination, consider not charging extra for the consultation as you should be doing a thorough physical examination anyway);
    a. The most important questions to ask are those that determine if the patient is inappetant (reduced appetite, "picky" eater, PU, PD, weight loss, lethargy, halitosis and vomiting). Train your staff to ACCURATELY measure every patient's weight at EVERY VISIT. In a cat, a loss of 150g can be quite substantial – you need to know!
2. Urine – collect by cystocentesis, and do the following:
    a. Sg
    b. Dipstick test
    c. Sediment (because we always do sediment on any urine obtained but this is probably not necessary in cases with a normal USG and negative dipstick)
        i. Sternheimer stain +
        ii. Diff-quick stain
    d. If there is proteinuria on the dipstick, measure the Urine Protein:Creatinine ratio on your vet-test; this may be an additional charge but is well worth it. For example, a 2+ proteinuria and 1.015 sg could be significant – how significant? Well, measure it, don't guestimate!
3. Blood – as a minimum, do a "preanaesthetic profile" + Albumin, Calcium and Phosphate.
    a. SDMA is a useful test (discussed later)
    b. Electrolytes if you can as well
    c. Haematology is also important if you can
    d. Total T4 to check for hyperthyroidism
4. Blood pressure (I do this after the examination, but before the blood tests, so that the patient is accustomed to me but not yet stressed out by clippers and needles!)
    a. Get 5 measurements which must all agree to within 15mmHg of the mean (The HDO monitor calculates this for you on the screen)

The value of this entire package would be ZAR3488 (= €231, including a vaccination) but we charge it out at about ZAR2500 (€166) to make it attractive. If you rip your clients off in the beginning, then you don't get to enjoy the benefits of the long-term relationship and your patient certainly doesn't benefit!

Apart from a blanket prescription of any cat ≥7 yo being at risk, are there any others at risk? Well, patients with polycystic kidney disease, for one; those with a history of previous long-term NSAID therapy might be (although this is controversial as one group suggests meloxicam can prolong survival in cats with CKD!)[5, 6]

The value of the different tools available to the general practitioner

It is generally accepted that the first "thing to go" is the ability to concentrate. Beware! This is not true of all cats! Occasionally we see cats that are already azotaemic, but have a urine SG >1.035.[4] Generally, however, this is uncommon and you can rely on a REPEATABLE USG in the 1.012-1.025 range to indicate early renal disease, when conjoined to other appropriate historical and clinical findings such as:

- Polydipsia (>45 ml/kg/day, certainly >60 ml/kg/day)
    - Remember to take into account that a cat eating wet food (80% moisture) and one eating kibbles (8% moisture) have the same fluid requirements overall, so you must calculate their fluid intake from their food intake, and, if necessary, have the client do a 5-day "measured water intake" trial with records.
- Polyuria
- Possibly decreased appetite
- Possibly weight loss or poor condition (DDx Diabetes mellitus and hyperthyroidism, as well as inflammatory bowel disease, infiltrative bowel disease, cholangiohepatitis, FIP, etc)

Proteinuria is NOT a clinical or historical finding but a clin path finding – you have to be looking for it (i.e. measuring it), in order to find it. There's no magical "clinical sign" for proteinuria. And herein lies the challenge – how many of us do a proper urinalysis? Another complication in cats is that albumin is NOT the principal protein in cat urine – a pre-pheromone protein called CAUXIN that is turned into "felinine", is the primary cat urinary protein.[7-9] This may not be clinically significant, but we don't know enough about this "fly in the ointment".[9] One article suggests cat urine should be passed through a special "filter" which enhances the utility of dipsticks but I haven't found this is widespread.[8, 10]

Firstly, you need to collect a urine sample from every elderly cat (≥7 years old), on an annual basis – even biannually on geriatrics (≥15 years old). Then, do the following:

- Urine sg on a refractometer, NOT the dipstick
- Dipstick for glucose, ketones, blood, protein and bilirubin/urobilinogen (other strips not helpful in cats)
- If there are abnormalities in the above, or a clinical suspicion:
    - Sternheimer stain for crystals, casts, gross cellular evaluation
    - Diff-Quick stain for bacteria
    - Urine protein:creatinine ratio

When evaluating a urine sediment, take note of the presence of bacteria and casts. Most casts are due to the production of Tamm-Horsfall proteins in the renal tubules.[11] They represent a "cytological brush biopsy" of the renal tubules and can be very helpful in understanding pathology.

I would argue that older cats should have a quantified (i.e. machine-measured) urine protein:creatinine ratio performed as well, if there is a low USG and a 2+ or greater proteinuria. If in doubt, MEASURE. If >0.2:1 (cats; dogs >0.4:1), it is significant and warrants attention. The urine protein:creatinine ratio (UPC) is associated with the development of azotaemia, but ageing in cats with CKD is not a risk factor for increasing proteinuria.[12] This means that if you can arrest proteinuria, you DELAY the onset of CKD or even (perhaps) mitigate it completely. Isn't that worthwhile?

At this point, we can turn to blood tests. Urea and/or creatinine elevations – azotaemia – are not particularly sensitive or specific for renal disease so should be interpreted with some caution. The use of "urea strips" is to be discouraged wherever possible as they are inaccurate, time-dependent, and temperature-dependent. They are best left to field conditions i.e. for cattle vets. In-hospital, an appropriate baseline evaluation, if you don't want to do a complete profile, and you are wanting to rule renal disease IN or OUT, is to ALWAYS ask for phosphate, calcium and potassium as well. Sometimes, an elevation in phosphate or decline in potassium is the first sign of problems, LONG before azotaemia. It can certainly be prognostic AND gives you SPECIFIC TREATMENT TARGETS. Always look for a target that you can treat – measure – evaluate – change/maintain your course of action.

Urea can be elevated by gastric ulceration or blood ingestion (eg bleeding gums). Cats rarely develop macroscopic GI ulceration but can develop microscopic gastritis from uraemia. It can also be increased by inflammation in some instances – again, dental disease is a common culprit.

Creatinine can be DECREASED by low muscle mass – so if a patient has sarcopaenia (and thus low creatinine generation) superimposed on renal disease, ALL you may see is a slightly raised urea. A creatinine of 11.9 (ref range 3.3-9.8) is SIGNIFICANT and if you cannot explain it away, you should investigate it.

Raised phosphate is rare but always significant. A Ca x P product of >6-7 (in mmol/L; >60-70 in mg/gL) is a negative prognostic indicator and means that you must diurese the patient immediately and aggressively, as well as scavenge phosphate from the diet, to prevent nephrocalcinosis and Ca-P complex deposition in other organs with proton pumps (renal tubules, gastric mucosa). In early renal disease, as the renal tubular epithelium (RTE) begin to fail, there is less excretion of phosphate. This stimulates the release of phosphatonin, or FGF-23 (fibroblast growth factor-23) from the bone, which increases phosphate excretion and lowers blood P (i.e. it is "phosphaturic").[13-17]

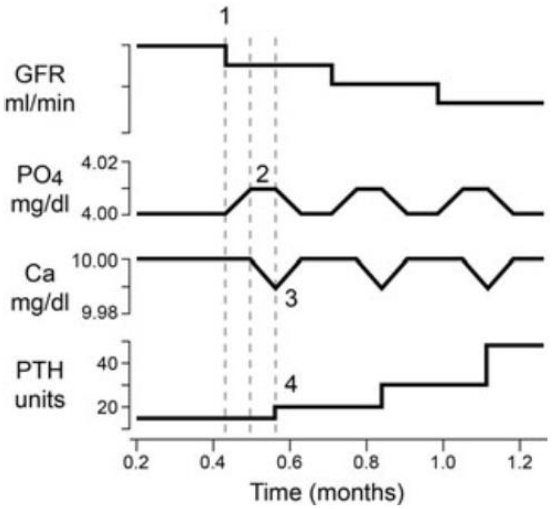


Figure 1. From de Brito (2013) - the classic model of the development of renal hyperparathyroidism

The IRIS advises on "target" phosphate levels – this is a very useful concept and again, gives you a therapeutic target. If you aren't measuring phosphate, you can't aim at a target, so phosphate binders become a bit meaningless. The targets take into account that the "permitted" maximum phosphate may be higher with increasing IRIS stage:

IRIS Stage / Creatinine	**Target plasma phosphorus (mmol/L)**
1 / <140μmol/L	Not applicable
2 / 140 – 249 μmol/L	0.81 – 1.45
3 / 250 – 439 μmol/L	0.81 – 1.61
4 / ≥440 μmol/L	0.81 – 1.94

Calcium balance is under-appreciated as an important component of renal function and failure. Unfortunately, calcium physiology is complex and hard to learn (and remember!). Simply put, *PTH is largely responsible for the minute-to-minute control of serum iCa concentration, whereas calcitriol maintains day-to-day control of serum iCa concentration; note that TCa is NOT as useful as iCa, but is more accessible to most veterinarians.*[13] *Ca complexes with phosphate hence knowing both can help you get a feel for the ebb and flow of renal disease. When blood calcium concentration falls, PTH secretion is stimulated and exerts direct effects on bone and kidney and indirect effects on the intestine through calcitriol. PTH increases synthesis of calcitriol by activating renal 1-α-hydroxylation of calcidiol derived from the circulation. Calcitriol, in turn, increases calcium absorption from the intestine. Calcitriol participates with PTH to stimulate osteoclastic bone resorption* [quoted from de Brito[13]]. The same group also conclusively made a case for the beneficial effects of calcitriol therapy in retarding the progression of RHPTH, which in turn retards the progression of CKD. There is benefit in managing CKD with both activated Vitamin D and RAAS inhibitors such as telmisartan and benazepril.

A recently-releeased test, SDMA (S-methyl diarginine), is an even more sensitive test for early renal insufficiency and has become the mainstay of our renal surveillance. There are a few references that show influences of cardiovascular (endothelial) disease and SDMA elevations[18] however most sources agree that SDMA is very sensitive for early declines in tubular function[19-22]. You can detect early kidney disease 9 months earlier (cats) to 14 months earlier (dogs) than with urea/creatinine.

I hope I have made a reasonably good argument for testing; in the second lecture I will explain how to USE these test results to manage a patient.

What does one do with this information? It is crucial that you place patients into an IRIS STAGE using this data. Pictorially demonstrate where the patient fits into the stage and explain to the client that the lower the stage, the longer the survival time. The stage determines the treatment and monitoring. Using staging you can explain the progression of treatment as the disease advances (which it invariably will, of course).

Blood pressure evaluations

Cats with CKD are often hypertensive due to changes in their neurohormonal and fluid homeostatic mechanisms. The kidneys are essential in controlling Na, H_2O and in doing so influencing cardiac output (CO) and BP as well as total vascular volume. In a similar fashion, BP is essential for the maintenance of renal perfusion, reducing proteinuria and surviving hypovolaemia. Sustained

hypertension causes damage to a variety of organs – the "End Target Organs/ETO". As well as being responsible for maintaining normotension, the kidneys are ETO. Consequences of sustained hypertension (on the kidneys at least) include proteinuria, microalbuminuria and progressive decreases in function. Most of these consequences can be diagnosed with the basic tests described beforehand but the cause – hypertension – requires measurement. So how do you know when to do it?

Firstly, it's a good idea to use BP measurements as part of regular evaluation of *apparently* normal senior or geriatric cats. Always take 5 measurements, which should be averaged and all should be within 20mmHg of each other. NEVER put a patient on antihypertensives or diagnose an apparently healthy cat without ETO TOD (target organ damage) without a repeated measure in 3-4 days.

If there IS TOD, then repeat the measurement within a few days, even hours, to ensure that a valuable opportunity to treat isn't missed. Once a retina detaches or a stroke occurs, it's too late to turn back the clock.

Always consider the important differential diagnoses for systemic HT: renal disease (acute or chronic, proteinuric or nonproteinuric); diabetes mellitus; hyperthyroidism; hyperaldosteronism (Conn's Syndrome); and phaeochromocytoma (very rare in the cat). A blood glucose, urine glucose, TT4, and K+ measurement are good basics that you might have already done and would only miss the last DDx.

So how common is HT? 20 – 65% of cats with CKD have it. Basically, there's a 1 in 2 to 3 chance that every CKD patient has HT. If you're not measuring it, and not managing it, you're undermanaging your patient.

Imaging – Radiographs and Ultrasound (mainly)

Most if not all general practices have X-ray machines. Before the age of ultrasound, radiographs played an important part in the diagnosis of renal disease.

Radiography only gives some information, and comes at a cost. Ultrasound gives distinctly different information, and has its own cost. You need to balance the risks associated with radiography, with the expected information. If you are looking for morphology, ultrasound may be better; or even US+tru-cut biopsy; but if you are looking for functional information, excretory urography can be better although contrast agents can be nephrotoxic. In some instances, eg if you are looking for liths, radiography is better than ultrasound if you are not an experienced ultrasonographer.

In every instance, the test needs to be tailored to answer a specific question that needs answering. Most cats with CKD do not have renolithiasis, so you might need to identify at-risk factors (eg young age; oxalate crystals on UA; Himalayan breed or Bulldog, Schnauzer or Yorkie) to justify radiography as a test in a newly-diagnosed CKD patient; most patients just don't need it and it doesn't add information that you can add on. It's the same for US; most patients with CKD do not reveal any more information that the basic minimum database reveals. However, whenever you have suspicions that something is not right – for example, asymmetrical kidneys on palpation; peculiar signalment; rapid progressive disease; renal pain; and so forth – then imaging can be helpful in the further evaluation or "EXTENDED DATABASE" (EDB) of a renal patient.

Biopsy

As stated before, UA is a form of "brush" cytology of the urinary tract (just as a blood smear is a "delayed" bone marrow aspirate). But in some instances, biopsy is worthwhile. If a patient is in CKD, the techniques for biopsy are probably specialist-level. A General Practitioner needs, however, to have a very clear idea as to WHEN and WHY to refer for a biopsy. For example, any proteinuria in an Abyssinian cat is significant, and should be evaluated by a specialist, as transcorticomedullary biopsy could be required to diagnose amyloidosis – this is a very tricky procedure! On the other hand, biopsying the kidneys of a Persian with US-obvious cysts is NOT generally indicated – nor is cystocentesis (a form of biopsy if you are liberal with definitions).

Biopsy should only be done when the results fundamentally change the prognosis and treatment of CKD eg suspected renal lymphoma or carcinoma; excessive proteinuria not ascribable to another cause; or to rule hereditary forms in or out (eg Alports-like syndrome).

Conclusion

No single test, including some not mentioned here such as fractional excretion tests, iohexol clearance tests or scintigraphy, is the be all and end all of renal function testing. The key ingredients are suspicion and surveillance; being rigourous with the fundamentals (examination & history; urine; bloods; blood pressure); and ACTING according to not only these results, but also those from ongoing monitoring. The next talk will focus on this ACTION.

II. CKD TREATMENT & MANAGEMENT – What do you need to know?

When managing CKD, your starting point is understanding HOW BAD IS THE SITUATION? You don't bring a flamethrower to a knife-fight! Well, the IRIS STAGING SCHEME tells you not only WHAT YOU NEED TO KNOW, but also guides you as to WHAT YOU DO. In other words, it tells you if this is a fistfight or an all-guns blazing fight to the finish. Only do what you absolutely have to, but don't ever UNDERtreat a patient or you will find yourself paddling furiously to get out of trouble – and it will be too late, in all likelihood.

To collect the information for the IRIS staging, understand that this stage is an educational guideline, and also a tool – it is not the be all and end all. With time, it will probably flex and adapt as we learn new things about CKD. For example, the "substages" that incorporate phosphate are a more recent development.

Use the IRIS stage to explain to clients where their pet is, and how you are keeping their pet out of the next stage. They need to carry out your instructions, so it is vital you include them as part of your treatment team. Don't just hand out tablets – ask if they can give them, and if their cat will accept

them! In this respect, medications and tools that owners can successfully administer are essential. Cats are difficult sometimes, just because they can be! Once daily medication has a definite advantage over q12h medication. If your client can reliably give the medication, more of your patients will do well. If more do well, your reputation will improve. Use the wrong medication or the right medication the wrong way – your results will be poor. For example, I am constantly surprised at how many of my colleagues use enalapril q24h. Firstly, enalapril would not be my drug of choice, being renally excreted itself, and known to precipitate CRF. Secondly, it's a q12h drug. Thirdly, many people give enalapril to cats without knowing their BP (it can reduce it – but if the cat is normotensive to start with, this is not ideal) or if they are proteinuric (and this is all it does – reduce proteinuria!). Amazing! It's analogous to giving an antibiotic to a patient without having ANY evidence for an infection…. And then being surprised when the patient doesn't recover!!

A very useful tool for remembering what tools you have available to manage CKD was published by Joe Bartges[23]:

N Nutrition
E Electrolytes
P pH (Acid-base status) AND Proteinuria
H Hydration
R Retention of wastes
O Other insults must be avoided
N Neuroendocrine dysfunction – hyperparathyroidism, hypoproliferative anaemia, hypertension
S Serial monitoring – it is progressive and irreversible

(see chart, overleaf)

The next step is to consider some of the "substages" of your primary IRIS stage. First up is **proteinuria**:

<0.2 = non-proteinuric (NP substage)

0.2 – 0.4 = borderline proteinuric; seek another cause and retest in 4 weeks, then biannually (BP)

>0.4 = proteinuric; seek a cause and manage (monitor efficacy of your intervention) (PR)

It should be mentioned that when you act or investigate is also affected by the CONTEXT. If you do UPC in an otherwise healthy animal, or find proteinuria in a nonazotaemic patient, the criteria at which you investigate is >1.0 (investigate) and >2.0 (intervene).

Also note that proteinuria in hypertensive patients SHOULD DECLINE with treatment!

I treat from 0.2 or more, but only once I have confirmed it on a 2nd or 3rd reading, and excluded other causes. I wouldn't wait until 0.4, data suggests that may already be too high

IRIS SYSTEM				
Stage	Creatinine µmol/L	Comment	Notes	Intervention
1	<140	Non-azotaemic	Does not exclude other renal abnormalities such as: (1) inadequate concentrating ability; (2) renal proteinuria; (3) abnormal renal palpation or imaging; (4) abnormal biopsy results	• Renal diet • ACEI/ARB if proteinuric
2	140-249	Mild renal azotaemia	Clinical signs often absent however stage 2 often falls within the reference ranges for some labs so further investigation is advised for patients at the upper limits of the reference range*	• Add sevelamer or lanthanum phosphate binder to achieve target P level
3	250-439	Moderate renal azotaemia	Many systemic signs are present	• K supplements if hypokalaemic • EPO if anaemic • Amlodipine if hypertensive • (Vit C, E and β-carotene for antioxidative effects)
4	≥440	Severe renal azotaemia	Many extrarenal signs	• Antiemetics • Gastroprotectants • Appetite stimulants and/or feeding assistance eg tube • Calcitriol? • Alkalinisation • EFAs (in diets) • ACEI or ARB even if non-proteinuric?

* in other words, get out of the habit of calling the reference range "normal" – it's not.

Secondly, we consider the patient's **phosphate**:

Phosphate is NOT a "substage" in the truest sense of the word but as mentioned earlier, there are phosphate targets for each stage.

Lastly, consider the patient's **BP**:

SBP	DBP	Substage	Risk
<150	<95	AP0	Minimal risk (N)
150-159	95-99	AP1	Low risk (L)
160-179	100-119	AP2	Moderate risk (M)
180+	120+	AP3	High risk (H)

You can use these guidelines as TARGETS. For example, I will tell my client what the pet's BP is – I even give them a printout and encourage them to keep copies and notes (eg "no treatment"/ 1/8th tablet once daily" etc) – I help them understand WHAT WE ARE AIMING FOR. This involves them in the process.

So let's talk about treatments. There are different grades of evidence for each of these, which I will mention briefly. Your approach to formulating a treatment plan goes as follows (adapted from Polzin, 2013)[24]:

1. Confirm that patient HAS renal disease (renal function tests, UA, UPC +/- urine culture; imaging possibly);
2. Confirm that it is CHRONIC KD (from the history, examination and possibly imaging studies);
3. Establish the IRIS stage (2 fasting creatinine values in a well-hydrated patient, 2-3 UPC and 5 averaged BP values);
4. Develop a treatment plan
    a. Determine what options are appropriate (discuss with client, clinical appraisal, stage)
    b. Prioritise based on owner, pet and medical factors
    c. Review and discuss with an owner to ensure that what you suggest, can and will be carried out and achieves the goals both you and the client understand you can and both WANT to achieve
5. Schedule your review assessments NOW
6. Train and book your staff to regularly check up on patients to monitor compliance with your plan and assess the owner's understanding on an ongoing basis. Ask about any issues or difficulties
7. Assess patient response to therapy to decide whether to change dosages, treatment or monitoring frequencies, and so forth.

Dietary Therapy

(Strong Evidence)

To quote David Polzin: *"feeding a kidney diet (diets … manufactured specifically for managing dogs or cats with CKD) is the therapeutic intervention most likely to enhance long-term survival and quality of life for patients with IRIS CKD Stages 3 and 4. As a consequence, feeding a kidney diet to …. cats with IRIS CKD Stages 2–4 should be considered the current standard of care".*[24]

Dietary therapy is the CORNERSTONE of therapy.[25] But the cat must eat it. If you are looking for an appetite stimulant, do NOT use oral diazepam! Rather use cyproheptidine (1 – 2mg q12h) or mirtazapine (2.5mg q24-48h). Discourage clients from home-prepared diets; they have been found to be inferior to commercial diets.[26]

Fluid therapy

Cats with CKD are exquisitely sensitive to the effects of dehydration. In fact, some clients precipitate "acute-on-chronic" crises by using water restriction to limit the "annoying" polyuria – this is bad news! Dehydration leads to lethargy, depression, inappetance, constipation and worsening uraemia.

The best route for water is orally, either via moister foods, drinking water or even a feeding tube. I have, on occasion, used subcutaneous administration of fluids. Evidence for its effects is weak, but there are patients who benefit from intermittent (every 1-3 days) SC administration of 50 – 150 ml of water. Be careful of overzealous administration of fluids, never use calcium- or dextrose-supplemented fluids and be aware that the sodium content can aggravate or work against oral antihypertensives or may worsen renal function. The patients that respond, do respond well and you can continue; those that don't respond well, rarely do well with a higher dose.

In some instances, acute-on-chronic crises occur. For these, and after discussion with clients about exactly what we are trying to achieve, we will admit the patient for 2 – 6 days. Patients are cautiously diuresed while paying attention to lowering phosphate; stimulating appetite; avoiding fluid overload and hypertension; and we dose bloods every 48 hours. After the first 48 hrs I try to get at least a 33% reduction in urea, creatinine and phosphate. If the patient does not improve clinically and biochemically, it is doubtful whether further fluids will change the status and euthanasia should be considered. If the patient is clinically better but bloods aren't improved, consider increasing fluids and retesting after 24-48 hours further. If the patient has responded well, consider another 1 – 2 days of fluids, then retest, and drop to maintenance. Wait 24 hours, reevaluate and retest. If it slips back, that's bad news; if it restabilises, then consider home care with SC fluids for a week or two and go from there.

Phosphate binders

As mentioned in the previous talk, the goal is to restrict phosphate to BELOW the standard upper reference range limits, to prevent phosphate RETENTION, which leads to hyperphosphataemia. These ranges are based on expert opinion, not lots of science, but are a good start – use them. The first step in phosphate restriction involves DIET. Products such as Hill's k/d, Eukanuba Renal or Royal Canin Renal are well-established and well-described. After starting such a diet, recheck a FASTING phosphate level a month later. If you cannot get the phosphate under control within 2-3 months, additional phosphate scavenging is necessary. In the past, aluminium-based antacids were the main phosphate binders, but I have had much better success with sevelamer (anecdotal evidence I know; but a study is underway). By combining a diet with a PB, you reduce your dependence on these drugs. By combining an Al-containing PB with a sevelamer or lanthanum-based PB (very $$$), you can reduce the risk of aluminium neurotoxicity. Whatever you do, take into account that these are SLOW-ACTING and you should RECHECK and dose according to the response obtained, every 4 – 6 weeks; changes probably wont occur sooner than that.

Potassium supplements

Mild hypokalaemia is often subclinical, but nonetheless, significant and should be managed aggressively. K-gluconate containing gels are the best way to manage this, and can alter K+ within a week, although clinical improvement occurs within a few days in my experience. Hypokalaemia is relatively common in IRIS 2-3 (20 – 30% of patients) but as renal function declined, RAAS activation is more pronounced, anorexia plays a bigger role and hypokalaemia is quite rare in Stage 4. Any cat with persistent K <3.5 mmol/L should be treated, however (weak evidence).

Alkalinisers

Chronic metabolic acidosis becomes more common as IRIS stage advances (from 10% stage 2-3 to 50% in Stage 4) and affects protein nutrition and causes metabolic abnormalities. A low serum HCO_3^-

or low pH is an absolute indication for therapy; potassium citrate gel or liquid is probably best, as it also helps you manage hypokalaemia. Aim to give 40 – 60mg q8-12h and retest within a week.

Haematopoietics

Some patients develop anaemia due to loss of renal mass and EPO production. In the past we used erythropoietin (Eprex) but I found this difficult to titrate if using the prefilled syringes and it tends to produce neutralising antibiodies in many patients, within a few months. These days, I get the 10µg/0.4ml Aranesp (darbopoietin) syringes/pens and give that once weekly, to a target Ht of 25-30, then drop to every 2 – 3 weeks and keep monitoring the Ht/PCV! Some patients also benefit from weekly injections of Vit B12 (eg Catosal) and even a single injection of iron dextran. The latter must go IM and these patients are sometimes sarcopaenic so it can hurt! Any patient with a HT <25 should be considered for darbopoietin therapy. Aranesp is expensive and its monitoring is a cost to be considered when advising clients. Evidence level is weak.

Anabolic steroids

These are of anecdotal benefit but may benefit patients by stimulating appetite and as (weak) bone marrow stimulants. Generally 25 – 50 mg of laurabolin once monthly is adequate.

Gastroprotectants

Uraemic gastritis is probably more as a result of micro-bleeds than big ulcers, but can cause inappetance and discomfort. In instances where appetite stimulants and appropriate dietary therapy are not working, or where the urea elevation is >> creatinine, or there is a thrombocytosis or thrombocytopaenia or anaemia, consider antacids. I use Nexiam paediatric sachets (esomeprazole), with a 10mg/15ml sachet lasts up to 7 days refrigerated, and is palatable. Give 0.5 – 1 mg/kg once daily PO. Cimetidine and ranitidine are NOT particularly effective and cimetidine (a) affects the metabolism of other drugs (b) requires q6-8h dosing (c) is renally excreted. Smaller sachets are also available. Do not crush pantoprazole or omeprazole to make a syrup. Omeprazole in particular is enteric-coated for a reason.

Antiemetics

There is no doubt that many patients with uraemia are nauseous. PTH, hyperphosphataemia, hypocalcaemia, hypokalaemia and other uraemic toxins, as well as gastritis, can all contribute to this – ensure you have addressed these causes before just giving antiemetics. In this day and age, maropitant (Cerenia) is definitely the way to go. Be wary of metoclopramide, as cats are more susceptible to its effects (extrapyramidal dyskinesia). Never exceed 0.5 mg/kg q12h in this species. I am not convinced odansetron works any better than the other drugs, but it may help certain individuals.

Antihypertensives

Systemic HT (SBP >150 mmHg) should be managed, monitored and therapy adjusted accordingly. The #1 drug of choice is amlodipine.[27] ALWAYS TAPER UP. Start with 1/8th (or for very small cats, even 1/16th, by dissolving powder in syrup simplex) of a tablet q24h. Recheck BP in 5 – 7 days and adjust dosage up slowly. In rare instances, a second-tier drug, usually an ACEI (ACE inhibitor) or ARB (ACE receptor blocker) or a β-blocker such as atenolol may be required; in Europe, you should be using Semintra as your second-tier drug, as there are case reports describing its efficacy in selected cases; ACEI are, at best, poor antihypertensives. Be careful in the case of patients already on calcium

channel blockers such as diltiazem, or when adding a β-blocker – you can cause profound hypotension. Gently gently and slowly increase. Always recheck 5 – 7 days after any dosage change.[27, 28]

Antiproteinurics

Antiproteinurics fulfil an important, if incompletely understood role in CKD. Not all CKD patients are azotaemic, but could be proteinuric; heavy and/or sustained proteinuria overloads the cubulin-megalin protein scavenging system in the renal tubules, leading ultimately to tubular cell dysfunction, apoptosis and ultimately loss of concentrating ability and then azotaemia. Proteinuria can result from glomerular disease, systemic disease or hypertension combined with either of the two prior situations. Prevention of proteinuria is believed to improve survival time.[29] Although a direct causal link between proteinuria and the development of renal failure has not been proven, we are getting closer all the time and the process makes sense. We know proteinuria is correlated to the development of uraemia at a later date.[3] There is little benefit in treatment of non-proteinuric CKD patients, except as an adjunct to amlodipine in hypertensive CKD.[30] ARBs may overcome some of the theoretical weaknesses of ACEI, and the cough side effect so important in humans (but not reported in veterinary patients). They selectively bind the AT1 but not AT2 receptors, thereby apparently preventing the phenomenon of "ACE escape" or "angiotensin breakthrough", where aldosterone and Ang II levels rise to pretreatment levels, thereby blunting the benefits.[30]

Calcitriol therapy

With mild CKD, endogenous calcitriol levels decline, but this decline can be blunted by the use of phosphate-restricted diets. As disease progresses, calcitriol declines further and should be supplemented exogenously. For many years, small studies created uncertainty about the true value of calcitriol therapy. More recent advances in the understanding of the (very complex) calcium metabolism including the role of Vit D reclamation by the tubular epithelium and the role of PTH, FGF-23 and so forth, have clarified the role. Calcitriol therapy can be made complex by the size of the capsules and difficulties with measurement of iCa, PTH etc in private practice. The evidence of the use of calcitriol in Stage 3 and 4 CKD in dogs and humans is strong; but there is insufficient evidence (at this time) for or against its use in cats.[14, 24]

Conclusions

CKD is a complex degenerative-metabolic disease; it may have inflammatory undertones and its course is unpredictable. There is no "one" simple form of CKD; some forms are purely proteinuric, others are azotaemic; some are both. Hypertension lurks behind many cases of CKD, and being older cats, many have comorbidities which complicate treatment choices eg anaesthesia. Instituting proper in-clinic surveillance; understanding the value of different tests in the diagnosis and treatment monitoring; educating clients; and not under-managing CKD cases will improve the survival time of your patients.

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