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Proceedings notes

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Markers of acute kidney injury (AKI)

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Acute kidney injury (AKI) is characterized by an abrupt and sustained decrease in the glomerular filtration rate (GFR). It is a common disorder in companion animals and humans, and is associated with high treatment costs as well as high morbidity and mortality. Four phases are currently recognized in AKI: initiation, progression, maintenance, and recovery. Using the common clinicopathologic markers (e.g., serum creatinine), the disease is characteristically recognized only in the maintenance phase, when clinical signs are overt.

Despite advances in the management of AKI, including the introduction of renal replacement therapies, the mortality rate among human and animal patients remains unacceptably high. Over the past 50 years, mortality rates of human patients with AKI in intensive care units have remained as high as 70%.[1] One of the speculated reasons for the high mortality is the late recognition of the disease and consequently the narrow window of opportunity for therapy. Therefore, there is a need to recognize the disease early, before overt renal failure is evident, and when therapeutic intervention could potentially be more effective. The need for early diagnosis is further emphasized in veterinary medicine, because renal replacement therapies are not readily available.

Limitations of serum creatinine concentration

Despite the diagnostic advancements made in other medical fields (e.g., the use of biomarkers in cardiology), serum creatinine concentration (sCr) is still being used as a marker for decreased kidney function, despite its multiple shortcomings including: 1) High variability in sCr among dog breeds. Thus, the attempt to include all dog breeds under one reference range results in a wide reference range and consequently, decreased sensitivity and specificity. Therefore, sCr is not expected to rise above the reference range in most dog breeds until ~75% of nephrons become non-functional. 2) Due to extra-renal factors, particularly muscle mass, sCr lacks specificity. 3) sCr is a functional marker thus it is blinded to kidney injury that is not accompanied by decreased kidney function. 4) sCr does not represent the severity of the damage until a steady-state has been reached. Consequently, substantial changes in GFR at the early stages of the injury might be associated with relatively small changes in sCr.

The above limitations of sCr are reflected by the findings of several studies indicating that small, and even transient, increase in sCr is detrimental. In one study, as little as 0.5 mg/dL increase in sCr was associated with increased in-hospital mortality.[2] In another study, a transient rise of serum creatinine (for 1–3 days) was also associated with increased odds ratio for in-hospital mortality. [3] Finally, even a small and transient increase in sCr in patient that were discharged from the hospital, was associated with the need for chronic dialysis over the ensuing three years.[4] These and other studies indicate that

relying on sCr as the only marker for kidney function does not provide all the information needed to assess kidney function, to intervene in a timely manner, and to determine the prognosis.

Renal biomarkers – characteristics

In the recent years, research in nephrology has been growing in an attempt to identify sensitive and specific biomarkers. The perfect biomarker will have to fulfill several requirements: 1) measured in readily available material (i.e., plasma or urine), 2) be readily available, 3) cost effective 4) have high prediction of kidney injury (namely high sensitivity and specificity), 5) be etiology specific, 6) provide information regarding the location of the injury (i.e., glomerulus, tubules), 7) to be associated with the severity of the injury, 8) to indicate both kidney injury and processes of repair, and 9) to predict the outcome and likelihood of recovery. It is yet to be determined when and if biomarkers would fulfill all of these requirements; however it is unlikely that a single biomarker will provide all this information. More likely, an array of biomarkers will be needed, each of which will provide one piece of the puzzle, and all together will provide a comprehensive picture. A panel of biomarkers might be cost prohibitive, therefore, only a subset of biomarkers that are complimentary for each other will have to be selected for such a panel, each of which will provide specific and unique information.

Potential utilities of biomarkers

Early diagnosis of kidney injury

There are several potential advantages of biomarkers, of which early diagnosis is considered a major one. It has been shown that kidney injury can be identified days before any increase in sCr is documented, thus measurement of biomarkers may alert the clinician to ongoing kidney damage, before there is a measurable reduction in kidney function. If a nephrotoxic drug is being administered, for example, it would be more rational to monitor the patient using biomarkers that have the potential to indicate kidney injury, rather than using biomarkers that can only indicate presence of kidney failure. Once kidney injury is identified, the drug can be discontinued before kidney function occurs. This practice is expected to be associated with better outcome, since once kidney function decreases, recovery is expected to be prolonged and the patient might die before the kidney had the opportunity to recover (even if the latter is possible).

Screening patients at risk

It is accepted that biomarkers indicating injury are more sensitive compared to markers that indicate decreased function, therefore the former should be utilized to screen patients with high risk for kidney injury. It has been shown that the prevalence of AKI in hospitalized patients is relatively high once the IRIS guidelines for AKI grading are applied. These guidelines currently rely on changes in sCr (or reduction in urine production rate), and therefore probably represent an underestimation of the true prevalence of AKI in hospitalized patients in general, and in the ICU setting in specific. Early recognition of kidney injury in hospitalized patients will allow identification, and potentially

elimination, of the cause for kidney damage and might facilitate therapy before the injury progresses to a failure, thus is expected to be associated with a better outcome. It is yet to be determined the patient population that needs to be screened. The current limitation of this approach is low availability commercially available assays to assess candidate biomarkers; yet, if proven useful, availability of such assays is expected to increase in future years.

Differentiating upper and lower urinary tract infection

A recent study of neutrophil gelatinase-associated lipocalin (NGAL) suggests that a subset of dogs with apparently lower urinary tract disease have increase in urinary NGAL concentration, potentially indicating upper urinary tract involvement. Increase in urinary NGAL concentration might be the result of the local inflammation within the lower urinary system, and not necessarily due to kidney damage, since NGAL originates also from neutrophils that are being recruited as part of the local inflammatory process. Nonetheless, recent data suggest that other biomarkers, which are kidney specific, are also increased in dogs with apparently lower UTI, indicating that some of these dogs have subclinical pyelonephritis and ongoing kidney injury, which would typically go unnoticed based on the current guidelines. It is thus possible that without sensitive and specific tools available to differentiate upper and lower urinary tract infection, many of the patients with apparent cystitis, in fact sustain pyelonephritis, and consequently are being undertreated. With the growing availability of kidney-specific biomarkers, differentiation between upper and lower urinary tract infection may become easier, and sequential changes in the degree of biomarkers can guide treatment.

Progression of chronic kidney disease

The current conception is that AKI and chronic kidney disease (CKD) represent two distinct processes of kidney damage. AKI represents rapidly progressing active damage to different part of the nephrons, due to various etiologies, whereas in CKD, there is a slowly progressive ongoing damage. Both in dogs and cats with CKD, the etiology is often unidentified, but regardless of the etiology, the end result is gradual replacement of the normal kidney parenchyma with inflammation and scar tissue. It was thus unexpected that a subset of the dogs with stable CKD have increased biomarkers concentration, indicating an active kidney damage. This finding indicates that active kidney damage is also present is subset of dogs with apparently stable (based on sCr) CKD. This finding might account, at least in part, for the wide variation in progression rate of CKD that occurs among dogs and cats. Presence of active kidney injury likely predicts risk for rapid progression of the disease, whereas absence of active kidney injury predicts slowly progressive kidney disease. The documentation of ongoing active kidney damage in patients with CKD might suggest that the pathophysiology of AKI and CKD share more characteristics than currently recognized, and the main difference between these two types of kidney damage is the rate of disease progression.

Identification of markers of kidney damage in dogs with CKD might also facilitate the diagnosis of IRIS Grade I CKD, which currently challenging with the available tools. Early identification

of the disease will allow early intervention aimed to preserve kidney function. Moreover, assessment of biomarkers indicating active kidney damage in animals with CKD will allow the exploration of the utility of novel therapeutic interventions. Active injury biomarkers will be followed sequentially after the application of these therapies, at the same manner as ALT is being used to assess the efficacy of different interventions when treating liver diseases. The currently available markers of kidney damage preclude such an assessment, as short term interventions are unlikely to alter kidney function, despite either benefit or harmful effects.

Summary

Kidney biomarkers might change some of the common paradigms in veterinary nephrology in the next few years. At this point, data regarding the utilization of such biomarkers in veterinary medicine is still scarce, and further research is warranted. Each of the investigated biomarkers exhibits advantages and weaknesses and it is thus most likely that only an array of biomarkers will provide all the necessary information.

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New concepts in the management of AKI

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Acute kidney injury (AKI) is characterized by a sudden drop in some or all kidney functions and it affects most organs and body systems, leading, in severe forms, to a life-threatening condition with multi-organ failure. In milder forms of AKI, kidney damage may be restricted to the renal parenchyma and not cause overt functional impairment. An appropriate diagnostic database with clean characterization of the type and the extent of the injury is therefore essential for a successful management. The diagnostic evaluation should not be restricted to the assessment of the traditional markers of excretory renal function (i.e. serum creatinine and urea concentrations) but it should also include other markers of kidney injury, as well as it should assess secondary injury to other organs and systems, in particular heart and vascular system, lung, pancreas, and central nervous system. Since the outcome of AKI is strongly linked to the underlying etiology of the renal disease, a major diagnostic effort should be made to identify it. The nature of the cause of AKI will have direct consequences on the initial treatment, in particular in case of toxicoses or infectious diseases. Tables 1 and 2 summarize the major diagnostic steps and the parameters that should be included in the initial diagnostic evaluation of the animal with AKI.

Table 1 - Diagnostic steps in the work-up of an animal with AKI:

- Recognition of AKI
- Grading of the severity of the disease (IRIS system)
- Identification of the cause of AKI
- Characterization of the disease with a list of the affected organs and systems:
- Hydration, volemia, urine production
- Systemic hypertension
- Gastrointestinal manifestation (vomiting, diarrhea)
- Pulmonary complications
- Nutritional status
- Metabolic acidosis
- Electrolyte (K^+) and mineral (Pi) disturbances
- Anemia
- Hemorrhagic or thrombotic tendency
- Failure to excrete medications and drug interactions
- Pain

Table 2: Diagnostic evaluation of the animal with AKI as recommended for the design of an appropriate treatment plan

- Detailed history, incl. travel history, vaccination status, possible toxin exposure, drugs
- Thorough physical exam, incl. blood pressure measurement, fundic exam and rectal exam
- Complete blood count
- Chemistry profile
- Blood gas analysis (venous)
- Coagulation profile, ± thromboelastometry
- Urinalysis with urine culture and sensitivity
- ± Special urinary or serum biomarkers
- Abdominal ultrasound
- Thoracic radiographs
- ± Abdominal radiographs
- Infectious disease screening, depending on the geographic location (should include Leptospira, Leishmania, Babesia, Dirofilaria…)

Decision on therapeutic modality

This thorough diagnostic workup will guide the management of the animal with AKI. The suspected or diagnosed etiology will often influence the major therapeutic decisions (conventional vs. dialytic therapy), based on the estimated potential for renal recovery. However, the actual treatment itself is mostly guided by the individual problem list of the affected animal (table 1). The decision to restrict treatment to conventional therapy or to include dialytic support is very arbitrary and mostly the consequence of the availability or not of blood purification techniques. It does however not really reflect a medical difference since both types of therapy are complementary and interdependent. When available, the use of dialytic support for the treatment of the animal with AKI should be guided by the severity of the disease and the expected course of the renal injury. As a clinician, we have to realize that only the milder forms of AKI have a reasonable chance to recover sufficient renal function for survival in the 3-5 days we can support medically an animal with severe AKI. However, dogs and cats with tubular epithelial necrosis have a potential for recovery that extends far beyond this time and functional recovery may be observed after several weeks and even months of complete renal shutdown after a toxic injury. In such cases, the full potential for recovery can only be used when blood purification techniques are available. The time frame for recovery is typically shorter with infectious nephritis, most dogs recovering already partially within 3-5 days of presentation for acute leptospirosis. With this in mind, it becomes obvious that dialytic therapy belongs to the therapeutic armamentarium for treating severe forms of AKI and that the option to include this form of therapy for the treatment of an individual patient should be discussed early with the animal's owner.

Fluid therapy for AKI

Appropriate fluid therapy remains at the core of the treatment of AKI but unfortunately it is often the most misunderstood part of the management. Especially when restricted to conventional fluid therapy, the inherent lack of treatment response is commonly "compensated" by overdoing these therapies, in particular using overzealous fluid administration. The concepts of "flushing the kidney" or "pushing the kidney with fluids" are so deeply anchored in many clinicians that one feels almost obliged to exaggerate the fluid administration. However, the only reasonable goal of fluid therapy for AKI is to restore both the vascular volume and the hydration as close as possible to a physiological state. Additional fluid, especially in an oliguric or an anuric dog will accumulate in the interstitium and lead to edema in all organs, from the subcutaneous tissue to the gastrointestinal tract, the pancreas, the lung, and the kidney. Renal swelling in its non-expanding capsule will increase the parenchymal pressure and decrease further the glomerular filtration.

Fluid overload should therefore be actively avoided and high care should be given to monitor hydration and volemia in the renal patient. Attention to detail with repeated physical exams should avoid this complication, even in cases of abrupt worsening of renal function and acute oligo-anuria. Signs of fluid overload include serous nasal discharge, chemosis, subcutaneous edema, systemic hypertension, tachypnea, and weight gain. Prospective monitoring of body weight (1-4 x/day) and estimation of a target weight are easy measures that can be used in every practice. A moderately to severely dehydrated dog presented with suspected oligo-anuria can be estimated to be 10-12% dehydrated, corresponding to a water deficit of 10-12% of his body weight. Therefore, his target weight should be 10-12% (max. 15%) above the body weight at presentation. This simple calculation and careful attention to not exceed the target weight avoids most problems of severe iatrogenic fluid overload. The presence of vasculitis is commonly confounded with fluid overload as a cause of peripheral edema in AKI. In our experience, it is however far less common than suspected.

Fluid therapy strategy:

- Estimate volemia and hydration – estimate the target weight.
- Restore volemia rapidly with repeated boli of fluids (e.g. 10 ml/kg) until perfusion parameters are normalized.
- Restore hydration to correct fluid deficit (+ 2-3% buffer) over 24-48h.

After normalization of volemia and hydration, maintain the volume status as close as possible to a normal / physiological condition – many anuric dogs will not need any fluid at all at this stage!

Type of fluid:

- K-free crystalloid for initial stabilization;
- colloids or plasma when difficult to maintain vascular volume in rehydrated animal
- 5% glucose for compensation of insensible losses after volume correction in anuric patients
- K supplementation only with careful monitoring and typically only 1/3 – 1/2 of normal

Most common mistakes:

- too much fluid
- too high K-supplementation
- too much Na (free water deficit)

Use of diuretics in AKI

Diuretics are commonly used to try to induce diuresis in oligo-anuric animals with AKI. However, it is important to have reasonable expectations on their use. Despite multiple theoretical and pathophysiological justifications (i.e. energy-sparing for the tubular cells, antioxidant effect, free radicals scavenging, vasodilatation), human clinical trials have repeatedly shown their lack of benefit on outcome from AKI, even though they may induce diuresis in some cases. Induction of urination should be clearly distinguished from a positive effect on renal function. Therefore, diuretics may be tried in order to induce urination and thus facilitate the medical and nutritional management of the animal with AKI. However, even a positive response has no effect on global outcome from the disease. When renal replacement therapy Is provided, there is probably no benefit for diuretics since fluid removal can be obtained more efficiently by dialysis ultrafiltration.

The choice of diuretics lies typically between the loop diuretic furosemide and the osmotic diuretic mannitol. Even though their respective mechanisms of action are very different, the choice between these two molecules cannot be based on comparative studies and remains an individual preference. They are often combined for additional effect, but it is strongly recommended to discontinue them if they show no evidence of a positive effect. As negative side effects, furosemide can cause irreversible deafness and mannitol an osmotic nephropathy with tubular epithelial cell injury. Dopamine, even at the so-called renal dose is no longer recommended and it is even considered contra-indicated since its effect on the vasculature of the diseased kidney is often unpredictable. Even though it can cause a potentially beneficial vasodilatation in the normal kidney (improved renal perfusion), it can also induce a constriction of the renal vessels in the diseased kidney and thus compromise the renal perfusion. The long recommended protective use of dopamine during anesthesia of the renal patient should likewise be avoided.

Diuretic strategy:

Only use diuretics when really necessary for the management of fluid overload.

When diuretics are indicated, consider combining furosemide and mannitol – discontinue therapy if not effective within 12-24h.

Management of systemic hypertension in AKI

Systemic hypertension is a common manifestation of AKI, affecting approximately 40% of dogs at presentation and 80% during their whole hospitalization, independently of the underlying cause of the disease. Episodes of severe hypertension (>180 mmHg) were detected in over 60% of the dogs

during hospitalization. Even though the association with outcome has not been evaluated, systemic hypertension can cause serious complications such as retinal detachment, acute loss of vision, or cerebral hemorrhage. The frequent hemostatic disorders observed in canine AKI are likely to increase the risk of hypertensive complications. The pathophysiology of systemic hypertension in AKI is likely to be multifactorial. Many lines of evidence point to iatrogenic fluid overload and hypervolemia as a major contributor, very likely in association with a decreased fluid tolerance. Minimal change in fluid load leads rapidly to hypertension. Increased systemic vascular resistance (catecholamine release, receptor sensitivity to catecholamines, decreased concentration of vasodilators, activation of the RAAS system), increased vascular filling (Na and water retention), decreased vascular compliance (increased cytosolic Ca), and increased cardiac output (catecholamine release) have been shown in animal models to contribute to the sometimes dangerous elevation of systemic blood pressure. Counterintuitively, systemic hypertension does not improve tissue perfusion. The vascular beds of target organs tend to protect themselves from the high blood pressure by excessive vasoconstriction and the perfusion of these organs is typically decreased. For the diseased kidney data are somehow mixed with a loss of autoregulation mechanisms. A decreased in systemic pressure can therefore decrease renal perfusion and GFR, whereas an increased pressure can result in a slightly improved function.

In the absence of clear data to guide therapy of systemic hypertension in animals with AKI, it is recommended empirically to avoid severe hypertension (to avoid the risks of hypertensive retinopathy and encephalopathy), but also to not decrease blood pressure too low (to avoid decreasing GFR further). At the author's institution, a systolic blood pressure >180 mmHg is typically treated, a blood pressure persistently >160 mmHg is usually treated, and the target systolic blood pressure lies between 140-160 mmHg.

Treatment of systemic hypertension in AKI is based on volume control to avoid fluid overload, elimination of all potentially hypertensive drugs, and the use of amlodipine as a first-choice vasodilator if needed. Since amlodipine is typically an oral medication, its use may be hindered in animals with frequent vomiting. It can however be dissolved in water and administered at the same dose rectally. ACE inhibitors and angiotensin receptor blockers are contraindicated in AKI since they can further decrease a seriously compromised GFR and they increase the risk of hyperkalemia. If needed, other vasodilators can be added, including hydralazine or acepromazine, depending on their availability.

Antihypertensive strategy:

- Treatment trigger: SBP >180 mmHg or persistently >160 mmHg
- Treatment target: SBP 140-160 mmHg
- Treatment strategy: 1° correct fluid overload; 2° eliminate the use of pro-hypertension drugs; 3° use vasodilators (amlodipine – no RAAS blockade).
- Monitor treatment response

Management of hyperkalemia in AKI

Hyperkalemia is often the limiting factor of conventional medical therapy for severe AKI. Decreased urine output impairs the elimination of potassium that can accumulate and reach life-threatening serum concentrations despite GI losses and decreased intake from anorexia. Bradyarrhythmias with typical ECG changes, including loss of P waves, wide QRS complexes and spiked T waves, should at least alert the clinician of a high likelihood of hyperkalemia. The manifestation of hyperkalemic cardiotoxicity is also to a great extent dependent on other electrolyte (calcium) and acid-base (metabolic acidosis) alterations. However, especially in cats, severe hyperkalemia is not always associated with the expected ECG changes, even a short time before cardiac arrest. Therefore, potassium concentration measurement should always have a high priority in AKI, particularly in anuric animals.

A common misunderstanding in the fluid management of anuric patients is the potential effect of even low K concentrations in administered fluids, overestimating the dilution effect to be expected. The easiest way to represent this is to think in terms of K balance and not to forget the potential extent of intra-extracellular K-shifts. Every mEq of potassium coming into the patient increases the risk of hyperkalemia, even if diluted in commonly used crystalloids (K 4-5 mEq/L). It is always impressing to watch how an anuric patient can have its potassium concentration going from a safe 5 mEq/L to a potentially life-threatening 8-9 mEq/L, while receiving only a maintenance rate of lactated Ringer's solution (4 mEq/L) or Plasmalyte-A (5 mEq/L) overnight. This change may clearly precipitate an early euthanasia or accelerate the need for dialysis. The anuric animal is clearly different from the freshly unblocked cat with a urinary catheter in this regard.

Changes in acid-base balance can also contribute to worsening hyperkalemia and attention should be paid not to increase metabolic acidosis in these animals. Sedation or anesthesia for diagnostic or therapeutic procedures can also cause dangerous potassium shifts from the intra- to the extracellular compartment and contribute to fatal arrhythmias in anuric animals. Hyperkalemia should be therefore at least partially corrected before anesthesia to avoid unexpected complications. A target potassium concentration of 6-6.5 mEq/L should ideally be reached before induction of anesthesia and ECG monitoring should be maintained throughout the procedure.

Treatment of hyperkalemia is warranted for potassium concentrations higher than 6-7 mEq/L and the effect of the treatment should always be monitored, as its efficacy tends to be quite unpredictable. The use of loop diuretics, glucose bolus, insulin – glucose combinations, sodium bicarbonate, hypertonic saline or albuterol (see textbooks for protocols) have all been described and the choice is most often based on individual preferences, lacking comparison studies under clinical conditions. The animal with severe life-threatening hyperkalemia should further receive calcium gluconate as a slow careful intravenous bolus to improve cardiac tolerance for the hyperkalemia and correct quickly the dangerous arrhythmias while waiting for potassium decreasing measures to take effect. The effect of all these measures is temporary and the potassium will eventually come out of the cellular stores within a few hours. If the kidney function cannot be restored in the meantime, blood purification

techniques will be the only ones to achieve an effective potassium removal from the body and to definitively correct this dangerous complication.

Hyperkalemia correction strategy:

Evaluate the possibility of hyperkalemia in every animal with AKI, particularly when oligo-anuric.

K-concentration measurement should be associated to an ECG evaluation.

Avoid worsening hyperkalemia (i.e. K-containing fluids, anesthesia).

Medical treatment of hyperkalemia aims at either improving potassium elimination from the body (fluids, loop diuretics), shifting potassium to the intracellular compartment (insulin, glucose, bicarbonate), or improving myocardial tolerance for high potassium concentrations (calcium).

Dialysis therapy is very efficient to remove excessive potassium from the body stores. It should be considered for severe hyperkalemia since medical therapy will only have a short-lived effect.

Anticipate the next steps: hyperkalemia does not allow a passive approach and needs to be actively corrected, as it is often the limiting factor in the conservative treatment AKI.

Management of hyperphosphatemia in AKI

Serum phosphate concentration tends to increase very fast with acute loss of renal excretory function since typical compensation mechanisms such as hyperparathyroidism are not fully effective at this time. Affected dogs are therefore at high risk for tissue calcification due to precipitation of calcium phosphate compounds is soft tissues, particularly in the stomach, kidneys and lungs. This mechanism may contribute to the residual damage post-AKI and it should be avoided. Severe acute hyperphosphatemia can sometimes also lead to a reciprocal hypocalcemia, and it has been associated with seizures in some dogs and cats with severe AKI.

Treatment of hyperphosphatemia is very limited in animals with AKI and mostly based on improving metabolic phosphate use by providing nutrition and providing a low phosphate diet when the animal is eating or being fed. The administration of phosphate binders to anorexic animals with AKI is clearly not efficient and their use should always be associated with food administration, since they only bind phosphate present in the food and cannot mobilize phosphate from body stores. The difficulties to implement these phosphate-reducing measures in the anorexic animal with minimal renal function show the importance for an early active nutritional support.

Blood purification techniques are however very efficient at removing phosphate accumulation even before nutritional support can be fully functional and these techniques should be considered early to avoid deleterious soft tissue calcifications. Normalization of serum phosphate concentrations should be considered one of the major goals of dialytic intervention.

Hyperphosphatemia correction strategy:

- Requires active nutritional support!
- Based on phosphate-reduced diets and intestinal phosphate binders.

- Consider dialytic intervention.

Hemorrhagic or thrombotic tendency in AKI

Hemostatic disturbances are commonly encountered in animals with AKI, either as a pro-thrombotic tendency, as an increased risk of hemorrhage, or with mixed patterns of hemostatic disorders. A thorough evaluation of the type of hemostatic disorder is therefore strongly recommended in AKI, testing both the primary (platelet count, buccal mucosal bleeding time) and the secondary hemostasis (PT, PTT, fibrinogen). Thromboelastometry, a global assessment of hemostasis, has provided new insights in hemostatic disorders of animals with AKI, especially for the evaluation of a pro-thrombotic status that is otherwise difficult to assess under clinical conditions. Except for severe hemorrhagic disorders clearly requiring a therapeutic intervention (e.g. DIC), the evidence is still very thin and mostly theoretical concerning potential benefits to intervene therapeutically in milder forms (e.g. moderate pro-thrombotic tendency). Prospective studies are clearly needed in this regard.

Nutritional support in AKI

Major progress has been achieved in recent years in our understanding of the need for nutritional support of the animal with AKI. The severe weight loss and the loss of lean body mass has been observed for many years already in affected animals that are literally melting away while trying to recover from their disease. A weight loss of 1-2 % per day has been observed in dogs with AKI. Such a severe catabolic condition is clearly anything but optimal for recovery and it needs to be actively addressed.

Progress has further been made in our ability to provide nutritional support, even in animals with severe gastrointestinal disease. This management requires a combination of medical therapy to decrease nausea and vomiting with highly efficient antiemetics, and the use of feeding tubes (e.g. esophageal or esophago-jejunal tube). Using these techniques, dogs with dialysis-dependent severe AKI can be fed to their caloric requirements with 2 days of presentation already.

Major questions remain concerning the optimal type and composition of the diet recommended for animals with AKI. The optimal protein content is still matter of debate, but most clinicians seem to prefer highly digestible diet with normal or even increased protein content, at least in the initial stage of the disease. Prospective studies are clearly needed to evaluate various models of diets for AKI in small animals and to validate some of the concepts of critical care nutrition for the renal patient.

Nutrition support strategy:

Use feeding tubes from the first day of hospitalization!

Combine with efficient antiemetic therapy and gastric protection.

Type of diet: initially based on high digestibility; no evidence to support protein restriction.

Feeding intensity: a goal of 140-150% RER seems to be a minimum.

Blood purification techniques

The use of blood purification techniques (e.g. hemodialysis, peritoneal dialysis) has markedly improved our ability to treat animals with AKI. For severe forms of AKI, these therapies clearly represent the only way we have to fully use the recovery potential of the diseased kidney. A thorough discussion of the use, indications, limitations and expectations of blood purification techniques is far beyond the scope of this talk and the interested reader is referred to specialized literature for this.

However, as clinicians we have to recognize the limitations of conventional therapy and to know when to refer interested clients for additional support. Early referral for specialized evaluation and intervention is often the key to a successful therapy. Optimal timing for referral is clearly not the last minute with a severely fluid overloaded patient suffering major gastrointestinal complications, pulmonary edema or aspiration pneumonia. Based on a high number of dogs, we estimated that every day dialytic therapy is delayed requires another 2-3 days to bring the dog back to its previous clinical status. Similarly, anuric cats with severe fluid overload may require up to one week of intensive (and expensive) therapy, just to correct the iatrogenic complications that have arisen with conventional therapy.

Dialytic support strategy:

- Consider the use of blood purification technique early in the course of the disease and plan accordingly.
- Restricting the treatment of animals with severe AKI to conventional medical therapy is almost like considering surgery without a scalpel blade!

Despite all the above mentioned advances in our understanding of the disease and its management, many **open questions** remain, especially:

- How to evaluate the recovery potential of the animal with AKI early in the course of disease? When is it worth pursuing therapy?
- What is qualitatively the optimal nutritional support for dogs and cats with AKI?
- What is the ideal renal replacement strategy for small animals with AKI?
- Optimal timing of initiation, intensity of therapy, treatment modality and role of convective modalities need to be evaluated prospectively and not just rely on indirect evidence and extrapolation from human data.
- Can we influence renal recovery and the risk of residual disease? Can we decrease the risk and the extent of chronic-on-acute kidney disease by targeting epithelial-mesenchymal transition and progressive fibrosis?

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Prognostic factors in AKI

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Acute kidney injury (AKI) is associated with high morbidity and mortality in small animals and even the use of renal replacement therapies does not completely avoid the risk of fatal complications. Therapies required for the optimal case management are typically expensive and very work intensive. Therefore, clinicians and animal owners need some basis for the prognostic evaluation of the affected animal. Since most of the available studies are based on the retrospective evaluation of outcome-associated variables, it is not always possible to identify true prediction parameters. For example, when clinicians are convinced *a priori* that a certain parameter is associated with poor outcome, they will tend to communicate this to the owners who may take the decision to discontinue therapy and to euthanize the animal. A later analysis of the outcome of dogs from this clinician will likely show an association between the suspected parameter and a negative outcome. This does however not necessarily prove that there is a real medical link between them, it could simply be that such a link was just suspected. Therefore, outcome prediction models should always be used with extreme care for treatment decisions, as they may be severely biased, based on current understanding and hypotheses. Furthermore, their prediction accuracy should always be validated in separate and independent patient populations in which these models have not been used for decision-taking purposes. Moreover, outcome of the individual patient being a yes/no occurrence, only its likelihood (in %) can be predicted and this may be confusing for some animal owners. Even with a 10% likelihood of negative outcome, when this happens (in 10% of the animals), it is always a 100% occurrence for this particular individual. These models should therefore not replace proper clinical assessment or serve as the sole prognostic tool to guide treatment decisions.

When used and interpreted carefully, properly validated models can however offer an unsurpassed basis for treatment decisions, far superior to the data from univariate analyses of single parameters typically used for this (e.g. presence of anuria, yes or no). They can also significantly contribute to our understanding of the disease by pointing out to some of the most relevant clinical manifestations in terms of outcome. And they may serve as an objective basis to compare the severity of the disease in different patient populations for clinical trials and thus be used for the stratification of study groups.

Factors associated with outcome in canine and feline AKI

The actual reversibility of kidney injury depends mostly on the nature of the underlying cause of AKI and its severity. Whether this potential for recovery can be used or not depends also on additional factors, including the presence of AKI complications and comorbid diseases, and the medical and surgical treatment options available. Several retrospective studies have tried to identify clinical parameters associated with outcome in order to better estimate the prognosis of the individual

animal affected with AKI. The results of these analyses are very variable, depending among others on the characteristics of the patient population, but altogether the most significant associations were with the underlying etiology and the presence of oligo-anuria.

Typically, ischemic insults from systemic cardiovascular disturbances or drug side effects (NSAIDs and RAAS-blockers) are considered favorable with a good potential for recovery. Similarly, renal injury from infectious diseases (leptospirosis, pyelonephritis) are highly likely to recover if the animal can be stabilized and additional infection-associated comorbidities can be managed successfully. Nephrotoxicoses have a variable prognosis that can be considered favorable for drugs causing an ischemic type of injury or for aminoglycosides, moderately favorable for plant toxicoses (grapes, lily), but very poor for ethylene glycol intoxication. The outcome of ureteral obstruction in cats is largely dependent on the availability and the degree of expertise for surgical correction and it can be considered favorable under optimal conditions. Hospital-acquired AKI as a group tends to show the worst overall prognosis, likely due to the multiple comorbid conditions that very often dictate the prognosis more that our ability to maintain or to compensate for decreased renal function. The willingness of the owner to pursue therapy is typically also very different in this group, with the occurrence of additional complications such as AKI in these otherwise already severely affected cases. Unfortunately, the inciting cause of AKI is very often not known at the time of presentation, when major treatment decisions have to be taken and other parameters typically have to guide our outcome prediction in clinical practice.

Further parameters associated with outcome vary between studies but tend to include factors related to the animal (body weight), the inciting cause of the disease (underlying etiology), its severity (serum creatinine, grade of AKI, urine output, serum phosphorus and calcium concentrations, anion gap), the presence of complications and comorbidities (body temperature, presence of fluid overload, anemia, vomiting, number of organ systems involved, respiratory involvement, neurologic signs, DIC, serum potassium, albumin, ALT, presence of proteinuria), and the treatment options available (especially dialysis; for cats, advanced surgery for ureteral obstruction).

Development of outcome prediction tools

Different strategies have been used for the establishment of appropriate prediction tools. Various models have been defined initially based on arbitrary data inspired from the human medicine or from expert opinion. The generated grading systems were then sometimes tested retrospectively or prospectively in groups of affected animals and the association between the disease grade and the outcome has been evaluated. The prototypes of these models are the IRIS-proposed AKI grading system, the veterinary AKI scoring system and various adaptations of the human RIFLE or AKIN classification systems. Another approach is more statistical, analyzing large sets of data to identify the most relevant parameters associated with outcome and to build a scoring system predicting survival in these animals. Such models have been proposed for critical care patients (Survival Prediction Index, SPI2), and more recently for dogs and cats with acute kidney injury treated with hemodialysis (Segev

et al.). As mentioned above, the prediction performance of such models should always be evaluated and validated in independent patient populations to decrease major institution biases.

IRIS, VAKI, RIFLE and other grading systems for AKI in small animals

Different research groups have proposed their own grading systems for small animal AKI, typically based on serum creatinine concentration at presentation or on the change in serum creatinine during the course of disease. The occurrence of AKI defined by an increase in serum creatinine by >50% from baseline or an absolute increase >26.5 µmol/L was clearly associated with an increased mortality in critically ill dogs admitted to ICU, when compared to dogs with stable kidney function (Thoen et al, 2011). In this study, the proposed veterinary AKI (VAKI) stage was significantly associated with mortality. In a similar study, Harison et al (2012) showed the important prognostic implication of even small increases in serum creatinine in a large population of 645 dogs and 209 cats. These and other studies indicate a prognostic value to the degree of renal dysfunction, at least in the tested populations of hospitalized animals. In these animals, the degree of renal functional impairment seems to reflect the extent of the renal damage and thus to correlate with outcome of hospital-acquired AKI.

For most small animal patients presented with AKI in its maintenance or established phase of the disease, a baseline creatinine is not available and the grading system cannot be based on actual changes in serum creatinine. For this reason, the International Renal Interest Society (IRIS) has recently proposed a grading system for small animal AKI based on the actual serum creatinine concentration, with an approach similar to the one used for their CKD staging system. Obviously in AKI, serum creatinine concentration is constantly changing with the evolution of the disease and this grading system does not reflect a steady state condition. The disease grade will likely worsen in the first days of presentation and may decrease again later with renal recovery. The grade of disease at presentation or the maximum grade (peak) of disease during the course of hospitalization may therefore be used as markers of disease severity. The association between AKI grade and outcome has however not yet been evaluated prospectively in small animals and its use remains at this stage mostly indicative, helping the characterization of the disease.

Outcome prediction models for dogs and cats with AKI treated with dialysis

Models derived from a rigorous statistical analysis of large sets of data are expected to be intrinsically more robust than those defined based on arbitrary cutoffs. Obviously, they also have their limitations and they are highly dependent on the population from which the data originate (i.e. type and severity of disease, level of care). Two major series of models have been recently developed by Segev et al. for the prognostic evaluation of dogs and cats treated with hemodialysis.

In the canine (Segev et al, 2008), four different models have been developed, depending on the information available at presentation and the use of either categorical data (e.g. serum creatinine ≤ or >13.2 mg/dl) or the actual numerical value of the parameters (actual serum creatinine). The optimal

cutoff scores were calculated for each model, in order to minimize the number of misclassifications. In the initial evaluation of the 3 best models in the population in which they were designed, 81-87% of the dogs' outcomes were classified correctly, with high sensitivities (77-83%) and specificities (85-90%). In a receiving-operator characteristic (ROC) curve analysis, the area under the curve (AUC) was 0.88-0.91, indicating a good prediction performance of these three main models. A later validation of these models in independent populations of dogs with AKI from 2 other institutions (Segev et al, 2016) indicated, as expected, a slightly lower performance with 74-80% of the dogs correctly classified, sensitivities of 71-75% and specificities of 75-86%. ROC AUC in this dog population varied between 0.80-0.85.

Using a similar approach, five models were generated in the feline (Segev et al, 2013). Their performance was good, but slightly lower than that of the canine models. 75-77% of the cats' outcomes were classified correctly, with good sensitivities (62-66%) and specificities (75-88%) and a ROC-AUC of 0.81-0.86.

These small animal models performed similarly well as human prediction models and they can thus be used to provide objective support when assessing prognosis for dogs and cats with AKI. How well these models perform in other populations with very different disease characteristics or in dogs and cats not treated with hemodialysis still remains to be evaluated. And again, these models, as well as they may perform, should never be used as the sole basis to take a decision to treat or to euthanize an animal. Clinical decisions and prognosis of dogs and cats with AKI should always be based on a thorough clinical evaluation and these scores should be included as additional information for their global assessment.

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The effect of NSAIDs on the feline and the canine kidney

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It is not uncommon to have a clinical need to provide pain relief, often on a chronic basis, for dogs and cats with chronic kidney disease (CKD). Usually long term pain relief is provided by using non-steroidal anti-inflammatory drugs (NSAIDs), which have a number of effects on the kidney and the potential promote acute kidney injury (AKI) when applied in particular situations. This presentation will review the pharmacology of NSAIDs, the role of cyclooxygenases in the kidney and the renal toxicity of NSAIDs to support their benefit/harm assessment in the specific patient with or without renal disease.

The pharmacology of NSAIDs, defining the important properties of the main drugs used clinically

The NSAIDs are a diverse class of chemical compounds widely used in veterinary medicine for their antipyretic, analgesic and anti-inflammatory actions.

The main known mechanism of action of NSAIDs is through inhibition of a cell membrane-bound enzyme: cyclooxygenase (COX). The principal role of COX is to transform arachidonic acid, in an intermediate product, prostaglandin (PG)H_2, which is the common parent to physiologically active eicosanoids subsequently generated by prostaglandin synthases further down the cascade. Eicosanoids are lipid mediators acting locally as autacoid agents in transmembrane signalling cascades. The main eicosanoids of interest in renal physiology are PGE_2, PGI_2 (also named prostacyclin) and thromboxane (Tx)A_2. Specific G protein-coupled receptors have been described for each eicosanoid: four types of receptors for PGE_2 (EP_1 to EP_4), IP receptor for PGI_2 and TP receptor for TxA_2.

Two isoforms of cyclooxygenase, COX-1 and COX-2, encoded by two different genes, were identified in 1991. The understanding, at the time, was that COX-1 was expressed constitutively in a variety of tissues and was involved in the maintenance of physiological 'housekeeping' functions. It would ensure: protection of the gastric mucosa against acid pH and increase epithelial perfusion; maintenance of glomerular filtration rate; and generation of TxA_2 from platelets for initiation of aggregation and blood clotting. The COX-2 isoform was considered to be an inducible isoform that played a leading role, through generation of PGE_2, in the clinical manifestation of inflammation following an injury. The pharmaceutical industry postulated during the 1990s that preferentially or selectively inhibiting COX-2 rather than COX-1 would result in a lower incidence of gastrointestinal (GI) adverse effects. Current knowledge is that COX-2 is actually expressed constitutively in several mammalian tissues, including the kidney (see below) and the digestive tract (where it plays a protective and healing role) in the absence of inflammation (Warner *et al.*, 1999).

The potency and selectivity of NSAIDs (in terms of IC_{50} COX1:COX2 ratios) are species-specific and there are important differences between dogs and cats. A good understanding of NSAID pharmacodynamics and pharmacokinetics provides the pharmacological basis for understanding the

effects of COX-1 and COX-2 inhibition by NSAIDS on renal physiology and toxicity, in the experimental as well as in the clinical setting.

The role of the main target of NSAIDs (cyclo-oxygenase) in normal renal physiology

Understanding of the lipid metabolites produced by COX enzymes in renal physiology has developed significantly since the recognition that both COX-1 and COX-2 are involved in important physiological functions of a number of tissues. There are three main areas in which COX products are thought to play an important role in regulating homeostatic mechanisms in the kidney. These are in the:

- Process of glomerulotubular feedback which ensures that the GFR, and therefore the filtered load that the tubules have to deal with, remains stable over a range of perfusion pressures (intrinsic autoregulation)
- Response of the kidney to reduced water intake, ensuring that the concentrating mechanisms of the kidney function effectively without leading to kidney damage
- Response of the kidney to increased sodium intake, ensuring that sodium excretion increases to match sodium intake (natriuresis).

In a well hydrated normotensive dog or cat taking in a standard amount of sodium in its diet, inhibition of COX enzymes is unlikely to lead to any untoward physiological effects, however renal production of prostanoids helps the kidney to achieve its homeostatic functions under stressful situations.

It is clear that the kidney expresses COX-2 constitutively and that the prostanoids it generates play key roles in helping the kidney adapt to a number of stressful stimuli. The PGs generated locally in the kidney are renoprotective, especially in the inner medullary and papillary areas, when animals become dehydrated. The renoprotective COX is not just COX-1, as might be the case in other tissues; COX-2 expression is influenced by a number of physiological stimuli and the prostanoids it generates in the kidney assist in maintaining homeostasis.

Renal toxicity of NSAIDs

Toxic effects of NSAIDs:

- Are dependent on the physiological state of the animal, with dehydration and hypovolaemia being important risk factors
- Vary with species and with drug according to species because of the relative importance of the different isoforms (COX-1 and COX-2) for kidney function (e.g. in the dog COX-2 is important in the kidney whereas in humans it is less important)
- Are difficult to reproduce safety studies in target animal species conducted in well hydrated laboratory dogs or cats fed a normal diet.

Acute kidney injury with NSAIDs use are promoted by the combination of hypotension (possibly related to anaesthesia), blood loss or dehydration. This combination results in renal production of

prostaglandins to counterbalance the decreased renal blood flow alongside RAAS activation and vasopressin. The end result of this sequence of events is ischaemic and hypertonic damage to the kidney, leading to papillary necrosis in particular and tubular damage in general. This occurs at therapeutic dose rates, which are effective in blocking renal PG production at a time when it is needed

A more difficult issue to understand is whether low-grade, long-term damage occurs with chronic use of NSAIDs. Chronic kidney damage occurs in humans secondary to lifetime abuse of NSAIDs; NSAID drug use is most common in elderly humans (and dogs and cats), where the prevalence of CKD is also at its highest. Large-scale epidemiological studies are lacking in veterinary medicine. Nevertheless, experience from human medicine suggests that NSAIDs should be used with caution in ageing patients with deteriorating kidney function, owing to the reliance on PGs generated by COX enzymes (both isoforms) in protecting the kidney in the face of dehydration and hypotension.

Contrary to the above discussion, it has been suggested that in some forms of kidney disease, upregulation of COX enzymes may drive intrinsic progression via their involvement in altering renal haemodynamics and creating the conditions for hyperfiltration to occur. There is some evidence that COX-2 may be involved in this process in experimental renal reduction models in the rat, particularly when used in combination with inhibitors of angiotensin II (Goncalves et al., 2004). This may be due in part to upregulation of COX-2 expression in the macula densa contributing to hyperfiltration in rat remnant kidney studies. In the same experimental renal reduction models, COX-2 is also upregulated in the glomeruli, arterioles and the cortical interstitium, mostly at inflamed or sclerosing areas, and celecoxib inhibited the inflammation and renal injury occurring in this model (Fujihara et al., 2003).

Benefit/Harm assessment for the use of NSAIDs in canine and feline patients with kidney disease

The dilemma of whether to use NSAIDs or not occurs mainly with cats, which are more prone to spontaneous CKD. In two clinical situations, the risk-benefit ratio of NSAIDs administration has to be evaluated on a case-by-case basis:

- when NSAIDs are administered to animal with normal renal function but whose kidneys are exposed to risk factors (intraoperative period, drug interaction, long treatment duration in the context of perioperative analgesia)
- when NSAIDs are administered to patients with some evidence of CKD for the management of acute musculoskeletal pain and chronic osteoarthritis pain.

Judicious use of NSAIDs in dogs and cats with chronic pain and inflammation and concomitant CKD may be considered. A multifactorial decision takes into account the following factors:

- Individual patient factors
- Possible drug interactions
- Prudent therapy principles

- Efficacy and safety monitoring
- Owner willingness to participate to monitoring
- Favourable formulations
- Alternatives to NSAIDs

If the therapeutic response to the NSAID is good, the improvement in the quality of life of the animal may outweigh the potential harm these drugs might cause to the kidney. If the CKD is stable and the patient continues to eat well, maintains good hydration status and is free from GI side effects, continuous therapy may be possible, although the dose should be titrated to the lowest possible. Care should be taken to ensure owners are aware that dogs and cats on NSAIDs are susceptible to sudden deterioration in renal function should they go off their food or develop GI side effects and urgent attention should be sought should this happen. Care should be taken to be aware of all drugs the patient is receiving, and the clinician should be aware that certain combinations heighten the risk of a uraemic crisis.

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Update of the World Small Animal Veterinary Association Renal Pathology Initiative on Classification and Treatment of Glomerular Diseases in Dogs

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Standard therapy for dogs with glomerular disease currently consists of feeding a renal diet and administration of drugs for reducing activity of the renin-angiotensin system and aspirin. In addition, management of edema and hypertension may be indicated in some dogs with GD. These therapies have been the primary approach for management of canine GD patients for over a decade. While widely accepted and likely to slow progression of glomerular disease, it is clear that this therapeutic approach rarely if ever fully reverses the course of canine glomerular diseases.

It is recognized that many of the mechanisms underlying kidney diseases are immune in nature. Thus, interest has shifted toward considering immunomodulatory therapy (IM therapy) that may offer more promise in halting the typically progressive course of canine CD. Recommending IM therapy requires a risk-benefit assessment comparing the legitimate risks of the proposed therapy versus the likelihood of achieving an important therapeutic benefit for the patient. In making this assessment, it is important to recognize the risk of not providing a potentially effective treatment because GD itself represents a significant risk to the patient.

A significant limitation to applying IM therapy to dogs with GD has been the lack of suitable diagnostic tests (renal biopsies including light, electron, and immunofluorescent microscopy) for establishing which patients should receive IM therapy and which patients are unlikely to benefit from such therapy. Renal biopsy is important because it may provide information that can be used to estimate the likelihood that IM therapy will benefit the patient. Specifically, a biopsy finding evidence supporting an immune mechanism contributing to GD may support intervention with IM therapy, whereas finding irreversible chronic damage and/or absent evidence of IM lesions would generally fail to support intervention with IM therapy.

Glucocorticoids and immunomodulatory agents are an important tool used to manage GD in dogs and humans. However, the rationale underlying etiological treatment of primary glomerulonephritis remains lacking. Nonetheless, clinical studies have supported the effectiveness of glucocorticoids and immunomodulating agents in some subtypes of GD in humans. As stated earlier, it is highly desirable to choose patients with forms of GD likely to respond to such therapies to minimize the risk of exposing patients unlikely to respond to therapies that may have significant complications. Unfortunately, one of the principal justifications for considering using glucocorticoid and immunomodulating agents in dogs with GD is the success seen in some forms of GD in humans. The specific subtypes of canine GD likely to respond to immune therapy are not yet known.

Glucocorticoids (GCC) have been widely used with variable success in all subtypes of primary GD in humans. They have been shown to have efficacy (with or without other immunomodulatory drugs) against minimal change disease, primary focal segmental glomerulosclerosis, idiopathic membranous nephropathy, and ANCA-associated vasculitis; however, they have failed to cure several progressive

GD variants, although they extended patient and kidney survival. In humans, they are the most effective anti-inflammatory agents and interfere with immune response, although they are more effective against cellular immunity than humoral immunity. Glucocorticoids suppress multiple inflammatory genes; interfere with the traffic of inflammatory cells; and at high doses may reduce generation of superoxide anion radicals, inhibit production of platelet-activating factor, modify the composition of the glomerular basement membrane, and inhibit complement-induced granulocyte aggregation. The principal problem with glucocorticoids is it their low therapeutic index. High dose intravenous "pulses" of methylprednisone (MPP) are used in human patients with rapidly progressive renal disease. Theoretically, such therapy is thought to have more rapid and more effective interference with inflammatory and immune processes than other oral glucocorticoids.

The primacy of glucocorticoids in managing GD may relate to its role as an anti-inflammatory agent. Many of the other immunosuppressive drugs seem to perform better (in humans) when combined, at least for some period of time, with steroids. How important this is in managing dogs with GD is as yet unclear, but optimum therapy may require both anti-inflammatory effects and immunosuppression.

Glucocorticoids have generally been avoided in dogs with GD because of their tendency to promote proteinuria. However, dogs with spontaneous hyperadrenocorticism typically do not become azotemic or hypoalbuminemic despite their marked proteinuria. Empirically, some dogs with GD treated with glucocorticoids have appeared to go into remission for their GD. Nonetheless, when these drugs are used in dogs with GD, it is usually for limited courses in order to minimize the adverse effects and proteinuric enhancement. Further studies are needed to clarify the role of glucocorticoids in treatment of canine GD.

Mycophenolate and azathioprine are nucleotide synthesis inhibitors that have previously been used primarily in transplant and autoimmune diseases. They inhibit B/ and T-cell lymphocyte functions, B-cell proliferation and antibody synthesis and natural killer cell activity.[8] Principal toxicities of mycophenolate are bone marrow suppression, gastrointestinal signs and viral infections. Toxicities of azathioprine include bone marrow suppression, hepatic toxicity, infections and risk of neoplasia. Mycophenolate has been suggested for use for prolonged treatments due to its relative safety (primarily seen as diarrhea in dogs); however, the extent of its effectiveness has not yet been determined. In humans, mycophenolate may be most effective when combined with steroids. An important benefit of mycophenolate may be its rapid onset of effect.

Mycophenolate appears to have become the most common immunosuppressive drug for dogs with GN (both confirmed and non-conformed), but confirming clinical studies have not been performed to confirm the value of this drug. However, empirically mycophenolate appears to be very effective in some dogs. The duration of therapy is not well established. Some dogs that have experienced clinical remission have been found to again develop to proteinuric kidney disease after withdrawal of mycophenolate (and other drugs), sometimes as much later as 1-2 years.

When Immunomodulatory Therapy Should Not Be Used? Immunomodulatory therapy should not be used when an immune mechanism is not thought to be a significant contributor to GD. Important

examples include: canine hyperadrenocorticism, hemodynamically mediated glomerular injury associated with chronic kidney disease (CKD), deposition diseases such as amyloidosis or other fibrillary glomerular diseases, GD due to hereditary structural defects, and chronic glomerular disease where fibrosis is advanced and evidence of active immune processes cannot be established. These conditions are unlikely to respond to IM therapy and, in some instances, may be exacerbated by IM therapy (e.g. glucocorticoids for hyperadrenocorticism). Because hyperadrenocorticism can masquerade as proteinuric kidney disease (UPC values may exceed 10), it is important to exclude this cause for proteinuria. Glomerular hypertension accompanying CKD can generally be recognized as mild proteinuria (UPC typically < 2-3) in an azotemic patient with evidence of CKD (e.g. imaging studies). Amyloidosis may be confirmed by light microscopic examination when a complete renal biopsy cannot be performed. Hereditary glomerulopathies of a structural nature may be recognized from family history, but absent an adequate family history, a complete renal biopsy is required to confirm this diagnosis. Confirming chronic GD absent active immune lesions may require a renal biopsy.

The Cardiovascular-renal Axis in Companion Animals

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Introduction

With development of water and salt preserving mechanisms in animals, a mutual relationship between the cardiovascular system and kidneys was established. The bidirectional clinical interactions between these synergistic but competitive organ systems have been recognized increasingly by cardiologists and nephrologists for the important functional and pathological interactions they impose on each other. These systems are responsible in concert for maintaining hemodynamic balance in health, but when maladaptive, they become mutual and interactive participants in the pathophysiology of cardiovascular and renal disease. The clinical consequences of these interactions must be recognized by both cardiologist and nephrologist, and the further definition, classification, and understanding of the relationships have become the bases for the clinical entity termed Cardiorenal Syndrome (CRS) in human medicine. Cardiorenal Syndromes are only beginning to be characterized in veterinary medicine, but a recent attempt has been made to define a consensus for cardiovascular-renal disorders (CvRD) of the dog and cat.[5] The definition of CvRS includes a variety of acute or chronic conditions in which the primary failing organ: the heart, the kidney, or both, promotes dysfunction and/or failure of the other organ system.[4,5]

Identification of Kidney Maladaptation: The Search for Active Injury Markers

Recognition and amelioration of the early maladaptive changes in kidney function leading to kidney injury is key to the prevention of the progressive kidney contributions to CvRD and prevention of progressive kidney disease in patients with heart failure. Early episodes of kidney maladaptation or injury may escape functional detection and remain unrecognized clinically until the persisting or episodic damage exceeds the renal reserve capacity or compensatory adaptations of the kidneys. Only at this stage will there be evident worsening of steady-state function and clinical markers predicting kidney dysfunction and increases in acute kidney injury (AKI) Grade or CKD Stage. Independent of progressive or worsening heart disease these underlying subclinical maladaptive responses or kidney stresses may perpetuate cellular insults that direct sustained injury to the kidney, but this ongoing damage may remain undetectable until parenchymal loss exceeds functional compensations. Conventional static kidney function tests only detect the impact of these active processes after substantial functional or structural damage has occurred.

Sensitive and specific predictors of kidney stress or early injury would provide tremendous diagnostic and therapeutic advantage for patients with progressive cardiovascular disease or managed with therapies with potential to impact kidney compensations or function. Such markers could provide earlier opportunity to correct subclinical conditions which might predispose ongoing injury to the kidneys and proactive opportunity to modify therapeutic interventions or institute more timely monitoring of the cardiovascular disease and kidney responses to the disease. If a therapeutic regimen failed to convert the patient to a non-progressive status, there might be justification to modify the therapy before additional loss of kidney function occurred.

There has been growing interest and research in human nephrology directed at discovering biomarkers that would predict the early onset of AKI.[6-9] Similar efforts are underway in veterinary medicine and show great promise.[10-18] However, this restricted focus to AKI constrains their broader and potentially important application to other clinical settings in which the kidneys are responding to diverse stresses or disruption of normal cellular function. In CvRD these same markers have potential to signal the early, specific, and sensitive existence of cardiovascular-induced kidney injury and are perhaps better termed "active kidney injury" biomarkers. An "active kidney injury" biomarker could expose ongoing or progressive kidney injury in advance of conventional diagnostic methods that document consequent alterations in glomerular filtration rate or substantive loss of functional parenchyma over time.

Many candidate serum and urinary biomarkers have been assessed in human medicine and many of the promising markers are now being evaluated and validated in animals. Some of the most promising candidates include urinary proteins that reflect functions or cellular processes specific to the kidney that become disrupted by pathophysiologic events secondary to injury or cellular stress. Retinol binding protein, cystatin C, cystatin B, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, interleukin-18, liver-type fatty acid-binding protein, tissue inhibitor metalloproteinase-2, and IGF-binding protein 7 are among the most actively pursued.

Active Kidney Injury in Acute and Chronic CvRD

Acute and chronic CvRD are clinical conditions in which the kidney are subjected to subclinical and potentially sustained active injury secondarily to disease, failure, or management of the primary cardiovascular disease. Severe and persistent heart failure is commonly associated with progressive CKD that may be punctuated by episodes of acute kidney decompensation concurrent with decompensation of cardiac function or escalation of drug therapy. Active kidney injury biomarkers may facilitate timely recognition of the incipient kidney damage. This would permit more conscientious management of the cardiac disease and proactive preservation of kidney function and protection from sustained kidney injury with its management. Preliminary observations have demonstrated the utility of acute kidney injury biomarkers to announce the development and of kidney injury in response to acute decompensated heart failure and its resolution with management; progressive venous congestion (congestive nephropathy) subsequent to right heart failure and the

development of ascites and increased intraabdominal pressure and its resolution with abdominocentesis; and prediction of progressive and ongoing kidney injury associated with progressive cardiac disease.

Sensitive and specific active kidney injury biomarkers are likely to lead to new insights into CvRD and facilitate new diagnostic and therapeutic approaches. It is easy to foresee new opportunities and applications for biomarker diagnostics and their applications for early recognition of kidney injury associated CvRD. If validated for specificity, sensitivity, and clinical utility, to be useful diagnostically, clinicians will need to be proactive in testing patients at risk for active kidney injury associated with the assessment and management of cardiac disease before the kidney consequences of cardiac disease are identified by conventional diagnostic parameters or overt clinical signs. The established use of "active kidney injury" biomarkers will require changes in practice patterns related to CvRD. Cardiologist by necessity will need to recognize and anticipate the potential risks and clinical circumstances that might predispose to progressive kidney injury including hypertension; pre-existing kidney disease; heart failure; congestion; use of ACEI, diuretics, antimicrobials, NSAIDs, vasoactive drugs; and diagnostic and therapeutic procedures including anesthesia, interventional surgery, and contrast administration. Therapeutic approaches may be prescribed to biomarker endpoints and logically adjusted or extended until the biomarker activity is nullified.

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The pathogenesis of feline chronic kidney disease: New insights

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Chronic kidney disease (CKD) is a common condition in the ageing feline population defined as an alteration in structure or function of the kidneys that has been present for typically 2-3 months. Early studies report that between 20-30% of cats over the age of 12-15 years will have evidence of CKD (Lulich et al., 1992, Bartlett et al., 2010) and that whilst up to 50% of cases may have a specific underlying renal pathology (e.g. polycystic kidney disease, renal dysplasia, renal amyloidosis) the remainder have evidence of tubulointerstitial nephritis (Dibartola et al., 1987, Lucke, 1968, Minkus et al., 1994). More recently, studies specifically evaluating a first opinion population of cats would support that the prevalence of primary renal pathology is somewhat lower (~16%) (Chakrabarti et al., 2012a) with the majority of cats demonstrating non-specific chronic tubulointerstitial nephritis. The degree of tubular degeneration, interstitial inflammation, fibrosis, glomerulosclerosis correlates, as may be anticipated, with International Renal Interest Society (IRIS) staging (McLeland et al., 2014) and the severity of lesions identified in IRIS stage 3 and 4 supports that, in order to modify the development and progression of CKD, we need to target therapies at a much earlier time.

Aetiology of feline chronic kidney disease

The underlying aetiology of feline CKD is poorly understood. There is evidence to support that by the time azotaemic CKD is diagnosed there is already substantial renal damage present (McLeland et al., 2014). Indeed evidence of tubulointerstitial inflammation can be identified in cats that are considerably younger than the typical CKD demographic (Lawler et al., 2006) raising the theory that the changes identified are part of a natural ageing process in the cat. Furthering this concept of the 'ageing feline kidney' recent work has supported telomere shortening in proximal and distal tubular epithelial cells from cats with CKD when compared with both healthy geriatric and young cats (Quimby et al., 2013). Other factors such as diet (Hughes et al., 2002, Dibartola et al., 1993), feline immunodeficiency virus (White et al., 2010, Baxter et al., 2012), morbillivirus infection (Woo et al., 2012) and vaccination (Lappin et al., 2006, Lappin et al., 2005, Whittemore et al., 2010) have been investigated as potential contributing factors, although remain largely unsubstantiated. Similarly, other key events in the course of an individual cat's life may be contributory e.g. exposure to nephrotoxic drugs, episodes of acute kidney injury, episodes of hypoperfusion/hypotension and ureterolithiasis but their relative importance on the development of CKD in the feline population is unknown.

Progression of renal disease

The course of disease for cats with naturally occurring CKD can be very variable. However, irrespective of the inciting cause, CKD is ultimately considered a progressive condition. Early studies proposed that haemoadaptive mechanisms occurring as a consequence of nephron loss resulted in

the development of glomerular hypertrophy, hypertension and hyperfiltration in order to maintain single nephron GFR (Brenner, 1985, Hostetter et al., 1981) and that, although initially beneficial in terms of maintaining GFR, ultimately these adaptations were detrimental resulting in the loss of further nephrons and progression of disease. Evidence supporting this occurrence in the cat has been demonstrated experimentally in renal ablation models (Brown and Brown, 1995).

Proteinuria both as a consequence of glomerular hypertension and hyperfiltration is proposed to contribute to the development of renal inflammation and fibrosis (Abbate et al., 2002, Eddy, 2004, Perico et al., 2005). In cats proteinuria has been significantly associated with the development of azotaemia (Jepson et al., 2009), having a progressive phenotype of CKD (Chakrabarti et al., 2012b), renal fibrosis score at post-mortem examination (Chakrabarti et al., 2012a) and survival of cats with both CKD (Syme et al., 2006) and hypertension (Jepson et al., 2007). However, although both angiotensin converting enzyme inhibitors and angiotensin receptor blockers significantly reduce magnitude of proteinuria in cats, the benefit in terms of slowing progression of CKD or improving survival in cats with CKD has yet to be demonstrated with anti-proteinuric therapies (King et al., 2006).

The renin-angiotensin-aldosterone system is widely accepted to be upregulated in patients with CKD and RAAS activation has been reported in cats with experimentally induced renal disease (Watanabe and Mishina, 2007). However, plasma concentrations must be interpreted with caution as they may not correlate with tissue RAAS (Kobori et al., 2007). RAAS has a direct role in altering renal haemodynamics and mediating glomerular hypertension and hyperfiltration. However, angiotensin II is also known to mediate alteration in glomerular permiselectivity (Benigni et al., 2004) and to be one of the strongest stimuli for TGFβ production and mediators of renal fibrosis such as connective tissue growth factor and endothelin (Remuzzi et al., 2005). Although beneficial effects of RAAS inhibition have been identified in human patients with a variety of aetiologies of renal disease, a beneficial effect in terms of progression of renal disease or improving survival has not been identified to date in cats.

Hypoxia has also been proposed as mechanisms intrinsically linked to renal inflammation, fibrosis and the progression of CKD. A number of mechanisms contribute to the development of hypoxia (Kawakami et al., 2014).

Renal oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and anti-oxidant defense mechanisms. Oxidative stress occurs in CKD when hyperfiltration and hyperfunctioning of remaining nephrons leads to increased production of ROS. Other factors such as age, proteinuria, RAAS activation and angiotensin II, hyperphosphataemia, inflammation and regions of ischaemia and hypoxia can also contribute to the generation of ROS. There is limited information about oxidative stress (Keegan and Webb, 2010, Krofič Žel et al., 2014) both supporting some degree of anti-oxidant mechanism activation in cats with CKD.

Finally hyperphosphataemia has been associated with progression of renal disease. The proposed pathogenesis is through renal mineralization promoting inflammation and fibrosis. Alternative proposed mechanisms include an association between hyperphosphataemia and vascular calcification and endothelial dysfunction leading to areas of ischaemia and hence stimulating pro-fibrotic mechanisms (Cozzolino et al., 2005).

Renal fibrosis: the final common pathway

The kidney has a limited capacity for expression of pathology and tubulointerstitial fibrosis is recognized as the final common pathway in the progression of all renal disease whereby gradual expansion of fibrosis destroys normal tissue architecture. Commensurate with this, renal fibrosis has been reported, both in humans and in cats, to be the histopathological finding which correlates best with renal function and plasma creatinine concentration (Chakrabarti et al., 2012a, Farris et al., 2011). If preventing the initiation of CKD is not possible, it becomes important to understand the pathophysiology and factors influencing the progression of tubulointerstitial inflammation and fibrosis such that future therapeutics can target these pathways with the goal of slowing progression of disease. Recent work has utilized an ischaemic nephrectomy model in the cat and demonstrated that cats which undergo an acute ischaemic insult ultimately develop interstitial fibrosis where the pathological appearance is very similar to that identified in naturally occurring CKD patients. This model offers the opportunity for future study of factors influencing fibrosis and the possibility of novel therapies to address the development and progression of fibrosis (Schmiedt et al., 2015).

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Updates on nutrition of dogs and cats with CKD

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Introduction

Chronic kidney disease (CKD) is a major cause of morbidity and mortality in dogs and cats.[1] Nutritional modification has been the cornerstone in the long-term management of this condition and has been shown to increase quality of life (QOL) and survival rates significantly.[2,3,4,5] Nutritional management, as a standard of care for cats and dogs with CKD, is included in the treatment guidelines established by the International Renal Interest Society (IRIS), 2016 consensus guidelines of the International Society of Feline Medicine (ISFM), and the 2004 ACVIM Consensus recommendations for management of proteinuria in cats and dogs.[6,7,8]

Dietetic renal foods

Whilst there are many management options recommended for cats and dogs with CKD, only one has been shown to improve survival and QOL in both cats and dogs with CKD and that is dietetic renal food. Based on all available evidence, the IRIS recommends a renal food as the standard of care for dogs and cats with all stages of CKD. In stage 1 this recommendation is for patients with proteinuria (a urine protein/creatinine ratio > 0.4 in cats and 0.5 in dogs).

The question remains what the best time is for the introduction of dietetic renal foods in the earlier stages, such as non-azotaemic, non-proteinuric IRIS stage 1 and 2. Jepson *et al.* assessed the prevalence of development of azotaemia within 12 months of presentation in a population of healthy geriatric cats and reported that 30% of cats recruited had developed azotemia by 12 months.[9] The authors concluded that the incidence of azotemia in this population is high and that it is imperative to monitor geriatric cats. In the absence of sufficient research data in this category of CKD cats, knowing that the incidence of azotaemia in the geriatric feline population is as high as 30%, the safest recommendation at this time is to feed a non-acidifying, phosphorus restricted, low sodium food. Addition of n-3 fatty acids and antioxidants can be considered.

Lean body mass in pets with CKD

Changes in lean body mass (LBM) and appetite can reduce the QOL in some CKD patients. There is growing recognition among the veterinary profession that cachexia (loss of LBM due to disease) and sarcopenia (age-related loss of LBM) occur in our geriatric CKD patients, both impacting on QOL and contributing to the morbidity of the disease. In humans, loss of LBM due to cachexia is directly associated with decreased survival times and reduced quality of life.[10] Maintaining muscle mass in our geriatric CKD patients is therefore important and concerns are growing over the controlled protein levels of renal foods. While studies have demonstrated that many cats and dogs with CKD on a renal food actually maintain their muscle mass, recent awareness has led to increased focus on

optimisation of LBM in these at-risk patients. The mechanisms involved in cachexia are multifaceted and include changes in cytokine, catecholamine and insulin production, as well as changes in muscle fibre synthesis and type.[10] The cause of cachexia is multifactorial; therefore it is not surprising that a single, effective treatment for this condition has yet to be identified.

Studies investigating the impact of controlled protein foods on geriatric cats and cats with CKD are available. It has been demonstrated by Yamka *et al*, using dual-energy X-Ray absorptiometry technology, that healthy senior cats (n=12, average age 10 years) fed k/d Feline for 4 months did not show significant changes in body weight and lean body mass.[11] In another study of cats with naturally occurring CKD (n=10) and healthy control cats (n=9), all cats maintained lean body mass and nitrogen balance when fed foods containing 20 and 24% metabolizable energy (ME) from protein.[12]

Nutrients offering additional benefits to cats with CKD include l-carnitine and omega-3 fatty acids from fish oil. Carnitine promotes oxidation of fatty acids over oxidation of amino acids for energy metabolism, so that instead amino acids can be used for protein synthesis.[13] This may partially explain why healthy cats fed a complete and balanced food with 500 ppm added carnitine gained significant LBM (P<0.01), as assessed by dual-energy X-ray absorptiometry, compared to healthy control cats.[14] Furthermore, mitochondrial efficiency has been shown to decrease with age and this decrease is thought to contribute to fatigue seen in ageing humans. Carnitine supplementation may help to improve mitochondrial function in aging individuals through improved efficiency of energy metabolism. This may partially explain why healthy, mature, adult cats fed carnitine-enhanced food demonstrated an increase in overall youthful energy, as reported by their owners.[15] _ENREF_14 Carnitine is primarily excreted by the kidneys and is conserved by renal reabsorption. In many species, reabsorption of carnitine is as high as 90% but efficiency of reabsorption is impacted by kidney disease, further highlighting the rationale for carnitine supplementation.[16]

Supplemental omega-3 fatty acids derived from fish oil have also been found promising in the management of cachexia and sarcopenia. Omega-3 fatty acids have been demonstrated to down-regulate protein catabolism in cachexia through attenuation of proteasome expression, to decrease inflammatory cytokines and to have benefits on muscle mass in dogs with cardiac cachexia.[17,18] Studies, investigating the beneficial effects of omega-3 fatty acids in the management of sarcopenia, suggest fish oil may further enhance protein synthesis in response to an anabolic substrate, such as amino acids.[19]

Palatability of dietetic renal foods

Inadequate caloric intake further perpetuates loss of LBM in patients with CKD. To further combat the causes of muscle loss, Hill's recently introduced a new patent-pending flavour enhancing technology: Enhanced Appetite Trigger (EAT)™ Technology™ to Hill's™ Prescription Diet™ k/d™ Feline dry. Fritsch

et al have shown in a study with 9 cats with CKD that the average daily caloric intake of Prescription Diet™ k/d™ Feline dry with flavour enhancing EAT™ Technology™ was significantly greater than that of three of commercially prepared feline renal dry foods when compared in four, 7-day food intake studies.[20] Furthermore, the food intake studies found that while cats fed k/d gained an average of 1% of body weight, cats fed the other commercially prepared renal foods lost weight. Cats fed k/d Feline dry ate an average of up to 34% more daily calories compared with the other renal dry food. This important addition to k/d Feline dry will further ensure that muscle loss is minimised in cats with CKD eating k/d.

Ageing in dogs and cats is associated with CKD and osteoarthritis

The prevalence of both CKD and osteoarthritis increases with age. Epidemiological studies have shown that 4 out of 5 dogs >8 years of age suffer from degenerative joint disease (DJD)[21] and that radiographic evidence of DJD is as high as 90% in cats that are ≥12 years old.[22] Furthermore, Marino et al have shown that the prevalence of CKD in a cohort of 128 diagnosed with DJD was high at 69%, which was more than previously reported.[23] To address the nutritional needs of patients that suffer from these two concurrent conditions, Hill's Pet Nutrition combined the science and nutrition of k/d and j/d into a single dietetic food Prescription Diet™ k/d™+Mobility Canine and Feline. This formula combines benefits of dietetic renal food with clinically effective doses of omega-3 fatty acids (EPA and DHA) shown to alleviate clinical signs of osteoarthritis in dogs and cats.[24,25]

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Early Diagnosis of Chronic Kidney Disease in cats

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Chronic kidney disease is a heterogeneous syndrome characterised chronic and persistent renal parenchymal pathology which usually displaces normal functioning renal tissue leading to reduced function. Persistence is not always well defined but is usually taken to mean persists for more than 3 months. Indeed, kidney pathology that results in loss of function usually does not resolve.

The most common kidney function assessed is excretory function. For substances for which there is no tubular secretory mechanism, the rate limiting step in their excretion involves glomerular filtration. Glomerular filtration rate (GFR) at the whole body level represents the sum of the filtration rate for each individual nephron and so global GFR is a measure of the number of functioning nephrons. An experimental method of assessing urinary inulin clearance is the gold standard for measuring GFR but this procedure, which requires timed urine collection and constant rate infusion of inulin to a stable plasma concentration, is too cumbersome for routine clinical practice. Plasma clearance methods involving exogenously administration of substances (e.g. iohexol) which are confined to the extracellular fluid and whose excretion from the body is entirely dependent on GFR (freely filtered, not reabsorbed nor secreted and having no non-renal routes of elimination) can be used in the clinic to assess GFR. Usually this involves taking 3 blood samples during the elimination phase of the plasma clearance and using mathematical modelling of the data to ensure the calculated elimination rate constant best reflects GFR.

However, clinically we usually use surrogate markers of GFR to assess renal excretory function. Creatinine is the traditional and best characterised marker used in veterinary medicine. The new marker, symmetric dimethylargine (SDMA) is the subject of other presentations at this meeting. In general, changes in surrogate markers in the early stages of CKD are relatively small for a given reduction in GFR because of the exponential relationship between GFR and plasma concentration of the marker. This generally means that plasma markers measured on a spot sample are likely to be relatively insensitive in detecting reduced renal mass (and therefore reduction in GFR). How insensitive will depend on how wide the reference range needs to be to take account of non-renal factors influencing the rate of production of the marker. For example, muscle mass is a major factor influencing production of creatinine. This is a particular problem in the dog where muscle mass varies widely between different sizes of dog. In the cat, attempts to use zoometric measurements to adjust plasma creatinine concentration to better reflect GFR (so called estimated or eGFR) have not proved beneficial.

A reduction in GFR may not be the earliest indicator of CKD. Renal pathology leading to loss of nephrons evokes a compensatory response in the remaining functioning nephrons which leads to nephron hypertrophy, glomerular capillary hypertension and hyperfiltration, compensating for the loss of functioning nephrons and initially limiting the reduction in GFR. Much of our understanding of

this process comes from experimental renal reduction models. Extrapolation from these models to naturally occurring disease should be undertaken with caution. Nevertheless, early detection of hyperfiltration has been suggested to be a way of identifying active compensation of loss of functioning nephrons before evidence of reduced excretory function is possible to detect.

Glomerular capillary hyperfiltration may be detected by measurement of urinary protein excretion. Due to the increased hydrostatic pressure in the glomerular capillary bed, an increased in the amount of protein that traverses the glomerular filtration barrier may result. In the remnant kidney models, hyperfiltration is associated with an increase in urine protein excretion as assessed by the urine protein to creatinine ratio. Measurement of protein in the urine assesses the functioning of the glomerular filtration barrier and the ability of the tubules to reclaim the filtered load of protein. Large proteins, like albumin, are largely excluded by the normal glomerular filter due to their size and, in the case of albumin, its negative charge. Nevertheless, because of its abundance in plasma, albumin is the protein present in the glomerular filtrate at highest concentrations. Lower molecular weight proteins (e.g. retinol binding protein) traverse the normal glomerulus more easily and their excretion in urine in increased amounts is indicative of tubular dysfunction. The proximal tubule should reclaim the majority of filtered proteins by pinocytosis and digestion of the reclaimed proteins to amino acids. Proteins can also be released from tubular epithelial cells and appear in urine as a result of tubular stress (hypoxia, oxidative stress). Measurement of individual proteins (be they markers of hyperfiltration such as albumin, markers of reduced tubular function, such as retinol binding protein, or markers of tubular stress, such as N-acetyl-beta-D-glucosaminidase) in feline urine has not, to date, added to the information obtained by measuring total protein in urine, which is predictive of the onset of azotaemia (Jepson et al., 2009). However, the pattern of multiple proteins excreted in the urine might be expected to provide more specific and sensitive information about renal pathology (hyperfiltration, tubular damage/stress, tubular dysfunction). Urinary proteomics is a way of characterising the proteins found in urine based on their mass and charge. The pattern of peptides measured may give a 'fingerprint' of particular types of kidney disease, although its routine use to screen patients at risk of CKD would need to be underpinned by extensive research involving longitudinal studies to identify the predictive value of this powerful diagnostic technique (Ferlizza et al., 2015).

Loss of functioning nephrons activates compensatory mechanisms in the body to defend against retention of metabolites that would otherwise occur with loss of renal mass. Recent work suggests that phosphate homeostasis is disturbed in CKD prior to the onset of azotaemia. The most predictive biomarker of disturbances in phosphate homeostasis is increased circulating concentrations of the phosphaturic hormone, fibroblast growth factor 23 (FGF-23). FGF-23 is a peptide hormone released from osteocytes and osteoblasts in response to increased levels of phosphate in the body. The exact mechanism by which phosphate triggers FGF-23 releases is poorly understood. As a protein hormone of MW 30Kd, the clearance of FGF-23 is dependent on GFR. Thus, both phosphate overload and reduced GFR can contribute to the plasma FGF-23 concentration measured in a particular cat.

Nevertheless, evidence suggests that in cats undergoing health screens, plasma FGF-23 proved to be an independent predictor of the development of azotaemia, this despite the fact no attempt was made to control dietary phosphate intake in these cats (Finch et al., 2013).

In conclusion, early detection of CKD currently involves a number of different approaches. Research has demonstrated that plasma creatinine, proteinuria and elevated FGF-23 levels are independent predictors of impending azotaemic kidney disease. However, whilst these factors work at the population level, it is difficult to find cut of values that are sufficiently sensitive or specific enough to make them clinically useful for individual cats. The predictive value of direct measurement of GFR or the use of urinary proteomics has yet to be assessed in a large group of cats. It seems likely that multiple markers will need to be used if improvements are to be made in detecting CKD at an early stage of the disease, however.

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SDMA a New Renal Biomarker

Jane Robertson IDEXX

SDMA - The Clinician Perspective

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Symmetric dimethylarginine (SDMA) is a novel kidney biomarker in dogs, cats and humans. SDMA, a methylated form of the amino acid arginine, is released into the circulation during ongoing intranuclear protein degradation and is excreted almost exclusively by renal filtration (≥90%). It's small size and cationic properties allow it be ubiquitous and freely filterable by the glomerulus. During the process of protein degradation arginine is methylated resulting in formation of numerous molecules including two dimethylarginines, asymmetric dimethyarginine (ADMA) and SDMA. ADMA is an endogenous inhibitor of nitric oxide synthase and is associated with endothelial dysfunction, vasoconstriction, and elevation in blood pressure. It is cleared by metabolism within the liver and by the kidneys. In contrast, SDMA has not been found to participate in endothelial dysfunction or management of blood pressure and has been shown to have little physiologic activity. It is eliminated primarily by the kidneys with little or no liver metabolism. Renal clearance is through filtration, without tubular reabsorption.

Serum SDMA concentrations correlate well with GFR in cats and dogs. In dogs with X-linked hereditary nephropathy, serum SDMA correlated well to both creatinine and GFR estimated by iohexol. In a canine model of CKD, there was a significant correlation between GFR and SDMA which was stronger than the correlation between GFR and creatinine. In 69 client-owned cats with CKD, SDMA concentrations were increased and correlated with creatinine; SDMA also correlated well with a range of GFRs in aged cats.

SDMA has been shown to be a marker for early kidney disease in dogs, cats and humans. Dogs with X-linked hereditary nephropathy rapidly progress from normal at birth to end stage renal disease. In a cohort of male X-linked hereditary nephropathy dogs the measurements of serum SDMA, creatinine and GFR estimated by iohexol clearance were followed over the course of their disease. SDMA increased earlier than creatinine by identifying a GFR decline as early as a 30% decline compared to serum creatinine that did not increase until there was a 50-60% loss of kidney function. Creatinine was evaluated both as a single serum cutoff value and as trending over time and in both instances SDMA proved to be an earlier indicator of loss of kidney function. Trending of serum creatinine increases the sensitivity of serum creatinine in detecting changes in kidney function. This study confirmed that trending creatinine is better than a single point in time measurement of creatinine; however, SDMA outperformed creatinine trending and proved to be a better indicator of early kidney disease.

Retrospective longitudinal studies in dogs and cats that developed CKD provided further evidence that serum SDMA increases earlier than creatinine. Two retrospective studies that looked at both dogs and cats over several years as they developed naturally occurring CKD showed SDMA increased before creatinine by a mean of 17 months in cats (range 1.5-48 months) and 10.2 months in dogs

(range 0.5-32 months). SDMA identified a reduction in GFR on average 40%, and in one case early as a 25%.

SDMA is useful for identifying and monitoring kidney disease in sarcopenic patients. A major shortcoming of creatinine is its relationship to muscle mass. Increased muscle mass promotes higher creatinine values while reduced muscle mass is associated with lower creatinine values. For example, aged cats with CKD often develop severe sarcopenia. Because of loss of muscle mass in these cats, serum creatinine concentrations will be low relative to GFR thereby underestimate the severity of renal dysfunction. In contrast, SDMA is minimally impacted by muscle mass in dogs and cats. In a study in dogs comparing the relationship between lean body mass, age, serum creatinine and SDMA showed that lean body and age were significant variables for serum creatinine concentration but not SDMA.

SDMA is best interpreted as a complement to existing kidney tests. Serum SDMA concentrations exceeding 14 ug/dl are considered abnormal in dogs and cats (exceeding 15 ug/dl in puppies, kittens and greyhounds). An elevated SDMA and serum creatinine concentration with concurrent inappropriately concentrated urine is consistent with the diagnosis of kidney disease. An elevated SDMA with a concurrent normal serum creatinine concentration suggests early kidney disease. However, when SDMA persists elevated over months this is stronger evidence of the diagnosis of kidney disease. Further, SDMA documented to be elevated for at least 3 months duration in dogs with serum creatinine <1.4 mg/dl or cats with serum creatinine <1.6 mg/dl are consistent with a diagnosis of IRIS CKD Stage 1.

Unlike creatinine, SDMA is not influenced by lean body mass and will therefore be a better marker of kidney disease in animals with low body condition scores. The IRIS board provides tentative guidelines for using SDMA to modify treatment recommendations in patients with low body condition scores.

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