Chronic kidney disease in cats and dogs: managing proteinuria

Chronic kidney disease (CKD) is defined as a chronic sustained reduction in renal function and/or structural change. CKD therefore, by this definition, includes patients with tubulointerstitial nephritis, considered the typical finding in CKD, and also patients with primary glomerular disease. The distinction between these is important as they may differ in aetiology and approach to management. In patients with CKD, proteinuria can develop as a result of tubular or glomerular injury. In addition, proteinuria may cause renal injury and contribute to the progression of CKD. This article will review the pathophysiology of proteinuria in CKD, its diagnostic workup and management.

CHRONIC kidney disease (CKD) is not a single disease entity, but a heterogeneous syndrome caused by a plethora of congenital, familial or acquired factors resulting in loss of functioning renal mass. CKD is a significant cause of morbidity and mortality in cats and dogs with the UK prevalence reported to be 4 per cent (O’Neill and others 2013) and 0.37 per cent (O’Neill and others 2014), respectively. Disease prevalence increases with age in both species and familial nephropathies are recognised in certain breeds.

Diagnosis and staging of CKD

CKD is suspected when consistent historical or clinical findings are present. There should be evidence of disease chronicity, functional and/or structural change and/or renal damage. Diagnostic work-up generally involves complete physical examination, blood and urine testing, as well as imaging.

Following the diagnosis of CKD, staging is performed. The International Renal Interest Society (IRIS) has established a staging system that is applied to patients with normal hydration status and stable renal function and is based on fasting serum/plasma creatinine concentration (Table 1).

Substaging is performed for urine protein:creatinine ratio (UPC) (Table 2) and systolic blood pressure (SBP) (Table 3). This is important as proteinuria and hypertension are therapeutic targets for management aimed at slowing disease progression.

Proteinuria in CKD

Proteinuria contributes to the progression of CKD by promoting tubulointerstitial inflammation, fibrosis and atrophy. Although its role is not fully understood, proteinuria has been shown to be a negative prognostic indicator in cats and dogs with CKD and it is suggested that it may play a role in disease progression. The mechanisms by which proteinuria may cause renal injury have not yet been fully elucidated, but may include direct toxicity to tubular cells, inciting inflammatory responses or the formation of proteinaceous casts resulting in tubular obstruction. Alternatively, it may be the presence of other solutes that are filtered through a damaged glomerulus alongside protein that are damaging to the tubules.

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Carrier filters water and small solutes from plasma through a pressure-driven process. It is charge and size selective thereby restricting the filtration of large (>60 KDa) negatively charged solutes. The glomerular filtration barrier comprises the fenestrated endothelium, glomerular basement membrane and the podocytes (Fig 2).

As the glomerulus is regarded as the sole filtration barrier to protein, the degree of proteinuria is considered to be greater with glomerular injury than tubulointerstitial injury. Glomerular proteinuria is often the result of primary glomerular disease. It is generally accepted that most dogs with a UPC of greater than 2.0 will have glomerular disease, while a UPC of less than 2.0 can be associated with both glomerular and tubulointerstitial disease. Tubulointerstitial disease is more closely associated with decreased glomerular filtration rate (GFR). Primary glomerular disease is rarely recognised in cats since secondary changes are quite common in CKD, especially when hypertension is present.

**Tubulointerstitial proteinuria**

Tubulointerstitial proteinuria can develop as a result of defects in protein reabsorption in damaged renal tubular cells or a tubulopathy (eg, Fanconi syndrome) and is also likely to be exacerbated by accelerated tubular flow rates. Tubulointerstitial inflammation may cause exudation of protein into urine. Tubular damage, tubulointerstitial inflammation and fibrosis may also be induced by direct toxicity from filtered proteins.

Lesions initially localised to one portion of the nephron may result in the formation of lesions in other portions and proteinuria itself may contribute to tubulointerstitial disease. Injured tubular cells can lose their capacity to regenerate and, as a result, undergo apoptosis. This can lead to tubular atrophy and, consequently, non-functional glomeruli.

**Differentiating glomerular and tubular proteinuria**

The magnitude of proteinuria may be suggestive of whether it is glomerular or tubular in origin, but cannot be used definitively. The use of urine electrophoresis to determine the presence of low or high molecular weight proteins or a mixed pattern has been suggested as a useful method to differentiate between glomerular and tubulointerstitial proteinuria. High molecular weight proteinuria may be expected in glomerular damage, while low molecular weight proteinuria may be expected with tubular damage. In addition, the measurement of certain urinary biomarkers such as neutrophil gelatinase-associated lipocalin may indicate tubular injury (Cobrin and others 2013, Wang and others 2016). These methods are largely research tools and further research is required to evaluate their clinical utility in proteinuric patients.

**Proteinuria in hypertension**

The kidney is susceptible to target organ hypertensive damage. The presence of hypertension will result in transmission of high systemic arterial pressure to the glomerulus. This in turn will increase hydrostatic pressure at the glomerular filtration barrier, resulting in the development of, or worsening of, pre-existing proteinuria. In addition, hypertension can contribute to renal injury.

Management to restore normotension will reduce proteinuria and thus specific therapy for proteinuria is not generally required as well. Renin-angiotensin-aldosterone system (RAAS) inhibition has been shown to result in only a small reduction in blood pressure (approximately 15 per cent) and therefore doses in the high end of the therapeutic range may be required for the management of hypertensive patients.
In canine patients, therapy using angiotensin-converting enzyme inhibitors (ACEi) should be initiated if the patient is not already receiving this. However, if there is severe hypertension (SBP >200 mmHg) or evidence of ocular or neurological target organ damage, administration of both an ACEi and a second agent is recommended. There are no studies or consensus demonstrating the most effective second agent and we generally recommend the calcium channel blocker amlodipine. However, some clinicians may prefer the use of angiotensin receptor blockers. Amlodipine as a sole agent is the recommended initial therapy of choice for hypertensive cats. The goal of treatment should be a SBP between 120-150 mmHg in dogs and 120-160 mmHg in cats.

Clinical assessment of proteinuria
Following diagnosis of CKD, an important part of disease staging is to determine if a patient is proteinuric. Evaluation of proteinuria includes assessment of its localisation, persistence and magnitude.

The localisation of proteinuria can be categorised as pre-renal, renal or postrenal (Box 1).

Proteinuria is characterised as persistent if it is confirmed on three or more occasions, two or more weeks apart. The magnitude of proteinuria can be assessed using quantitative methods to determine urine protein concentration.

Diagnostic testing for proteinuria

Semiquantitative methods

Dipstick
The reagent pad colorimetric method (‘dipstick’) is a widely available, simple to perform, in-house test. The urine dipstick primarily detects albumin in the urine. However, it is associated with both false positives and false negatives in patients with highly concentrated urine, pigmenturia or very acidic or alkaline urine and it has poor sensitivity and specificity, particularly in the cat. The sensitivity of conventional urinary protein dipsticks for albuminuria in canine and feline urine (a trace positive reaction or greater) was 81 per cent and 90 per cent, respectively, but the specificity was only 48 per cent and 11 per cent (Lyon and others 2010).

Sulfosalicylic acid turbidimetry
The sulfosalicylic acid turbidimetric method (SSA) is more reliable than the dipstick; however, samples must be sent to a reference laboratory for analysis. Similar to the dipstick test, false positives or negatives can also occur. The SSA detects both albumin and globulin in the urine.

Both dipstick and SSA results need to be interpreted in the light of urine specific gravity (USG) and sediment examination.

Quantitative methods

Urine protein:creatinine ratio
UPC is considered the most clinically appropriate method for quantification of proteinuria and should be performed in any patient with a positive dipstick or SSA result or when investigating renal proteinuria. Both in-house testing and analysis at reference laboratories are available.

A single UPC measurement (spot sample) measured from either a fresh catch or cystocentesis sample correlates with 24-hour urine quantification in both cats (Adams and others 1992) and dogs (Grauer and others 1985). There is also excellent correlation between free catch and samples obtained via cystocentesis in both cats and dogs (Beatrice and others 2010, Vilhena and others 2015).

Measuring UPC in a pooled sample from two to three urine collections is a reliable and cost-effective alternative to assessing two to three serial UPC measurements, but cannot be used for demonstrating persistence (LeVine and others 2010). A normal dog, female cat or neutered male cat would be expected to have a UPC less than 0.2 (Table 2). However, in an intact male cat, the UPC may be less than 0.4, most likely due to the presence of urinary cauxin.

Urine albumin
Urine albumin can be measured using a species-specific assay. When performing analysis of spot samples, urine albumin can be normalised to a standard USG or, more commonly, to creatinine (urine albumin:creatinine ratio (UAC)).

In human patients, microalbuminuria is defined as 30-300 mg/day of urinary albumin excretion. Microalbuminuria is an important risk factor for cardiovascular disease in people and therefore is routinely measured in many patient groups. However, it does not appear to be a similar risk factor in cats and dogs. The clinical benefit of measuring urine albumin in cats and dogs remains unclear. Indeed, measurement of UAC offered no advantage over UPC in predicting the onset of azotaemic CKD within 12 months in cats (Jepson and others 2009).

Additional screening
Patients with glomerular proteinuria should be evaluated to determine if there are any potential infectious, inflammatory or neoplastic diseases that may serve as a trigger for glomerulonephritis or amyloidosis.

Renin-angiotensin-aldosterone system in CKD
Activation of the RAAS occurs in patients with CKD (Jensen and others 1997) (Fig 3). Within the glomerulus, the effect of this is vasoconstriction of the efferent arteriole with an increase in glomerular capillary hydrostatic pressure. This results in an initial improvement in GFR. However, in the long term, RAAS activation is a mediator of progressive renal injury via increasing glomerular capillary pressure and associated filtration of plasma proteins. RAAS

### Box 1: Localisation of proteinuria

- **Prerenal proteinuria** results from the inability of the tubules to reabsorb the high plasma content of small proteins that can freely pass across the glomerular barrier. Examples include immunoglobulin light chains in multiple myeloma, myoglobin in rhabdomyolysis and haemoglobin in intravascular haemolysis. Serum protein electrophoresis or other diagnostics are useful in excluding prerenal proteinuria.

- **Renal proteinuria** results from glomerular or tubulointerstitial pathology. Functional proteinuria as a result of fever, seizure activity or strenuous exercise is possible, although it is rarely recognised in clinical patients.

- **Postrenal proteinuria** results from the entry of proteins into the urine derived from exudative or haemorrhagic processes in the lower urinary tract or genital tract. Urine sediment examination should be performed to exclude postrenal proteinuria.
Angiotensin II type-1 receptor, AT1
Angiotensin-converting enzyme, AT1
Angiotensin II type-2 receptor, AT2
Angiotensin II type-2 receptor
Angiotensinogen
Angiotensin I
ACE
ACE inhibitors
Angiotensin receptor blockers
Angiotensin receptor antagonists
Renin
Renin inhibitors*
Aldosterone receptor
Aldosterone
Management of proteinuria
The passage of proteins across the glomerular filtration barrier is influenced by haemodynamic factors and is thus logical that altering renal haemodynamics should reduce proteinuria. RAAS inhibition has been the main therapeutic target in the approach to reducing proteinuria. Agents that target RAAS include ACEi (eg, benazepril, enalapril), angiotensin receptor blockers (ARBs) (eg, telmisartan, losartan) and aldosterone receptor antagonists (eg, spironolactone) (Table 4). Renin inhibitors are used in people, but have not been used to any great extent in dogs or cats.

Current IRIS guidelines suggest initiating management for persistent proteinuria in cats with a UPC greater than 0.4 and dogs with a UPC greater than 0.5. Some clinicians have advocated treatment for cats with borderline proteinuria, since these cats have been shown to have a poorer prognosis compared to cats with non-proteinuric CKD (Syme and others 2006).

Angiotensin-converting enzyme inhibitors
The most important mechanism by which ACEi reduce proteinuria is through preferential dilation of the efferent arteriole in the glomerulus to decrease glomerular capillary hydrostatic pressure. ACEi inhibit the conversion of angiotensin I (AT-I) to angiotensin II (AT-II) (Fig 3).

The use of ACEi has been shown to increase survival and delay progression of CKD in dogs and people. Despite a significant reduction in proteinuria, no survival benefit has been shown in proteinuric cats; however, studies to date have included only small numbers of patients. In one study, there was no correlation between the intrarenal expression of renin and AT-II and tubulointerstitial fibrosis in cats, but a positive correlation was found in dogs (Mitani and others 2013). These findings may suggest that intrarenal RAAS activation is not a significant mediator of interstitial fibrosis in cats compared to dogs and could explain why ACEi appear to be less effective in cats.

When administered to dogs with glomerulonephritis, enalapril delayed the onset and/or progression of azotemia (Grauer and others 2000). Despite this, enalapril is only licensed for the treatment of congestive heart failure in dogs and is not licensed in cats in the UK. Benazepril decreases proteinuria in both dogs and cats with proteinuric CKD. It is licensed in the UK for the management of proteinuric CKD in cats. We currently recommend its use only in proteinuric (UPC >0.4 for cats and >0.5 for dogs) patients; however, some clinicians advocate its use in borderline proteinuric patients (UPC 0.2–0.5). Benazepril undergoes both renal and hepatic elimination, which could offer a potential advantage over enalapril in terms of safety when administered to animals with late IRIS stage CKD.

There are no other ACEi licensed for use in cats and dogs in the UK. Studies evaluating the use of other ACEi such as lisinopril, ramipril and imidapril in cats and dogs with proteinuric CKD are lacking. There is no current evidence to suggest the efficacy of one ACEi to be greater than any other (Table 4). Efficacy is likely to vary between patients due to pharmacodynamic effects and, consequently, therapy should be tailored to the individual.

Administration of ACEi can result in hypotension, hyperkalaemia or a decrease in GFR that can worsen pre-existing azotaemia. Therefore, patients should be stable, adequately hydrated and normotensive before initiating ACEi therapy.

Angiotensin receptor blockers
Most of the functions of AT-II are mediated through the AT-II type-1 receptor (AT1). One of the effects of AT-II binding to AT1 is vasoconstriction and this can exacerbate systemic hypertension and proteinuria. The AT-II type-2 receptor (AT2) is considered to have renoprotective actions by promoting vaso dilatation and natriuresis, inhibiting renin secretion and exerting anti-inflammatory and antifibrotic effects on the kidneys. ARBs selectively inhibit AT2, preventing AT1-II binding.

Several ARBs, including telmisartan and losartan (Table 4), have been studied in people with proteinuria and were shown to result in a similar reduction in proteinuria compared to ACEi. Losartan was effective in reducing proteinuria in dogs, but not in cats (Jenkins and others 2015). However, this study was conducted in response to AT-II infusion and therefore may not extrapolate to patients with naturally occurring disease. It is not licensed in the UK in either species.

Telmisartan is licensed in the UK for reducing proteinuria in cats with CKD. Compared to benazepril, the decrease in UPC in cats given telmisartan appeared to be greater at all assessment points over the course of a six-month study although this did not reach statistical significance. However, there was a significant decrease in UPC compared to baseline in cats receiving telmisartan but not those receiving benazepril (Sent and others 2015).

Studies in people have shown that telmisartan decreased blood pressure as effectively as amlodipine, suggesting that it might be the drug of choice for concurrent hypertension and proteinuria. A study in healthy cats comparing the administration of benazepril, irbesartan, losartan and various doses of telmisartan found that telmisartan had a longer duration of action than benazepril and, at a higher dose (3 mg/kg), it attenuated SBP to a significantly greater degree than benazepril and all other treatments (Jenkins and others 2015). However, there was no dose escalation of benazepril and therefore with higher doses it is possible that this would also have been effective.

There are no systematic studies evaluating the efficacy of telmisartan administration in dogs with proteinuric CKD, although individual reports have been published and there are anecdotal reports of its efficacy.
Box 2: Aldosterone breakthrough and ACE-escape

Serum aldosterone concentration increases over time in a subset of human patients receiving even maximal doses of renin-angiotensin-aldosterone system (RAAS) inhibitors. This phenomenon is known as aldosterone breakthrough. In addition, angiotensin-converting enzyme (ACE)-escape, in which there is incomplete inhibition of the conversion of angiotensin (AT)-I to AT-II in patients given ACE inhibitors (ACEI) resulting in ongoing AT-II production, is also recognised. In people, the most favoured explanation for aldosterone breakthrough and ACE-escape is that non-ACE enzymes, such as chymase and cathepsin G, can cleave AT-I to form AT-II. This mechanism for aldosterone breakthrough mediated by AT-II might suggest that the phenomenon occurs less often in patients receiving aldosterone receptor blockers than in those receiving ACEI. However, this does not appear to hold true in human patients.

The mechanisms of aldosterone breakthrough and ACE-escape in cats and dogs are poorly understood and the incidence is unclear. It has been suggested that aldosterone breakthrough may develop in up to 33 per cent of dogs with proteinuric renal disease receiving RAAS inhibitors (Vaden and Elliott 2016). Persistently elevated aldosterone concentration is of concern as it may have adverse effects on the heart, systemic vasculature and kidneys.

Combination therapy

In human patients, combination therapy with an ACEI and an ARB may be recommended if monotherapy is not effective in reducing proteinuria. There are no published studies evaluating combination therapy in cats or dogs. However, it is potentially very dangerous given the results of a human study that found increased risk of kidney failure and death in elderly patients prescribed combination therapy.

Aldosterone receptor antagonists

Aldosterone receptor antagonists such as spironolactone have been used in people to counter aldosterone breakthrough (Box 2) and also in the management of proteinuric kidney disease. There are no published studies exploring the use of aldosterone receptor antagonists in dogs or cats with proteinuric CKD. Currently, spironolactone (Table 4) is licensed in the UK for the treatment of congestive heart failure in dogs. It may be considered in a patient with high serum aldosterone concentration and persistent proteinuria despite treatment with an ACEI and/or ARB; however, its use would be off licence.

Renal biopsy

Renal biopsy can potentially provide a definitive diagnosis of CKD, but can also provide information about the severity of the underlying renal injury. The collection of a renal biopsy should only be performed when it is believed that the identification of pathological changes may be useful for modifying therapeutic options for the patient. However, the risk of the procedure must always be weighed up against any potential benefit.

Renal biopsies should be obtained under sedation or general anaesthesia using ultrasound guidance by someone experienced with the procedure and should be handled with extreme care to ensure a diagnosis can be reached. A practical guide to obtaining a renal biopsy is beyond the scope of this article and it is recommended that a veterinary nephropathology centre is contacted beforehand for further instruction regarding collection and to ensure the correct fixatives can be provided.

Samples are obtained from the renal cortex rather than medulla as the cortex contains the glomeruli. In addition, if the corticomedullary junction is crossed, haemorrhage or infarction can occur due to damage to large vessels. Samples should be submitted to a veterinary nephropathology service to ensure appropriate processing and to provide a full diagnosis. A regular pathologist will be able to identify diseases such as lymphoma, amyloidosis or pyelonephritis, but an experienced nephropathologist will visualise the tissue using light microscopy and will be able to identify any ultrastructural changes using electron microscopy. Immunostaining techniques can also be applied to the sample (Table 5).

The primary aim of obtaining a renal biopsy to investigate glomerular disease in dogs is to determine if there is an

| Class                     | Drug                  | Formulation      | Licensed indication                                     | Initial dose                                      | Dose adjustments                                      |
|---------------------------|-----------------------|------------------|---------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|
| Angiotensin-              | Benazepril            | Tablet           | Cats: reduction of proteinuria associated with CKD       | Cats: 0.5-1.0 mg/kg orally once daily*            |                                                       |
| converting enzyme         |                       |                  | Dogs: treatment of congestive heart failure             | Dogs: 0.25-0.5 mg/kg orally once daily*          |                                                       |
| inhibitors                | Enalapril             | Tablet           | Dogs: treatment of congestive heart failure             | Dogs: increase to a maximum daily dose of 1 mg/kg orally once daily | Increase up to a maximum of 0.5 mg/kg every 12 hours |
| Angiotensin               | Telmisartan           | Oral solution    | Cats: reduction of proteinuria associated with CKD       | 1 mg/kg orally once daily                        | Not applicable                                        |
| receptor blockers         |                       |                  |                                                         |                                                  |                                                       |
| Aldosterone               | Spironolactone        | Tablet           | Dogs: treatment of congestive heart failure caused by    | 2 mg/kg orally every 12-24 hours                 | Not applicable                                        |
| receptor antagonists      |                       |                  | valvular regurgitation                                  |                                                  |                                                       |

* A lower starting dose is recommended in patients with late International Renal Interest Society (IRIS) stage 3 or stage 4 CKD
immunopathogenesis present requiring immunosuppressive therapy. This can be identified by the finding of electron-dense immune deposits in different locations (subepithelial, subendothelial, intramembranous or mesangial) of the glomerulus when visualising the biopsy using electron microscopy or by the presence of positive immunostaining when visualised using immunofluorescence microscopy. Specific treatment can be tailored based on renal biopsy findings. Consensus guidelines have been produced by IRIS for the management of glomerular disease in dogs using data obtained from the WSAVA Renal Standardization Project. No similar projects have been undertaken in cats to date.

### Immunosuppressive therapy

Immunosuppressive treatment should be reserved for patients in which a renal biopsy has been performed and there is evidence of immune-mediated disease. Furthermore, any underlying infectious disease should be excluded and underlying disease for which immunosuppression would be contraindicated should not be present. There is currently a lack of controlled clinical trials evaluating immunosuppressive therapies in glomerular disease in dogs and this makes evidence-based recommendations difficult. The immunosuppressive agent or agents prescribed are dependent on the severity of disease and its progression. IRIS consensus guidelines for the management of confirmed immune complex glomerulonephritis have suggested that glucocorticoids, mycophenolate, cyclo-

### Table 5: Glomerular diseases in dogs and associated findings on renal biopsy

| Disease                              | Specific findings                                                                 | Not applicable                                                                 |
|--------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Amyloidosis                          | Specific findings                                                                 | Not applicable                                                                 |
|                                      | • Green birefringent material when stained with Congo red and viewed using polarised light |                                                                                   |
|                                      | • Fibrilar material present in the mesangium and glomerular basement membrane using electron microscopy |                                                                                   |
|                                      | Non-specific findings                                                            |                                                                                |
|                                      | • Eosinophilic material on haematoxylin and eosin staining using light microscopy |                                                                                |
| Immune complex glomerulonephritis    | Specific findings                                                                 | Not applicable                                                                 |
|                                      | • Electron-dense immune complex deposits in different locations (subepithelial, subendothelial, intramembranous or mesangial) of the glomerulus using electron microscopy |                                                                                   |
|                                      | • Positive immunostaining using immunofluorescence microscopy                    |                                                                                |
|                                      | Non-specific findings                                                            |                                                                                |
|                                      | • Immune complexes detected using Masson’s trichrome on light microscopy         |                                                                                |
|                                      | • Glomerular basement membrane remodelling (spikes, holes, double and irregular contours) using Jones methenamine silver staining on light microscopy |                                                                                   |
|                                      | • Glomerular endocapillary hypercellularity using light microscopy                |                                                                                |
| Non-immune complex glomerulonephritis| Specific findings                                                                 | Focal segmental or global glomerulosclerosis                                   |
|                                      | • Absence of findings consistent with immune complex glomerulonephritis using electron microscopy and immunofluorescence |                                                                                |
|                                      | Non-specific findings                                                            | Glomerular basement membrane abnormalities                                       |
|                                      | • Smooth contours of the glomerular basement membrane using light microscopy     |                                                                                |
|                                      | Note: Glomeruli that are reported to be normal using light and electron microscopy and immunofluorescence should not be considered to have non-immune complex glomerulonephritis and an alternative cause of the proteinuria should be investigated |                                                                      |
|                                      |                                                                                    | Congenital or developmental nephropathies                                       |

The onset of action may be less important in these cases. Approximately 50 per cent of dogs from which renal biopsies have been evaluated had evidence of immune complex glomerulonephritis, similar immunosuppressive therapies can be prescribed; however, agents with a rapid onset of action may be less important in these cases.

It is important to remember that immunosuppressive therapy should be prescribed in combination with standard therapy such as RAAS blockade. Currently, there is a lack of published literature exploring glomerular disease in cats; however, clinically this does not appear to be a common diagnosis. When glomerular disease does occur, the most common underlying diagnosis is membranous nephropathy (rather than membranoproliferative glomerulonephritis, proliferative glomerulonephritis or amyloidosis). Among cats with membranous nephropathy, a greater proportion will have an immune-mediated aetiology (rather than feline leukaemia virus, feline immunodeficiency virus, feline infectious peritonitis). Therefore, immune complex glomerulonephritis is considered to be rare in cats and immunosuppressive therapy would not be recommended in the management of a proteinuric cat unless there is a biopsys-conﬁrmed immunopathogenesis.

### Adjunctive therapies

#### Dietary therapy

Renal diets are protein restricted and the feeding of such diets is considered to decrease proteinuria through decreasing the amount of protein presented to the glomerular filtration barrier and through reducing intraglomerular capillary pressure. However, they are rarely useful as a monotherapy, as they only marginally reduce proteinuria.

#### Omega 3 and omega 6 polyunsaturated fatty acids

Dietary supplementation with omega 3 [n3] polyunsaturated fatty acids (PUFA) decreases the magnitude of proteinuria, while supplementation with omega 6 [n6] PUFA increases GFR in dogs. The recommended n6:n3 ratio is 5:1 and this is found in most formulated renal diets. For proteinuric patients that are not fed a renal diet, supplementation with n3 PUFA and specifically docosahexaenoic acid and eicosapentaenoic acid can be recommended. The dosage is 0.25–0.5 g/kg of docosahexaenoic acid and eicosapentaenoic acid. In an uncontrolled retrospective study evaluating various renal diets fed to cats with CKD, the diet with the highest eicosapentaenoic acid [n3] content was associated with the longest survival compared to control cats, although all diets studied improved survival (Plantinga and others 2005). However, a causal rela-
Drug Advantages Disadvantages Evidence for use

Glucocorticoids Inexpensive, readily available Adverse effects (e.g., polyuria, polydipsia, increased proteinuria, systemic hypertension, polyphagia, risk of thromboembolism, adrenal suppression) IRIS consensus guidelines for glomerular disease recommend short-term administration in fulminant cases requiring immediate immunosuppression (usually in combination with other drugs) or in cases of multisystemic immune-mediated disease

Risk of development of infection (e.g., urinary tract infection)

Mycophenolate Less toxicity (e.g., myelotoxicity, hepatotoxicity) than other alkylating agents, rapid onset of action Adverse effects (predominantly gastrointestinal) are dose-dependent and reversible following withdrawal Single case report describing its use in a dog with glomerulonephritis of unknown pathology

Ciclosporin Readily available Expensive Adverse effects (e.g., gastrointestinal signs, gingival hyperplasia) IRIS consensus guidelines recommend ciclosporin as the first drug of choice for managing dogs with acute or rapidly progressive glomerular disease

Cyclophosphamide Rapid onset of action Adverse effects (e.g., gastrointestinal signs, myelosuppression, haemorrhagic cystitis) Strict regular monitoring required

Azathioprine Inexpensive Adverse effects (e.g., gastrointestinal signs, myelosuppression, hepatotoxicity, acute pancreatitis) IRIS consensus guidelines describe uncontrolled anecdotal clinical experience supporting its efficacy, usually when combined with chlorambucil

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Table 6: Immunosuppressive therapy options in the management of canine immune complex glomerulonephritis

- **Antithrombotic therapy**
  - Thromboembolism is recognised in both human and canine proteinuric patients, with the prevalence reported to be up to 25 per cent of dogs with glomerular disease. The pathophysiological mechanism remains to be fully elucidated, but factors that are likely to be involved include loss of antithrombin into the urine, an increase in plasma procoagulant factors and fibrinogen, an increase in platelet reactivity and endothelial dysfunction. Unfortunately, there is a lack of evidence for the optimal drug and dosage and when to institute prophylactic treatment in dogs. The IRIS consensus guidelines for managing canine glomerular disease recommend the administration of low-dose aspirin (1-5 mg/kg daily) to all dogs with proteinuric glomerular disease, provided that they are normotensive and well-hydrated.

- **Clopidogrel** may also be an effective antithrombotic therapy; however, there is no evidence that it is superior to aspirin and it is significantly more expensive.

- **Thromboembolism** is not generally recognised in cats with proteinuric CKD and, to our knowledge, there are no studies exploring antithrombotic therapy in these patients.

- **Targets and monitoring of treatment**
  - The optimal therapeutic target for proteinuric patients receiving standard therapy is to decrease UPC to less than 0.5 in dogs and less than 0.4 in cats. However, this is not achieved in many patients. Serial UPC measurements differ by at least 80 per cent in dogs with low UPC (approximately 0.5) and 35 per cent in dogs with high UPC (approximately 12). Therefore, a reduction in UPC close to this magnitude is probably required to conclude that treatment is effective. The IRIS consensus guidelines for canine glomerular disease recommend a reduction in UPC of greater than 50 per cent as an alternative target. Whether achieving any of these therapeutic targets offers any survival benefit is still unknown. It is important to note that in the later stages of disease, when the number of remaining functioning nephrons through which protein can be lost has decreased, a decrease in UPC may be seen.

- Following initiation or a change in dose of RAAS blockade therapy, UPC, SBP, serum creatinine and potassium should be measured after one to two weeks [Fig 4]. Hyperkalaemia can be a common side effect of RAAS inhibition in dogs, but not cats with CKD. Treatment modification consisting of ACEI or ARB dose reduction, discontinuation of spironolactone or feeding a potassium-deficient diet formulated by a veterinary nutritionist, is indicated if serum potassium concentrations greater than 6 mmol/l are seen. An increase in serum creatinine greater than 30 per cent would suggest worsening renal function requiring cessation of treatment or a dose reduction.

- The IRIS consensus guidelines for monitoring of dogs receiving standard therapy as management for glomerular disease recommend measuring SBP, evaluating UPC and performing biochemistry (to include albumin, creatinine and potassium) and urinalysis at least every three months. This is similar to the International Society of Feline Medicine consensus guidelines for monitoring of cats with stable CKD (Sparkes and others 2016). Recommendations for monitoring dogs receiving immunosuppressive therapy include re-evaluating the patient one to two weeks after initiating treatment followed by every two weeks for the first six weeks and then monthly for three months extending to every three months for long-term monitoring. Evaluation should include SBP, haematology, biochemistry (to include serum albumin, creatinine, urea, phosphorous, electrolytes, hepatic markers and cholesterol), UPC and urinalysis.

- **Nephrotic syndrome**
  - Nephrotic syndrome is characterised by the presence of hypoalbuminaemia, proteinuria, hypercholesterolaemia and fluid accumulation in interstitial spaces and/or body
Fig 4: Protocol for adjusting renin-angiotensin-aldosterone system inhibition therapy in dogs with glomerular disease.

**Tolerable limits:** Serum creatinine (SCr) change generally considered tolerable in chronic kidney disease (CKD) stage 1 or 2 if less than 30 per cent above baseline; in CKD stage 3 less than 10 per cent above baseline but in stage 4 no increase in SCr may be tolerable. Potassium (K) tolerable when less than 6 mmol/L. Systolic blood pressure (BP) should be 160-179 mmHg or lower; BP decline acceptable if systolic BP is over 120 mmHg. ACEi Angiotensin-converting enzyme inhibitor, ARB Angiotensin receptor blocker, UPC Urine protein:creatinine ratio (adapted from Brown and others 2013)

### Prognosis

Proteinuria has been shown to be a negative prognostic indicator in both dogs and cats with CKD in multiple studies. In people and dogs, reducing proteinuria has been shown to improve survival, delay disease progression and improve quality of life. In cats, multiple studies have concluded that the magnitude of proteinuria is inversely proportional to survival and that even mild proteinuria is strongly associated with, and predictive of, onset of azotaemia and progression of CKD. However, a survival benefit has not been shown in cats receiving therapy to reduce proteinuria.

### Conclusion

Management of proteinuria is primarily achieved by administering drugs that inhibit the RAAS system. Adjunctive treatments such as dietary therapy and n3 PUFA administration may also be beneficial in proteinuric patients with CKD. Approximately 50 per cent of dogs with glomerular disease may have an immune-mediated pathogenesis and immunosuppressive therapies may be indicated in these patients. Management of proteinuria should always be tailored to the individual patient and ongoing treatment should be based on regular assessment of clinical and laboratory parameters. Reducing proteinuria is an important therapeutic target with the aim of delaying progression of CKD and potentially improving survival.

### References

- Adams, L., Polzin, D., Osbourne, C. & O’Brien, T. (1992) Correlation of urine protein:creatinine ratio and twenty-four-hour urinary protein excretion in normal cats and cats with surgically induced chronic renal failure. *Journal of Veterinary Internal Medicine*, 6, 36-40
- Beatrice, L., Nizi, F., Callegari, D., Paltrinieri, S., Zini, E., DiPippo, P. & Zatelli, A. (2010) Comparison of urine protein-to-creatinine ratio in urine samples collected by cystocentesis versus free catch in dogs. *Journal of the American Veterinary Medical Association*, 236, 1221-1224
- Brown, S., Elliott, J., Francy, T., Polzin, D. & Vaden, S. (2013) Consensus recommendations for standard therapy of glomerular disease in dogs. *Journal of Veterinary Internal Medicine*, 27, 527-543
- Chakrabarti, S., Syne, H., Brown, C. & Elliott, J. (2012) Histomorphometry of feline chronic kidney disease and correlation with markers of renal dysfunction. *Veterinary Pathology*, 50, 147-155
- Cobrin, A., Blois, S., Kruth, S., Abrams-Ogg, A. & Dewey, C. (2013) Biomarkers in the assessment of acute and chronic kidney diseases in the dog and cat. *Journal of Small Animal Practice*, 54, 647-655
- Dibartola, S., Rutgers, H., Zack, P. & Tarr, M. (1987) Clinicopathologic findings associated with chronic renal disease in cats: 74 cases (1973-1984). *Journal of the American Veterinary Association*, 90, 1194-1202
- Finch, N. (2016) Measurement of glomerular filtration rate in cats. *Journal of Feline Medicine and Surgery*, 19, 116-121
- Grauer, G., Greco, D., Getzy, D., Cowgill, L., Vaden, S., Chew, D., Polzin, D. & Barsanti, J. (2000) Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. *Journal of Veterinary Internal Medicine*, 14, 526-533
- Grauer, G., Thomas, C. & Eicker, S. (1995) Estimation of quantitative proteinuria in the dog, using the urine protein-to-creatinine ratio from a random, voided sample. *American Journal of Veterinary Research*, 44, 2116-2119
- Jacob, F., Polzin, D., Osborne, C., Neaton, J., Kirk, C., Allen, T. & Swanson, L. (2000) Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. *Journal of the American Veterinary Medical Association*, 226, 393-400

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JENKINS, T., COLEMAN, A., SCHMIDT, C. & BROWN, S. (2015) Attenuation of the pressor response to exogenous angiotensin by angiotensin receptor blockers and benazepril hydrochloride in clinically normal cats. American Journal of Veterinary Research 76, 807-813.

JENSEN, J., HENK, R., BROWNFIELD, M. & ARMSTRONG, J. (1997) Plasma renin activity and angiotensin I and aldosterone concentrations in cats with hypertension associated with chronic renal disease. American Journal of Veterinary Research 58, 535-540.

JEPSON, R., BRODBELT, D., VALLANCE, C., SYME, H. & ELLIOTT, J. (2009) Evaluation of predictors of the development of azotaemia in cats. Journal of Veterinary Internal Medicine 23, 804-813.

LEVINE, D., ZHANG, D., HARRIS, T. & VADEN, S. (2010) The use of pooled vs serial urine samples to measure urine protein:creatinine ratios. Veterinary Clinical Pathology 39, 53-56.

LYON, S., SANDERSON, M., VADEN, S., LAPPIN, M., JENSEN, W. & GRAUER, G. (2010) Comparison of urine dipstick, sulfosalicylic acid, urine protein-to-creatinine ratio, and species-specific ELISA methods for detection of albumin in urine samples of cats and dogs. Journal of the American Veterinary Medical Association 236, 874-879.

MITANI, S., YABUKI, A., TANIGUCHI K. & YAMATO, O. (2013) Association between the intrarenal renin-angiotensin system and renal injury in chronic kidney disease of dogs and cats. Journal of Veterinary Medical Science 75, 127-133.

O'NEILL, D., CHURCH, D., MCGREEVY, P., THOMSON, P. & BRODBELT, D. (2014) Prevalence of disorders recorded in cats attending primary-care veterinary practices in England. Veterinary Journal 202, 284-291.

O'NEILL, D., ELLIOTT, J., CHURCH, D., MCGREEVY, P., THOMSON, P. & BRODBELT, D. (2013) Chronic kidney disease in dogs in UK veterinary practices: prevalence, risk factors, and survival. Journal of Veterinary Internal Medicine 27, 814-821.

PLANTINGA, E., EVERTS, H., KASTELEIN, A. & BEYNEN, A. (2005) Attenuation of the pressor response to exogenous angiotensin by angiotensin receptor blockers and benazepril hydrochloride in clinically normal cats. American Journal of Veterinary Research 76, 807-813.

PRESSLER, B., VADEN, S., GERBER, B., LANGSTON, C. & POLZIN, D. (2013) Consensus recommendations for the diagnostic investigation of dogs with suspected glomerular disease. Journal of Veterinary Internal Medicine 27, 555-559.

SEGEV, G., COWGILL, L., HEIENE, R., LABATO, M. & POLZIN, D. (2013) Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology. Journal of Veterinary Internal Medicine 27, 544-554.