

Chronic Kidney Disease

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OVERVIEW

Chronic kidney disease (CKD) is the most common kidney disease in dogs and cats. Regardless of the cause(s) of nephron loss, irreversible structural lesions characterize CKD. After correcting reversible primary diseases and/or prerenal or postrenal components of renal dysfunction, further improvement in kidney function should not be expected in patients with CKD, because compensatory and adaptive changes designed to sustain kidney function have largely already occurred. However, unless additional kidney injury occurs or CKD is very advanced, rapid deterioration of intrinsic kidney function is also unusual. The magnitude of kidney dysfunction typically remains stable or slowly declines over months to years.^{1,2} However, it may not be necessary for the disease process responsible for the initial kidney injury to persist for progressive dysfunction to occur. Therefore, irrespective of underlying etiopathogenesis, CKD is often described as irreversible and progressive.

Patients with CKD often survive for many months to years with a good quality of life. Although as yet no treatment can correct existing irreversible kidney lesions of CKD, the clinical and biochemical consequences of reduced kidney function can often be ameliorated by supportive and symptomatic therapy. In addition, therapy may be designed to interrupt mechanisms that contribute to the self-perpetuation of progressive CKD.

Chronic Kidney Disease – Defining the Syndrome

Kidney disease is the presence of functional or structural abnormalities in one or both kidneys. It is recognized by reduced kidney function or the presence of kidney damage. Kidney damage is defined as either: 1) microscopic or macroscopic renal pathology detected by kidney biopsy or direct visualization of the kidneys or 2) markers of renal damage detected by blood or urine tests or imaging studies (table 1).³ The severity and clinical implication of kidney disease varies greatly depending on the magnitude of kidney involvement. Kidney disease is staged (described below) to reflect these variations.

Table 1 – Markers of kidney damage*

Blood markers:

Elevated blood urea nitrogen concentration
Elevated serum creatinine concentration
Hyperphosphatemia
Hyperkalemia or hypokalemia
Metabolic acidosis
Hypoalbuminemia

Urine markers:

Impaired urine concentrating ability
Proteinuria
Cylinduria
Renal hematuria
Inappropriate urine pH
Inappropriate urine glucose concentration
Cystinuria

Imaging markers – abnormalities in kidney:

Size	Density
Shape	Number
Location	Mineralization

* Markers must be confirmed to be of renal origin to be evidence of kidney damage.

Chronic kidney disease (CKD) is defined as: 1) kidney damage that has existed for at least three months, with or without decreased glomerular filtration rate (GFR), or 2) a reduction in GFR by more than 50% from normal persisting for at least three months. A duration of at least 3 months is used as the benchmark criterion for confirming the diagnosis of CKD based on the observation that renal compensatory hypertrophy and improvement in renal function may continue for up to three months following acute loss of nephrons.

Terms and Concepts Related to Kidney Disease, Kidney Failure, and Uremia

Use of the terms *kidney disease*, *kidney insufficiency*, *kidney failure*, *azotemia*, and *uremia* as synonyms may result in misdiagnosis and formulation of inappropriate or even contraindicated therapy. It is recommended that the term kidney be used in preference to the term renal, because clients know what a kidney is, but may not know what a “renal” is. The descriptors kidney insufficiency and kidney failure have not been uniformly and adequately defined; therefore have been replaced by a CKD staging system proposed by the International Renal Interest Society (IRIS; www.iris-kidney.com).

Kidney disease may affect glomeruli, tubules, interstitial tissue, and/or vessels. Some kidney diseases may be associated with dysfunction (e.g., some forms of nephrogenic diabetes insipidus and some forms of renal tubular acidosis) or biochemical abnormalities (e.g. cystinuria) without detectable morphologic alterations. Others may be associated with morphologic kidney disease (anomalies, infections, endogenous or exogenous toxin-induced lesions, immune-mediated lesions, damage caused by hypercalcemia and other mineral imbalances, traumatic lesions) that affects one or both kidneys with variable effects on kidney function. The specific cause(s) of kidney disease(s) may or may not be known; however, quantitative information about kidney function (or dysfunction) is not defined or implied by the term kidney disease; the extent of functional derangement is defined by the staging system.

Azotemia is defined as an abnormal concentration of urea, creatinine, and other nonprotein nitrogenous substances in blood, plasma, or serum. Azotemia is a laboratory finding with several fundamentally different causes. Since nonprotein nitrogenous compounds (including urea and creatinine) are endogenous substances, abnormally elevated concentrations in serum may be caused by an increased rate of production (by the liver for urea; by muscles for creatinine), or by a decreased rate of loss (primarily by the kidneys). Because azotemia may be caused by factors that are not directly related to the urinary system and by abnormalities of the lower urinary tract not directly related to the kidney, *azotemia* should not be used as a synonym for kidney failure or uremia. Although the concentrations of serum urea nitrogen and creatinine are commonly used as crude indices of glomerular filtration rate, meaningful interpretation of these parameters depends on recognition and evaluation of prerenal, primary renal, and postrenal factors that may reduce glomerular filtration rate.

Uremia is defined as (1) abnormal quantities of urine constituents in blood caused by primary generalized kidney disease *and* (2) the polysystemic toxic syndrome which occurs as a result of abnormal kidney function. When the structural and functional integrity of both kidneys has been compromised to such a degree that polysystemic signs of kidney failure are clinically manifested, the relatively predictable symptom complex called *uremia* appears, regardless of underlying cause. In some instances, uremic crises may suddenly be precipitated by prerenal disorders or, less commonly, postrenal disorders in patients with previously compensated primary kidney failure. Uremia is characterized by multiple physiologic and metabolic alterations that result from impaired kidney function.

Staging Chronic Kidney Disease

Patients with CKD can be categorized into stages along a continuum of progressive CKD.⁴ The value of staging CKD is to facilitate application of appropriate clinical practice guidelines for diagnosis, prognosis and treatment. The International Renal Interest Society (IRIS) has proposed a 4 tier system for staging CKD in dogs and cats (tables 2 and 3). Although the specific values used to categorize patients with CKD into these stages are inherently arbitrary, staging is nonetheless useful for establishing prognosis and managing patients with CKD.

The stage of CKD is assigned based on the level of kidney function. While not the only kidney function, the level of GFR is accepted as the best measure of overall kidney function in health and disease.³ Unfortunately, limitations on specificity and sensitivity of serum creatinine concentration as an estimate of GFR can lead to misclassification. Ideally, two or more serum creatinine values obtained when the patient is fasted and well hydrated should be determined over several weeks to stage CKD. Further, variations between laboratories, patient-specific characteristics (e.g. breed, age, gender, body condition and lean body mass) and transient prerenal and postrenal events may influence serum creatinine values. Reduced muscle mass, a common manifestation of advanced CKD, may result in a substantial reduction in serum creatinine concentration relative to true GFR. Greyhounds reportedly have higher serum creatinine concentrations, presumably due to their athletic nature.⁵ Because of these variations, published reference ranges for serum creatinine are often exceedingly broad. Using the staging system described here, some patients classified as having mild renal azotemia (stage 2) may have serum creatinine values within published reference ranges. As a consequence, the patient’s overall clinical status should be considered when interpreting serum creatinine concentration and other laboratory tests and when planning patient management. By stating that stage 2 CKD in dogs begins at a serum creatinine concentration of 1.4 mg/dl and in cats 1.6 mg/dl, we

have essentially increased the sensitivity of serum creatinine as a diagnostic tool for CKD; however, the specificity of the test is somewhat reduced.

Table 2 – Stages of Chronic Kidney Disease in Dogs and Cats

Stage	Serum Creatinine Values (mg/dl)	
	Dogs	Cats
Stage 1	<1.4	<1.6
Stage 2	1.4-2.0	1.6-2.8
Stage 3	2.1-5.0	2.9-5.0
Stage 4	>5.0	>5.0

Table 3 – Relationship Between Clinical Abnormalities and CKD Stage

Clinical consequence	Most Likely
	Observed in Stage(s)
Polyuria, polydipsia	2-4
Proteinuria	1-4
Hypertension (and associated events)	1-4
Urinary tract infection	1-4
Nephroliths, ureteroliths	1-4
Decreased appetite	3,4
Weight Loss	3,4
Dehydration	3,4
Constipation	3,4
Hyperphosphatemia	3,4
Metabolic acidosis	3,4
Hypokalemia	3,4
Anemia	3,4
Uremic signs	4

Stage 1 CKD includes dogs and cats with CKD that are not azotemic, while stage 2 CKD includes dogs and cats that are mildly azotemic (tables 2 and 3). Patients in these stages of CKD typically do not have clinical signs of kidney dysfunction with the exception of polyuria and polydipsia. Occasionally cats with stage 2 CKD may have weight loss or selective appetites. However, patients may have clinical signs resulting from their kidney lesions (e.g. acute pyelonephritis, nephrolithiasis). Patients with marked proteinuria or systemic hypertension due to CKD may have clinical signs related to these aspects of CKD. Renal function is often stable or only very slowly progressive for an extended period in non-proteinuric, non-hypertensive dogs and cats with stages 1 and 2 CKD. However, when progression does occur in this group of patients, it may occur largely as a consequence of their primary CKD.⁴ Patients with stages 1 and 2 CKD should be evaluated with the goals of identifying and providing specific treatment for their primary CKD. In addition, renal function should be monitored to assess for possible progression of their CKD.

Patients with moderate azotemia are classified as stage 3 CKD. Patients in this stage may have clinical signs referable to their loss of kidney function; however, with appropriate treatment, they typically do not have clinical signs of overt uremia. Patients with stage 3 CKD may progress due to inherent mechanisms of spontaneous progression as well as their underlying CKD. Therefore, in addition to identifying and treating primary CKD, therapy designed to modify factors promoting progression of renal disease may be of benefit to these patients.

Stage 4 CKD includes dogs and cats with severe azotemia (serum creatinine values greater than 5.0 mg/dl). This stage is also called chronic kidney failure and is frequently associated with clinical signs that occur as a consequence of loss of kidney function. Diagnostic and therapeutic initiatives in this stage include those appropriate for stage 3 patients as well as therapy designed to prevent or ameliorate signs of uremia.

It is useful therapeutically and prognostically to further subclassify patients according to their urine protein loss and systemic blood pressure. Proteinuria and hypertension may influence prognosis and may be amenable to therapeutic intervention. Classification of patients as proteinuric necessitates eliminating hemorrhage and/or inflammation as the cause for proteinuria and determination of the urine protein-to-creatinine ratio. Further, proteinuria should be shown to be persistent by reexamining the UPC ratio 2 to 3 times over at least one or two months. For both dogs and cats, patients are classified as proteinuric (P) when their protein-to-creatinine ratio exceeds 0.5 and 0.4, respectively (table 4). Patients with borderline proteinuria should be re-evaluated after two

months to reassess classification. In some patients, classification of proteinuria may change due to the natural course of their disease or in response to therapy.

Table 4 – Classification of Proteinuria by Urine Protein:Creatinine Ratio*

Classification	Urine Protein:Creatinine Ratio	
	Dogs	Cats
Proteinuric (P)	>0.5	>0.4
Borderline proteinuric (BP)	0.2-0.5	0.2-0.4
Non-proteinuric (NP)	<0.2	<0.2

* Based on ACVIM Consensus Statement on Proteinuria (Lees, 2005)

The lack of consensus as to what blood pressure values constitute hypertension in dogs and cats obfuscates any classification of patients as to their hypertension status. It is likely that “normal” blood pressure values for dogs and cats will change as more data becomes available. A 2003 ACVIM Hypertension Consensus Group has proposed the following hypertension classification system for dogs and cats. The same system is advocated by IRIS.

Table 5 - Blood Pressure Risk Groups for Dogs and Cats*

Risk Level (Designator)	Systolic Blood Pressure Range
Minimal (Mn)	<150/95 mmHg
Low (L)	150/95 to 159/99 mmHg
Moderate (M)	160/100 to 179/119 mmHg
Severe (S)	>180/120 mmHg

* The designator **complicated (c)** is added to the risk level designator when evidence of end-organ hypertensive injury is present in the patient; the designator **non-complicated (nc)** is added to the risk level designator when no evidence of hypertensive injury is evident in the patient.

Causes of Chronic Kidney Disease

Chronic kidney disease may be initiated by a variety of different familial, congenital, or acquired diseases. In a study of biopsy findings in 37 dogs with primary renal azotemia, chronic tubulointerstitial nephritis was observed in 58%, glomerulonephropathy occurred in 28%, and amyloidosis was observed in 6%.¹¹ In cats, tubulointerstitial nephritis was observed in 70%, glomerulonephropathy occurred in 15%, and lymphoma was observed in 11%, and amyloidosis occurred in 2%. Unfortunately, the initiating cause(s) of CKD often cannot be identified at the time of diagnosis. The initiating causes of diseases thought to originate in the tubulointerstitium have been especially elusive. Although bacteria can cause tubulointerstitial lesions, in our experience bacterial UTI appears more often to be a sequelae of the immunocompromised condition associated with CKD than the cause. In one retrospective study of CKD cats, bacterial UTI was detected in 20% of the patients.⁹ Glomerulonephropathies have been linked to a variety of neoplastic, metabolic, and infectious and noninfectious inflammatory processes.¹² Periodontal disease has been linked to microscopic renal lesions in dogs, but a cause and effect relationship has not been established.¹³ Feline immunodeficiency virus (FIV) has been linked to renal disease in cats, although few cats with CKD are FIV positive.^{14,15} Subcutaneous administration of feline herpesvirus 1, calicivirus, and panleukopenia virus vaccines grown in feline tissue culture systems to kittens have been shown to induce production of anti-feline renal tissue antibodies in serum (Lappin et al). This observation prompts the question as to whether repeated vaccinations play a role in development of chronic renal disease.

Difficulty in detecting the inciting cause of CKD is associated with three phenomena related to the evolution of progressive renal diseases. First, various components of nephrons (glomeruli, peritubular capillaries, tubules, and interstitial tissue) are functionally interdependent. Second, the functional and morphologic responses of tissues comprising the kidneys to different etiologic agents is limited number. Third, after maturation of nephrons, which occurs at approximately one month of age, new nephrons cannot be formed to replace others irreversibly destroyed by disease. Progressive irreversible lesions initially localized to one portion of the nephron are eventually responsible for development of lesions in the remaining but initially unaffected portions of nephrons. For example, progressive lesions (such as amyloid or immune complex disease) confined initially to glomeruli will subsequently decrease peritubular capillary perfusion. Reduced peritubular capillary perfusion will in turn result in tubular

epithelial cell atrophy, degeneration, and necrosis. Recent studies suggest that tubular epithelial cells may also be damaged as a consequence of glomerular proteinuria. Secondary tubular damage may be related, at least in part, to excessive tubular cell uptake of filtered proteins or protein-bound substances.¹⁶ Studies showing that the rate of disease progression correlates with the amount of proteinuria, and that therapy designed to reduce proteinuria retards progression, support the concept that glomerular proteinuria damages tubules. These processes are amplified by the secondary processes of inflammation and fibrosis. An influx of T-cells and macrophages into the interstitium may cause further tubular injury, and macrophages in particular produce profibrotic substances. Ultimately nephron destruction initiated by glomerular disease will simulate repair by substitution of functioning nephrons with nonfunctional connective tissue.

Similarly, generalized progressive interstitial disease initially caused by bacteria eventually destroys tubules and glomeruli and stimulates inflammation and fibrosis. Thus, irrespective of the initiating cause, replacement of the majority of the damaged nephrons with collagenous connective tissue results in overall reduction in kidney size and impaired renal function.

Because of the structural and functional interdependence of various components of nephrons, differentiation of different progressive renal diseases that have reached an advance stage is often difficult. Functional and structural changes prominent during earlier phases of progressive generalized renal diseases may permit identification of a specific cause and/or localization of the initial lesion to glomeruli, tubules, interstitium, or vessels. With time, however, destructive changes of varying severity (atrophy, inflammation, fibrosis, and mineralization of diseased nephrons), superimposed on compensatory and adaptive morphologic and functional of remaining partially and totally viable nephrons, provide a functional and morphologic similarity to the findings associated with these diseases.

Despite the irreversibility of generalized renal lesions associated with CKD, it is important to formulate diagnostic plans to try to identify the underlying cause and to determine if it is still active. Although specific therapy directed at eliminating or controlling the primary cause will not substantially alter existing renal lesions, it is important in context of minimizing further nephron damage. Renal diseases potentially amenable to specific therapy include bacterial pyelonephritis, chronic urine outflow obstruction, nephrolithiasis, renal lymphoma (particularly in cats), hypercalcemic nephropathy, and some immune-mediated diseases.

Acute onset of non-urinary disorders, especially those that interfere with compensatory polydipsia, may precipitate a uremic crisis in patients with asymptomatic CKD (so-called “acute-on-chronic” kidney disease). However, if acute decompensation of CKD has been caused by reversible factors, correction of them will often result in recompensation of the CKD.

Prognosis of CKD

With appropriate therapy, cats with stages 2 and 3 CKD commonly survive 1 to 3 years, while dogs with stage 3 CKD typically survive about 1 to 2 years. However, many survive much longer. A host of factors influence prognosis of CKD, both favorably and unfavorably. Included among these factors are the quality of medical care provided to the patient, the degree of interaction between the veterinarian and pet owner, and the level of owner commitment. The estimate of prognosis often influences the owner’s decisions about treatment options in complying with recommendations for management of the patient. A comprehensive evaluation of the patient is the best way to establish a reasonably accurate prognosis.

Prognosis for patients with CKD is usually subcategorized according to the probability of immediate survival (short-term prognosis) and survival over the subsequent months to years (long-term prognosis). A guarded prognosis indicates that the chances for recovery are unpredictable. Fair, good, or excellent prognoses indicate varying degrees of probable recovery, while poor or grave prognoses indicate that recovery is improbable or hopeless. Loss of renal function is irreversible in patients with CKD. In this context, recovery refers to improvement of biochemical deficits and excesses and amelioration of clinical signs rather than recovery of renal function.

Factors to be considered in establishing meaningful prognoses for patients with CKD include; 1) the nature of the primary renal disease, 2) severity and duration of clinical signs and complications of uremia, 3) probability of improving renal function (reversibility, primarily of prerenal, postrenal, and newly acquired primary renal conditions), 4) severity of intrinsic renal functional impairment, 5) rate of progression of renal dysfunction with or without therapy, 6) age of the patient. In addition, blood pressure and the magnitude of proteinuria are risk factors influencing prognosis in dogs with CKD.¹⁷

Severity of uremic signs is often a relatively good predictor of short-term prognosis. Patients with stable CKD without clinical signs of uremia usually have a good short-term prognosis. Untreated patients with severe

clinical signs of uremia typically have a guarded to poor short-term prognosis. However, it is best to determine whether renal function and clinical signs can be therapeutically improved in such cases before establishing the short-term prognosis. A uremic crisis often occurs in patients with CKD as a consequence of superimposed acute kidney injury (AKI) or prerenal or postrenal conditions (so-called acute-on-chronic uremic crisis). Although CKD is an irreversible condition, improvement of renal function is potentially possible when uremia results from the sum effects of CKD and a potentially reversible cause of azotemia. If treatment results in improved renal function and ameliorates clinical signs of uremia, the short-term prognosis often becomes guarded to good.

Severity of renal dysfunction as determined by serum creatinine concentration or measurement of GFR provides a less accurate means of assessing short-term prognosis than does the clinical condition of the patient. The relationship between magnitude of renal dysfunction and clinical signs of uremia is often unpredictable. Therefore, short-term prognosis should not be established on the basis of a single measurement of the severity of renal function. In addition, a single determination of renal function is unreliable as an index of the potential for improvement in renal function,

Assessment of the severity of renal dysfunction is typically more useful in establishing long-term prognoses. In general, severe renal dysfunction is associated with shorter long-term survival and, often, a lower quality of life. This generalization is supported by findings of a recent study of cats with spontaneous CKD.² For cats with CKD without apparent clinical signs and having a mean plasma creatinine concentration of 2.6 mg/dl, mean survival was 397 days. For cats with CKD with one or more clinical signs attributable to CKD and a mean plasma creatinine concentration of 3.6 mg/dl, mean survival was 313 days. Uremic cats with a mean plasma creatinine concentration of 10.3 mg/dl survived less than 3 days. However, in a recent clinical trial in dogs with spontaneous CKD, mean serum creatinine concentration did not appear to influence survival when dogs were fed a renal diet.¹⁸ Median survival for 21 dogs with a mean serum creatinine concentration of 3.3 mg/dl was 615 days. Median survival for a subpopulation of dogs in this group with serum creatinine values between 2.0 and 3.1 mg/dl was also 615 days. However, among 17 dogs fed a maintenance diet in this study, median survival for dogs with a mean serum creatinine of 3.7 mg/dl was 252 days, while survival for the subpopulation with serum creatinine values between 2.0 and 3.1 mg/dl was 461 days. In summary, the prognosis should be established in the context of the clinical condition of the patient, rate of progression of renal dysfunction, response to therapy, cause of the underlying renal disease (if known), and other complicating factors (e.g. urinary tract infection, nephrotic syndrome, etc.).

Systemic hypertension has been linked to progression of CKD in humans for decades.¹⁹ Increasing systolic blood pressure has been recently increased risk of uremic crises and death been shown to be associated with in dogs with spontaneous CKD.¹⁷ In this study, systolic blood pressure values determined at the time of initial patient evaluation was compared to long-term outcome. Increased risk of developing a uremic crisis and of death was observed in the patients with the highest blood pressure values. In addition, a greater decline in renal function over time was observed in these dogs. While this study was not designed to prove a cause-and-effect relationship between hypertension and progressive renal disease, it does indicate that initial blood pressure values should be considered in formulating a prognosis for dogs with CKD. The prognostic significance of blood pressure values in cats with CKD has yet to be established.

Results of a clinical trial from the University of Minnesota Veterinary Medical Center revealed that proteinuria may be a risk factor for uremia and death in dogs with spontaneous CKD.(Jacob et al 2004) In this study, the risk of death associated with CKD increased by 60% for each unit of urine protein-to-creatinine ratio above 1.0. Whether proteinuria conferred this adverse risk as an independent mediator of renal injury or as a consequence of the biological behavior of glomerular diseases is unclear. In dogs, glomerulopathies have been associated with poor long-term prognoses.¹² This may be related to the observation that proteinuria has been implicated in promoting progressive renal injury.²⁰ Therapeutic amelioration of proteinuria using angiotensin converting enzyme inhibitors may stabilize renal function in humans and dogs with glomerular disease, further suggesting a likely role for proteinuria in the progression of CKD.²¹ A similar relationship between proteinuria and progression of CKD has been observed in cats. (Syme, 2003)

Compared to the rate of progression of CKD in middle aged to older dogs with acquired renal disease, CKD often progresses at a much slower rate in dogs with congenital and familial nephropathies such as renal dysplasia. A comparably slower rate of progression has also been observed in young dogs with acquired CKD (e.g. following nephrotoxin exposure). Many of these patients appear remarkably resistant to developing clinical signs of uremia despite substantial elevations in serum creatinine and urea nitrogen concentrations.

CLINICAL CONSEQUENCES OF CHRONIC KIDNEY DISEASE

Uremia

Uremia is the clinical state toward which all progressive, generalized renal diseases ultimately converge. Diverse clinical and laboratory findings characterize uremia and emphasize the polysystemic nature of CKD. The term uremia was adopted originally because of the presumption that all of the abnormalities result from retention in the blood of end-products of metabolism normally excreted in the urine. However, uremia involves more than renal excretory failure alone. A variety of metabolic and endocrine functions normally performed by the kidney are also impaired, resulting in anemia; malnutrition; impaired metabolism of carbohydrates, fats, and proteins; defective utilization of energy; alterations in immunity and metabolic bone disease.

Urea, once thought to be “the” uremic toxin, is not a major cause of uremic toxicity, although it may contribute to some of the clinical abnormalities, including anorexia, malaise, and vomiting. Numerous nitrogenous compounds with a molecular mass of 500 to 12,000 Daltons (so-called middle molecules) are retained in CKD and appear to contribute to morbidity and mortality in uremic subjects.²² In addition to impaired excretion, many middle-sized molecules along with various cytokines and growth factors accumulate in CKD because the kidney’s capacity for catabolizing many substances is also impaired. Further, plasma levels of many polypeptide hormones, including parathyroid hormone (PTH), insulin, glucagon, luteinizing hormone, and prolactin, increase in patients with CKD because of impaired renal catabolism as well as enhanced glandular secretion.

Gastrointestinal Consequences

Gastrointestinal complications are common and prominent clinical signs of uremia. Anorexia and weight loss are non-specific findings that may precede other signs of uremia in dogs and cats. The patient's appetite may be selective for certain foods, and it may wax and wane throughout the day. Factors promoting weight loss and malnutrition include anorexia, nausea, vomiting and the subsequent reduction in nutrient intake, hormonal and metabolic derangements, and catabolic factors related to uremia, particularly acidosis.

Anorexia appears to be multifactorial in origin. Recent research, using a rodent model, has suggested that an “anorectic factor” in the plasma of uremic patients that can suppress appetite.²³ It appears to be a middle molecule in size and may be a peptide. Elevated serum leptin concentrations have also been implicated as a factor contributing to anorexia.²⁴

Vomiting is a frequent, but inconsistent finding in uremia. It results from the effects of as yet unidentified uremic toxins on the medullary emetic chemoreceptor trigger zone and from uremic gastroenteritis. The severity of vomiting correlates crudely with the magnitude of azotemia. Because uremic gastritis may be ulcerative, hematemesis may occur. Vomiting may be a more frequent complaint in uremic dogs than cats. Nonetheless, vomiting is reportedly found in one quarter to one third of cats with clinical signs of uremia.² Vomiting may impair compensatory polydipsia enhancing the risk of dehydration and exacerbating prerenal azotemia and clinical signs of uremia.

Uremic gastropathy is characterized microscopically by glandular atrophy, edema of the lamina propria, mast cell infiltration, fibroplasia, mineralization, and submucosal arteritis. Elevated gastrin levels have been implicated in development of uremic gastropathy.²⁵ Gastrin induces gastric acid secretion directly by stimulating receptors located on gastric parietal cells as well as by increasing histamine release from mast cells in the gastric mucosa. Enhanced histamine release may also promote gastrointestinal ulceration and ischemic necrosis of the mucosa through a vascular mechanism characterized by small venule and capillary dilatation, increased endothelial permeability, and intravascular thrombosis.²⁶ Because up to 40% of the circulating gastrin is metabolized by the kidneys, reduced renal function may promote hypergastrinemia. Elevated gastrin levels have been documented in cats with spontaneous CKD.²⁵ Although the prevalence of hypergastrinemia appeared to increase as renal dysfunction become more severe, there was great variability of gastrin levels among cats with similar degrees of renal dysfunction, suggesting that additional factors in addition to the degree of renal impairment likely affect serum gastrin levels in CKD.

Gastrin-induced gastric hyperacidity may lead to uremic gastritis, gastrointestinal hemorrhage, and nausea and vomiting. Back diffusion of hydrochloric acid and pepsin into the stomach wall may lead to hemorrhage, inflammation, and release of histamine from mast cells. Thus, the cycle may be perpetuated as mast-cell derived histamine causes further stimulation of parietal cells to produce hydrogen ions. However, gastric hyperacidity is not universally found with uremic gastritis. Some human uremic patients have hypochlorhydria. Thus, hypergastrinemia is not the only reason for uremic gastritis. Other factors implicated in the genesis of uremic gastropathy include: psychological stress related to illness, an increase in proton back-diffusion caused by high urea levels, erosions caused by ammonia liberated by bacterial urease acting on urea, ischemia caused by vascular

lesions, decreased concentration and turnover of gastric mucous, and biliary reflux due to pyloric incompetence (which may be an indirect consequence of elevated gastrin levels).

In a recent study of 80 cats with spontaneous CKD, dysphagia and oral discomfort occurred in 7.7% of uremic cats and 38.5% of cats with end-stage CKD.² Periodontal disease was observed in 30.8% of uremic and 34.6% of end-stage CKD cats in the same study. Halitosis was reported in 7.7% of cats in both groups. Moderate to severe CKD may result in uremic stomatitis characterized by oral ulcerations (particularly located on the buccal mucosa and tongue), brownish discoloration of the dorsal surface of the tongue, necrosis and sloughing of the anterior portion of the tongue (associated with fibrinoid necrosis and arteritis), and uriniferous breath. The mucous membranes may also become dry (xerostomia). Degradation of urea to ammonia by bacterial urease may contribute to many of these signs. Poor oral hygiene and dental disease may exacerbate the onset and severity of uremic stomatitis.

Uremic enterocolitis, manifested as diarrhea, may occur in dogs and cats with severe uremia, but it is typically less dramatic and less common than uremic gastritis. Owners of 80 cats with spontaneous CKD did not report diarrhea.² However, when present, uremic enterocolitis is often hemorrhagic. Considerable gastrointestinal hemorrhage may initially escape clinical detection. Intussusception may occasionally complicate uremic enterocolitis. Constipation is a relatively common complication of CKD, particularly in cats. It appears to be primarily a manifestation of dehydration, but can occur as a complication of intestinal phosphate binding agents.

Impaired Urine Concentrating Ability, Polyuria, Polydipsia, and Nocturia

Among the earliest and most common clinical manifestations of CKD is onset of polyuria, polydipsia, and sometimes nocturia due to reduced urine concentrating ability. Polydipsia was the single most commonly reported clinical sign reported in a study of 80 cats with CKD. Cat owners recognized polydipsia over twice as often as polyuria. Although urine specific gravity values of cats in stages 2, 3 and 4 CKD are usually below 1.035, the authors have seen cats that have remained persistently (up to 18 months) azotemic prior to losing adequate concentrating ability (i.e. specific gravity > 1.040).

A decrease in adequate urine concentrating ability results from several factors including: increased solute load per surviving nephron (solute diuresis), disruption of the renal medullary architecture and counter-current multiplier system by disease, and primary impairment in renal responsiveness to antidiuretic hormone. Loss of renal responsiveness to antidiuretic hormone may result from an increase in distal renal tubular flow rate, which limits equilibration of tubular fluid with the hypertonic medullary interstitium. Additionally, ADH-stimulated adenylyl cyclase activity and water permeability in the distal nephron may be impaired in uremia.²⁷ Polydipsia is of course a compensatory response to polyuria. If fluid intake fails to keep pace with urinary fluid losses, dehydration will ensue because of the inability to conserve water by concentrating urine. Dehydration subsequent to inadequate fluid intake is a common problem in cats with CKD.

Arterial Hypertension and Cardiovascular Consequences

Hypertension may be either a cause or consequence of CKD. When present, it may adversely affect long-term prognosis.¹⁷ It is a common complications of CKD, reportedly occurring in up to 66% of cats with CKD.²⁸ Although one recent study suggested that hypertension may be unusual in dogs with CKD,²⁹ other studies have reported incidences of from 30 to 93% of dogs with CKD.^{17,29} Dogs with glomerular diseases are at increased risk for hypertension.

Neuromuscular Consequences

ENCEPHALOPATHIES AND NEUROPATHIES

Metabolic encephalopathies and peripheral neuropathies may occur in dogs and cats with uremia.^{30,31} It is reported that as many as 65% of dogs and cats with primary renal insufficiency/failure have neurological manifestations. Of dogs with neurological signs, altered consciousness (31% of patients) and seizures (29% of patients) were the most common signs.³¹ In our experience, acute onset of altered mentation is an important neurological finding in dogs and cats with CKD that typically heralds a poor short-term prognosis. Other common signs include limb weakness, ataxia and tremors. Patients may develop what has been described as the “twitch-convulsive” state wherein there is the simultaneous combination of tremor, myoclonus, and seizures. In advanced CKD, patients may have neurologic signs that are cyclical and episodic, varying from day to day. The severity and rate of progression of neurological signs appears to vary directly with the rapidity with which CKD develops.

The pathogenesis of uremic neurological signs remains unclear, but important roles for parathyroid hormone and the uremic environment are suspected.³⁰ Both the sodium potassium adenosine triphosphate pump and several of the calcium pumps are altered in uremia. Alterations in the calcium pumps have been thought to be due at least in part to PTH acting through monophosphate-independent pathways. Calcium pumps are particularly suspected of playing a role in uremic encephalopathy because they mediate neurotransmitter release and information

transfer at nerve terminals. Clinical signs of tremors, myoclonus, and tetany may develop due to hypocalcemia. Arterial hypertension may also lead to neurologic signs in patients with otherwise well-controlled CKD. Clinical signs are acute in onset and may include seizures, behavioral changes, dementia, isolated cranial nerve deficits, and death. In our experience, many of the patients with acute onset of neurologic signs also had hypertension.

Imbalances of neurotransmitter amino acids within the brain have also been implicated in uremic encephalopathy. Analysis of cerebrospinal fluid in humans with uremic encephalopathy has shown decreased levels of glutamine and GABA, and increased levels of glycine, dopamine, and serotonin.

MYOPATHIES

Hypokalemic polymyopathy is occasionally observed in association with CKD, primarily in cats. Because of the impact of potassium on resting cell membrane potentials, potassium imbalances typically manifest clinically as neuromuscular dysfunction. Hypokalemia increases the magnitude (i.e. increases electronegativity) of the resting potential, thereby hyperpolarizing the cell membrane making it less sensitive to exciting stimuli. The cardinal and most dramatic sign of hypokalemia, regardless of cause, is generalized muscle weakness. In hypokalemic polymyopathy, muscle weakness and pain present clinically as cervical ventroflexion and a stiff, stilted gait.³² Mild cardiac rhythm disturbances may also occur. Serum creatinine kinase and other muscle enzyme activities may be elevated, and in severe instances, rhabdomyolysis may occur.

Muscle dysfunction unrelated to serum potassium concentrations may also occur in uremia. In humans with CKD, accumulation of a dialyzable uremic toxin derived from dietary protein has been shown to promote abnormalities in sarcolemma ion flux leading to reduced muscle membrane potential.

Hematological Consequences

ANEMIA

The anemia of CKD is usually characterized by normochromic and normocytic red blood cells. There is usually hypoplasia of the erythroid precursors in the bone marrow with little or no interference with normal leukopoiesis and megakaryocytopoiesis. On blood smears, spiculed and deformed red cells (burr cells or echinocytes) may be noted. Although affected by the patient's age, species, specific renal diagnosis, and concurrent diseases, the severity and progression of the anemia correlates with the degree of CKD and worsens with progressive CKD in both dogs and cats.³³

The hematocrit may become profoundly low. At these low hematocrits, compensatory mechanisms such as increased levels of 2,3 DPG, lowered peripheral vascular resistance and an elevated cardiac output (in the absence of previous cardiac disease) help maintain tissue oxygenation. Clinical signs of anemia include pallor of the mucous membranes, fatigue, listlessness, lethargy, weakness, and anorexia.

Anemia in patients with CKD is multifactorial and may be exacerbated by concurrent illness. Although experimental and clinical evidence exists for the supporting roles of shortened red cell life span, nutritional abnormalities, erythropoietic inhibitor substances in uremic plasma, blood loss, and myelofibrosis, erythropoietin deficiency has clearly emerged as the principal cause of anemia in humans and animals with CKD. The renal peritubular capillary endothelial cells are the major source of erythropoietin synthesis. It may also be produced by renal interstitial fibroblasts. The kidneys synthesize erythropoietin on demand in response to intrarenal tissue hypoxia due either to decreased oxygen carrying capacity (anemia) or decreased oxygen content (hypoxia). Many CKD patients have a relative, rather than absolute, erythropoietin deficiency in that plasma levels exceed the normal range.³⁴ However, when compared with equivalently anemic but non-uremic patients, plasma erythropoietin concentrations are lower. Anemic CKD cats have been reported to have plasma erythropoietin concentrations similar to normal cats.³⁵ Erythropoietin deficiency of CKD has been hypothesized to result from decreased renal mass resulting in an insufficient cellular capacity for new hormone synthesis.

Other clinically important causes for anemia in dogs and cats with CKD are iron deficiency and chronic gastrointestinal blood loss. In most patients, iron deficiency can only be detected by measuring serum iron, staining bone marrow biopsy samples for iron content, or through response to iron supplementation. Chronic gastrointestinal hemorrhage may occur even in the absence of characteristic color changes in the feces. It can be suspected on the basis of a hematocrit level that is unexpectedly low relative to the magnitude of renal dysfunction, and an elevation in the serum urea nitrogen to serum creatinine ratio.

HEMORRHAGIC CONSEQUENCES OF UREMIA

Uremia may be associated with a hemorrhagic diathesis that is characterized by as bruising, gastrointestinal hemorrhage with hematemesis or melena, bleeding from the gums, or hemorrhage subsequent to venipuncture. Gastrointestinal hemorrhage can be an important route of blood loss leading to anemia and exacerbating azotemia and uremia. In CKD, bleeding results from an acquired qualitative platelet defect, abnormalities in the interaction of platelets and the vessel wall, and biochemical and rheologic abnormalities in the blood itself.³⁶ Uremic platelet dysfunction appears to be multifactorial in origin. The platelet count is usually within the normal range or mildly

decreased. Abnormal platelet aggregability, diminished thromboxane-A₂ production, abnormal intracellular calcium mobilization, and increased intracellular cAMP have been described in uremic platelets.³⁶ Abnormal glycoprotein function may impair platelet adhesiveness to the subendothelium. In addition, uremia may be associated with increased release of prostacyclin and nitric oxide, which may also impair adhesion of platelets to the endothelium. The largest polymers of von Willebrand's factor, which predominate in the platelet adhesion process, are decreased in uremia. Uremic toxins have also been implicated in impairing platelet function. For example, elevated levels of plasma guanidinosuccinic acid, interfere with activation of platelet factor III by ADP, thus leading to abnormal platelet function. Administration of desmopressin (DDAVP) has been shown to shorten bleeding times and improve clinical bleeding in uremic humans.³⁶ DDAVP is thought to stimulate release of large multimeric von Willebrand's factor complexes from endothelial cells and platelets. Unfortunately, development of tachyphylaxis often limits usefulness of DDAVP after 2 or 3 doses. Alternative therapies have included administration of cryoprecipitates or conjugated estrogens, which may have similar effects. Increasing hematocrit values to above 30 by transfusion or administration of erythropoietin has also been shown to improve bleeding times in humans. Increasing hematocrit may improve bleeding times by a rheological effect or by increasing hemoglobin concentrations which may in turn inactivate the platelet-inhibiting effects of nitric oxide.

Renal Secondary Hyperparathyroidism

INCIDENCE AND PATHOPHYSIOLOGY

In a recent study of cats with spontaneous CKD, the overall prevalence of renal secondary hyperparathyroidism was 84%.³⁷ Hyperparathyroidism occurred in 100% of cats with end-stage CKD and 47% of asymptomatic cats with only biochemical evidence of CKD. Hyperparathyroidism was even detected in some cats with normal serum calcium and phosphorous concentrations. Plasma PTH concentrations have been reported to increase as serum creatinine concentrations increase.³⁸

The pathogenesis of hyperparathyroidism in CKD is multifactorial. Renal secondary hyperparathyroidism occurs in association with phosphorous retention, hyperphosphatemia, low circulating 1,25-dihydroxyvitamin D (calcitriol) levels, reduced blood ionized calcium concentration, and skeletal resistance to the calcemic action of PTH. However, in early to moderate CKD, it is difficult to dissect out the specific factors responsible for hyperparathyroidism because the increase in PTH serves to prevent hypocalcemia, hyperphosphatemia, and the decrease in calcitriol formation.³⁹ Phosphorous retention and hyperparathyroidism develop early in CKD while serum calcium and phosphorus concentrations remain within normal limits.⁴⁰ Phosphorous retention is intimately related to development of secondary hyperparathyroidism.^{41,42}

Relative or absolute deficiency of calcitriol has been hypothesized to play a pivotal role in development of renal secondary hyperparathyroidism.⁴³ Calcitriol, the most active form of vitamin D, is formed by 1 α -hydroxylation of 25-hydroxycholecalciferol in renal tubular cells. Parathyroid hormone promotes renal 1 α -hydroxylase activity and formation of calcitriol. In turn, calcitriol limits PTH synthesis by feedback inhibition. Phosphorous retention inhibits renal 1 α -hydroxylase activity. Early in the course of CKD, the inhibitory effects of phosphorous retention on renal tubular 1 α -hydroxylase activity limits calcitriol production. Because calcitriol normally inhibits PTH synthesis, reduced calcitriol synthesis promotes renal secondary hyperparathyroidism. Initially, the resultant hyperparathyroidism increases 1 α -hydroxylase activity despite continued phosphorous retention, thereby restoring calcitriol production toward normal. However, normalization of calcitriol production occurs at the expense of persistently elevated plasma PTH activities - a classic example of the "trade-off hypothesis." As CKD progresses, loss of viable renal tubular cells ultimately limits renal calcitriol synthetic capacity and calcitriol levels subsequently remain low. Deficiency of calcitriol leads to skeletal resistance to the action of PTH and elevates the set-point for calcium-induced suppression of PTH secretion. Skeletal resistance to PTH limits skeletal release of calcium, while elevating the set-point for PTH secretion allows hyperparathyroidism to persist even when plasma ionized calcium concentrations are normal or elevated.^{38,43}

Recent evidence suggests that phosphorous retention may also play a primary role in promoting hyperparathyroidism. Phosphorous has been shown to stimulate PTH secretion in parathyroid cultures.⁴⁴ Further, phosphorous restriction in dogs and humans with CKD has been shown to decrease PTH secretion without changing serum calcitriol levels.^{45,46} In untreated human patients with mild to moderate CKD (serum creatinine concentration \leq 3.0 mg/dl), serum phosphorous concentrations correlated directly with PTH, independent of serum calcium and 1,25-dihydroxyvitamin D levels.⁴⁷ Interestingly, this correlation was present despite the fact that most patients had serum phosphorous concentrations within the normal range. Notably, in both humans and cats, overt hyperphosphatemia may not be a prerequisite for phosphorous to have an effect on PTH secretion.^{37,47} It has been suggested that high phosphorous intake may accentuate uremia-induced abnormal phosphorous metabolism causing increased parathyroid cell phosphorous concentration.⁴⁷ In vitro studies have suggested that parathyroid glands

exposed to elevated phosphorous levels respond by increasing PTH secretion.⁴⁴ Reduced 1,25-dihydroxycholecalciferol may have a permissive effect and/or an additional direct effect on PTH secretion in this setting.⁴⁷

In more advanced CKD, only serum calcium concentration correlated with serum PTH activity.⁴⁷ Impaired intestinal absorption of calcium due to low serum calcitriol levels likely plays an important role in hyperparathyroidism in these advanced CKD patients. Blood ionized calcium concentrations are often reduced in cats with spontaneous CKD; in one study, over 50% of cats with advanced end-stage CKD were hypocalcemic.³⁷

CLINICAL CONSEQUENCES

Although renal secondary hyperparathyroidism and renal osteodystrophy, are well documented effects of CKD, clinical signs associated with renal osteodystrophy are uncommon in dogs and cats. In dogs, it most often occurs in immature patients, presumably because metabolically active growing bone is more susceptible to the adverse effects of hyperparathyroidism. For unexplained reasons, bones of the skull and mandible may be the most severely affected and may become so demineralized that the teeth become moveable and fibrous changes are obvious, particularly in the maxilla. Marked proliferation of connective tissue associated with the maxilla may cause distortion of the face. Jaw fractures can occur but are uncommon. Other possible but uncommon clinical manifestations of severe renal osteodystrophy include, cystic bone lesions, bone pain, and growth retardation.

Although excessive levels of PTH affect bones and kidneys, it affects the function of other organs and tissues, including brain, heart, smooth muscles, lungs, erythrocytes, lymphocytes, pancreas, adrenal glands, and testes as well.⁴⁸ Toxicity of PTH appears to be mediated through enhanced entry of calcium into cells with PTH or PTH2 membrane receptors. Sustained PTH-mediated calcium entry leads to inhibition of mitochondrial oxidation and production of ATP. Extrusion of calcium from cells is reduced because of the impairment in ATP production and disruption of the sodium-calcium exchanger. Persistently increased basal cytosolic calcium levels promote cellular dysfunction and death.³⁸

Potential non-skeletal clinical consequences of hyperparathyroidism include mental dullness and lethargy, weakness, anorexia, and an increased incidence of infections due to immunodeficiency.³⁸ Hyperparathyroid-induced cellular dysfunction may lead to carbohydrate intolerance, platelet dysfunction, impaired cardiac and skeletal muscle function (due to impaired mitochondrial energy metabolism and myofiber mineralization), inhibition of erythropoiesis, altered red cell osmotic resistance, altered B cell proliferation, synaptosome and T-cell dysfunction, and defects in fatty acid metabolism.^{38,49} Excess PTH levels may also promote nephrocalcinosis and consequent progressive loss of renal function.³⁸

Renal secondary hyperparathyroidism may be associated with substantial enlargement of the parathyroid glands. This finding may be of clinical importance in cats because of frequent coincident hyperthyroidism that may be suggested by the presence of a thyroid nodule palpable in the cervical region. In a recent report, hyperplastic parathyroid glands were palpable as paratracheal masses in 11 of 80 cats with spontaneous CKD.² Care should be taken to confirm hyperthyroidism prior to treatment as both hyperparathyroidism and hyperthyroidism can lead to paratracheal masses.

Plasma PTH concentrations should be determined by methods that measure intact PTH using a two-site immunoradiometric or immunochemiluminometric assay. The two-site method utilizes antibodies directed against two different regions of the intact PTH molecule. A commercially available two-site immunoradiometric assay (Allegro Intact PTH; Nichols Institute Diagnostics, USA) has been validated for use in dogs and cats. Only intact PTH will be recognized because it will be the only form of the peptide to have both determinants. Older midregion PTH assays typically detect those species of hormone containing amino acids 43-68 of the PTH molecule. However, because renal insufficiency/failure results in reduced renal clearance of the non-biologically active midregion PTH fragments, these methods do not accurately reflect parathyroid glandular secretion. Thus, renal secondary hyperparathyroidism is best monitored by use of a two-site assay for intact hormone.

Laboratory Findings

METABOLIC ACIDOSIS

Metabolic acidosis is a common manifestation of CKD. It results primarily from the limited ability of failing kidneys to excrete hydrogen ions, because of reduced ammoniogenesis, decreased filtration of phosphate and sulfate compounds, and decreased maximal renal tubular proton secretion.⁵⁰ Impaired renal tubular reabsorption of filtered bicarbonate may also contribute to acidosis. Bicarbonate wasting and chloride retention results in hyperchloremic (normal anion gap) acidosis. When phosphorous and organic acid (uric acid, hippuric acid, lactic acid) retention is sufficient, high anion gap acidosis results.

A combination of tubular reabsorption of filtered bicarbonate and excretion of hydrogen ions with ammonia and urinary buffers, primarily phosphorous, maintain normal acid-base balance. As renal function declines, hydrogen ion excretion is maintained largely by increasing the quantity of ammonium excreted by

surviving nephrons. However, at some level of renal dysfunction, the capacity to further increase renal ammoniogenesis is lost and metabolic acidosis ensues. Decreased medullary recycling of ammonia due to structural renal damage may also contribute to impaired ammonium excretion.

Chronic metabolic acidosis may promote a variety of adverse clinical effects including anorexia, nausea, vomiting, lethargy, weakness, muscle wasting, weight loss, and malnutrition. Alkalinization therapy is often of value in reversing these signs. In addition, chronic mineral acid feeding to dogs has been shown to increase urinary calcium excretion and progressive bone demineralization, the magnitude of which depends on age and dietary calcium levels. Studies on the effects of dietary acidification in cats have revealed that chronic metabolic acidosis can cause negative calcium balance and bone demineralization or negative potassium balance which may in turn promote hypokalemia, renal dysfunction, and taurine depletion.⁵¹

Severe acidemia may result in decreased cardiac output, arterial pressure, and hepatic and renal blood flows and centralization of blood volume.⁵² Centralization of blood volume results from peripheral arterial vasodilatation and central venoconstriction. Decreases in central and pulmonary vascular compliance may predispose patients to pulmonary edema during fluid administration, an effect that may be particularly important in patients with acute uremic crises requiring intensive fluid therapy. Acidemia also promotes re-entry arrhythmias and a reduction in the threshold for ventricular fibrillation. Severe acidosis may also influence carbohydrate and protein metabolism, serum potassium concentrations, and brain metabolism.

Chronic acidosis may promote protein malnutrition in patients with CKD. Protein catabolism is increased in patients with acidosis to provide a source of nitrogen for hepatic glutamine synthesis, glutamine being the substrate for renal ammoniogenesis.⁵³ The combined effects of reduced protein synthesis due to uremia and accelerated proteolysis due to acidosis promote elevations in blood urea nitrogen, increased nitrogen excretion, and negative nitrogen balance typical of uremic acidosis. Altered branched chain amino acid metabolism appears to be involved. Chronic metabolic acidosis increases the activity of muscle branched chain keto acid dehydrogenase, the rate-limiting enzyme in branched chain amino acid catabolism. This is important in that branched chain amino acids are rate limiting in protein synthesis and play a role in regulation of protein turnover. Alkalinization therapy effectively reverses acidosis-associated protein breakdown. There is speculation that changes in intracellular pH accompanying acidosis lead to alterations in gene transcription which increase the activity of the cytosolic, ATP- and ubiquitin-dependent protein degradation pathway. Severe chronic metabolic acidosis has the potential to induce a cycle of progressive protein malnutrition and metabolic acidosis. Excessive protein catabolism may lead to protein malnutrition despite adequate dietary intake. This process may then accelerate breakdown of endogenous cationic and sulfur-containing amino acids, thus promoting further acidosis.

Acidosis poses a particularly vexing problem for CKD patients consuming protein-restricted diets. Dietary protein requirements appear to be similar for normal humans and humans with CKD unless uremic acidosis is present. When acid-base status is normal, adaptive reductions in skeletal muscle protein degradation protect patients consuming low-protein diets from losses in lean body mass. Metabolic acidosis blocks the metabolic responses to dietary protein restriction in two ways: 1) it stimulates irreversible degradation of the essential, branched chain amino acids and 2) it stimulates degradation of protein in muscle.⁵³ Thus, acidosis may limit the ability of patients to adapt to dietary protein restriction. Metabolic acidosis also suppresses albumin synthesis in humans and may reduce the concentration of serum albumin. These findings have not yet been confirmed in dogs and cats.

AZOTEMIA

Azotemia is defined as an excess of urea or other non-protein nitrogenous compounds in the blood. Loss of renal function leads to accumulation of a wide variety of non-protein nitrogen-containing compounds, including urea and creatinine. Many waste products of protein catabolism are excreted primarily by glomerular filtration. Thus, patients with primary CKD have impaired ability to excrete proteinaceous catabolites because of marked reduction in glomerular filtration rate. Retention of metabolic waste may be further aggravated by impaired tubular secretion, and by extrarenal factors that promote renal hypoperfusion and increased catabolism of body tissues. While accumulation of wastes is largely the result of decreased renal excretion or increased protein catabolism, production of some compounds may also be increased (e.g. guanidine). Since these compounds are derived almost entirely from protein degradation, their production increases when dietary protein increases.

Urea is synthesized using nitrogen derived from amino acid catabolism. Urea may be excreted by the kidneys, retained in body water, or metabolized to ammonia plus carbon dioxide by bacteria in the gastrointestinal tract. Ammonia produced in the gastrointestinal tract is recycled to urea in the liver yielding no net loss of nitrogen or urea. Regardless of whether urea per se is toxic, BUN concentrations are typically directly related to the protein content of the diet. Further, in patients with CKD, BUN concentrations tend to correlate reasonably well with clinical signs of uremia. For practical purposes, BUN may thus be viewed as a marker of retained "uremic toxins."

In addition to increasing protein intake and declining renal function, BUN concentrations may also be increased by gastrointestinal hemorrhage, enhanced protein catabolism, decreasing urine volumes (due to prerenal factors such as dehydration), and certain drugs (eg. glucocorticoids). Urea nitrogen concentrations may decline with portosystemic shunts, hepatic failure, and low protein diets. Reduced BUN concentration may also indicate protein calorie malnutrition. Because many extrarenal factors may influence BUN concentration, creatinine is often used as a more reliable measure of GFR in patients with CKD.

Blood urea nitrogen concentrations should be interpreted with knowledge of simultaneously obtained serum creatinine values, particularly in patients consuming reduced protein diets. The ratio of BUN to serum creatinine concentration should decline when dietary protein intake is reduced. In patients consuming reduced protein diets, an increase in the ratio of BUN to serum creatinine concentrations may suggest poor dietary compliance, enhanced protein catabolism, gastrointestinal hemorrhage, dehydration, anorexia or declining muscle mass.

HYPERPHOSPHATEMIA

The kidneys play a pivotal role in regulating phosphorus balance because they are the primary route of phosphorus excretion. Renal phosphorus excretion is the net of glomerular filtration less tubular reabsorption of phosphorus. If dietary phosphorus intake remains constant, a decline in glomerular filtration rate will lead to phosphorus retention and ultimately hyperphosphatemia. However, during the early stages of CKD, serum phosphorus concentrations typically remain within the normal range because of a compensatory decrease in phosphorous reabsorption in the surviving nephrons. This renal tubular adaptation is largely an effect of renal secondary hyperparathyroidism. Increased parathyroid hormone (PTH) levels promote renal excretion of phosphorous by reducing the tubular transport maximum for phosphorous reabsorption in the proximal tubule via the adenylyl cyclase system. When glomerular filtration rates decline below about 20% of normal, this adaptive effect is maximized and hyperphosphatemia ensues.

In dogs with CKD, serum phosphorus concentrations typically parallel serum urea nitrogen concentrations. Thus hyperphosphatemia is common in azotemic patients, but unexpected in patients with non-azotemic renal disease. The primary consequence of hyperphosphatemia is development and progression of secondary hyperparathyroidism. Increases in serum PTH activities in dogs and humans with CKD are closely associated with the degree of hyperphosphatemia (figure 2).^{38,47} Hyperphosphatemia was found to be 72% efficient in predicting hyperparathyroidism in cats with CKD.³⁷

The combination of hyperphosphatemia and a normal plasma calcium concentration produces an elevated calcium-phosphate product ($\text{Ca} \times \text{PO}_4$ in units of mg/dL). If the calcium-phosphate product exceeds approximately 70, there is a tendency for calcium phosphate to precipitate in arteries, joints, and soft tissues. This process is commonly called metastatic calcification. Calcification is especially prominent in proton-secreting organs, such as the stomach and kidneys, in which basolateral bicarbonate secretion results in an increase in pH that promotes calcium hydrogen phosphate (brushite) precipitation.⁵⁴ However, myocardium, lung, and liver are also commonly mineralized in patients with CKD.

Hyperphosphatemia has been directly linked to increased mortality in humans and dogs with CKD.^{55,56} In humans with CKD receiving hemodialysis therapy, the adjusted relative risk of mortality was stable in patients with serum phosphorous concentrations below 6.5 mg/dl, but increased significantly above this level.⁵⁵ Patients with serum phosphorous in the 6.6-to 7.8-mg/dl range had 13% higher mortality than patients in the reference range (4.6 to 5.5 mg/dl). Patients in the 7.9-to 16.9-mg/dl range had a relative mortality risk 34% higher than patients in the reference range. Mild hyperphosphatemia (5.0 to 6.5 mg/dl) was not associated with an elevated mortality risk.

The calcium X phosphorous product showed a mortality risk trend similar to that seen for phosphate with patients with $\text{Ca} \times \text{PO}_4$ products greater than 72 having a relative mortality risk of 1.34 relative to products between 42 and 52 mg^2/dL^2 .⁵⁵ Mortality risk associated with hyperphosphatemia appeared to be independent of elevated PTH levels, which alone appeared to have only a weak association with mortality. However, the statistical association between PTH and mortality may have been impaired by use of multiple methods for PTH assay in the patients studied. Analysis of calcium revealed no correlation with relative risk of death.

HYPERCALCEMIA, HYPOCALCEMIA, AND HYPERMAGNESEMIA

Hypocalcemia is a common disorder of calcium found in patients with CKD. In a recent report, ionized hypercalcemia was detected in 6% and ionized hypocalcemia in 26% of 80 cats with spontaneous CKD.³⁷ Further, mean blood ionized calcium concentration was significantly lower in CKD cats in this study than in normal control cats, and over half of the cats with advanced end-stage CKD were hypocalcemic. However, when these same 80 cats were evaluated using total serum calcium concentrations, hypercalcemia was found in 21% of the cats, while hypocalcemia was detected in only 8%. Clearly, serum total calcium concentrations do not reliably reflect ionized calcium concentrations in cats with CKD. Similar discrepancies have been observed in dogs with CKD.⁵⁷ The

mechanism of serum total hypercalcemia in the face of normal to reduced blood ionized calcium concentrations is unclear, but may be related to increased concentrations of calcium complexed to retained organic and inorganic anions such as citrate, phosphate, or sulfate.

In patients with hypercalcemia, it is important to ascertain whether hypercalcemia is the cause, rather than result of CKD. Hypercalcemia due to malignancy or hypervitaminosis D is most likely to induce CKD. One way of discriminating the cause-effect relationship between hypercalcemia and CKD is to determine the patient's blood ionized calcium concentration. Only ionized hypercalcemia promotes CKD. However, true ionized hypercalcemia may occur in patients with CKD as a consequence of excessive dosages of calcitriol or calcium-containing intestinal phosphate-binding agents, or in patients with severe renal secondary hyperparathyroidism with marked hyperplasia of the parathyroid glands. We have also observed small increases in ionized calcium concentrations in dogs with early to moderate CKD that are not receiving calcitriol or calcium therapy and do not have advanced hyperparathyroidism. The mechanism of ionized hypercalcemia in these dogs is unclear.

Hypermagnesemia is common in CKD because the kidneys are primarily responsible for magnesium excretion.³⁷ Typically in CKD, the protein binding of magnesium is normal, complexed magnesium is usually increased and ionized magnesium may be increased, normal or decreased. Although the homeostatic mechanisms involved in the control of magnesium are not well documented, they appear to rely on the bone, gut and kidney, as found with calcium and phosphorous control.

HYPOKALEMIA

An association between CKD and hypokalemia has been recognized in cats by several investigators.^{58,59} In contrast, hypokalemia appears to be an uncommon finding in untreated dogs with CKD, occurring primarily as an iatrogenic complication of fluid therapy in this species. A particularly intriguing concept is that hypokalemia may be a cause of CKD in cats, rather than simply a consequence of it. In a recent uncontrolled study of the long-term effects of feeding a potassium restricted, acidifying diet, evidence of renal dysfunction developed in 3 of 9 cats and renal lesions consisting of lymphoplasmacytic interstitial nephritis and interstitial fibrosis were observed in 5 of the 9 cats.⁵⁹ However, it is not clear whether potassium depletion or hypokalemia precede the onset of CKD. In another study, 4 of 7 cats with induced CKD fed a diet containing 0.3% potassium developed hypokalemia while 4 cats with normal renal function fed the same diet did not develop hypokalemia.⁶⁰ Interestingly, muscle potassium content decreased in normokalemic cats with spontaneous CKD, indicating that a total-body deficit of potassium may develop well before the onset of hypokalemia.⁶¹ These findings support the concept that reduced renal function precedes development of hypokalemia.

The mechanism of hypokalemia in cats with CKD has remained elusive, but inadequate intake and increased renal losses appear to be likely candidates. Inadequate intake of potassium could reflect decreased appetite or insufficient dietary potassium content. Dietary risk factors for hypokalemia include acidifying ingredients, reduced magnesium content and high protein content. It has yet to be established that renal potassium wasting occurs in cats with CKD.

Potassium is normally regulated closely by the kidneys. Although large quantities of K^+ appear in glomerular filtrate, essentially all is reabsorbed before reaching the distal tubules. The majority of potassium appears in urine as a result of potassium secretion from tubular cells into the lumen in the distal nephron. Potassium excretion in these segments of the nephron is sensitive to tubular flow rates; rapid urine formation promotes potassium secretion, while slow urine formation limits potassium secretion. Distal potassium secretion is modulated by potassium reabsorption by the intercalated cells in the cortical and outer medullary collecting tubules. Thus, in potassium depletion, net potassium absorption rather than secretion may occur in the distal nephron.

In patients with CKD, the residual nephrons maintain potassium balance by increasing distal tubular secretion of potassium. Gastrointestinal secretion of potassium (primarily in the colon) also appears to increase in CKD, and may play an important role in modulating potassium balance. Because of these adaptations, most dogs and cats with CKD are able to tolerate normal dietary potassium intake (about 0.6% dry matter) until renal dysfunction is very severe. However, the ability to rapidly excrete a potassium load may be impaired in CKD resulting in transient hyperkalemia.

While hypokalemia continues to be detected with some regularity in cats with CKD, its neuromuscular manifestations are uncommon. Presumably this change is the result of an increase in the potassium content of feline diets that has occurred over the past decade in response to the problem of hypokalemia in cats with CKD.

Although generalized muscle weakness has been described as the cardinal sign of hypokalemia, decreased renal function and anorexia are probably more common manifestations of hypokalemia in cats with CKD. In many cats with CKD and hypokalemia, renal function improves following potassium supplementation and restoration of normokalemia, suggesting that hypokalemia may induce a reversible, functional decline in GFR. Recently, renal function was shown to be adversely affected in normal cats when an acidified, potassium restricted diet was fed.⁶²

Potassium depletion and acidosis appeared to have additive effects in impairing renal function in this study. On the basis of these results, it was hypothesized that in cats with CKD, a self-perpetuating cycle of excessive urinary potassium losses and whole body potassium depletion may develop which is likely to further decrease in renal function. Feeding acidified diets or dietary acidifiers to cats with CKD was suggested to exacerbate their tendency to develop potassium depletion.

Potassium imbalances may disrupt a variety of cell functions. Hypokalemia-impaired protein synthesis has been hypothesized to promote weight loss and poor hair coat.³² Marked potassium depletion has also been linked to polyuria resulting from decreased renal responsiveness to antidiuretic hormone (ADH). This antagonism to ADH appears to be due to interference with generation and action of cyclic AMP and to impairment of the countercurrent mechanism. Locally generated prostaglandins may mediate at least part of this effect.

Progression of CKD

A progressive decline in kidney function typically occurs over months to years in dogs and cats with naturally occurring CKDs.^{18,63} It is logical to assume that CKD progresses as a consequence of continuing renal damage induced by the disease process that initiated CRF. While this assumption may be at least partially correct for some patients, the initiating cause cannot be identified at the time of diagnosis of CKD in most patients. Instead, renal lesions observed in progressive nephropathies of diverse origins typically include focal segmental glomerulosclerosis and tubulointerstitial lesions (including tubular dilation and interstitial inflammation and fibrosis). Glomerular lesions accompanied by varying levels of proteinuria are typical of progressive kidney diseases including primary tubulointerstitial diseases. In humans, both the decline in glomerular filtration rate and long-term prognosis are more closely related to the extent of associated tubulointerstitial lesions than glomerular lesions.⁶⁴

In rodents, loss of a critical mass of functional renal tissue invariably leads to failure of the remaining nephrons, suggesting that CKD may progress through mechanisms independent of the initiating cause.⁶⁵ For example, removal of approximately three-quarters or more of the nephrons in rats by surgical resection, infarction, or a combination of these techniques, results in a syndrome of progressive azotemia, proteinuria, arterial hypertension, and, eventually, death due to uremia. Lesions that develop in the remaining kidney remnant include focal segmental glomerulosclerosis and tubulointerstitial lesions, including tubular dilation and interstitial inflammation and fibrosis. Progressive renal injury and loss of renal function occurs in this rodent model of kidney failure despite the fact that remaining kidney remnant was initially normal.

Numerous studies have been performed in an attempt to determine if findings obtained in partially nephrectomized rodents are relevant in dogs and cats. Reducing renal mass in dogs and cats resulted in mild proteinuria, glomerulopathy, and tubulointerstitial renal lesions.^{60,66,67} Although these findings are consistent with observations in rats, reducing renal mass by 7/8 or less did not consistently result in a progressive decline in GFR. In studies performed at the University of Georgia, progressive decline in GFR was detected in dogs in which renal mass had been reduced by 15/16.⁵⁶ These findings confirm that progressive renal disease develops in dogs; however, a marked reduction in renal mass may be necessary to initiate this process in an otherwise normal remnant kidney.

The preponderance of clinical and experimental evidence suggest that in dogs and cats with stages 3 and 4 CKD, progression of renal disease may result, at least in part, from factors unrelated to the activity of the inciting disease.^{4,68,69} These factors may include intraglomerular hypertension, glomerular hypertrophy, hypertension, proteinuria, tubulointerstitial disease, and intrarenal precipitation of calcium phosphate.

INTRAGLOMERULAR HYPERTENSION AND GLOMERULAR HYPERTROPHY

Long-term elevations in intraglomerular pressure, resulting from transmission of systemic pressures and/or glomerular hemodynamic processes, appear to be deleterious over time. Intraglomerular hypertension, with consequent glomerular hyperfiltration, occur as a compensatory event designed to maintain the total GFR as nephrons are lost to disease. In glomerular diseases, intraglomerular hypertension may also occur as a compensatory adaptation to reduction in permeability of the glomerular capillary wall to small solutes and water. In this setting, the fall in GFR is minimized by elevating intraglomerular pressure. Primary renal vasodilatation may occur in some diseases such as diabetes mellitus. A compensatory increase in glomerular size may also occur in all of these settings.

The mechanisms by which intraglomerular hypertension and hypertrophy injury glomeruli are incompletely understood, as multiple factors are involved. Intraglomerular hypertension may directly injure endothelial cells of the glomerular capillaries. In addition, increased glomerular diameter and increased capillary wall stress may cause detachment of glomerular epithelial cells from the glomerular capillary walls. The consequent focal areas of denudation permit increased flux of water and solutes through the glomerular capillary wall. However, macromolecules cannot cross the glomerular basement membrane and are trapped in the subendothelial space. The result is formation of characteristic “hyaline deposits” in glomeruli that progressively narrow the capillary lumens, thereby decreasing glomerular perfusion and filtration. Increased strain on mesangial cells can stimulate them to

produce cytokines and extracellular matrix. The release of cytokines, such as transforming growth factor- β (TGF- β) and platelet-derived growth factor, may mediate the rise in matrix synthesis.⁷⁰ The consequent expansion of mesangial matrix further encroaches on the capillary surface area.

While these effects lead to the characteristic glomerular lesions of progressive nephropathies, intraglomerular hypertension also impairs glomerular permselectivity leading to proteinuria. Proteinuria is an important pathophysiological link between glomerular injury, tubulointerstitial injury, and progression of renal disease.

SYSTEMIC HYPERTENSION

In humans, the association between systemic hypertension and CKD is well established. The Multiple Risk Factor Intervention Trial (MRFIT) identified systemic hypertension as a significant risk factor for development of end stage CKD.⁷¹ A similar association has recently been identified in dogs.¹⁷ Further, in the Modification of Diet in Renal Disease (MDRD) study, the level of systemic blood pressure was linked to progression of CKD among black and proteinuric human CKD patients.⁷²

Systemic hypertension leads to progression of CKD, at least in part, through unopposed transmission of systemic hypertension to the glomerular capillary bed resulting in glomerular injury. This event occurs particularly in patients with CKD because autoregulation of blood flow, which normally protects glomerular capillaries from excessive pressure, is impaired. Studies in dogs and cats have confirmed that reduced kidney function is associated with an adaptive preglomerular vasodilatation that permits transmission of systemic hypertension to the glomerular capillaries.^{69,73}

PROTEINURIA

Proteinuria itself may contribute to progressive renal injury.²⁰ Proteinuria is a strong, independent risk factor for progression to end-stage CKD in humans.⁷⁴ Studies performed at the University of Minnesota Veterinary Medical Center have shown proteinuria to be a risk factor for uremia and death in dogs with naturally occurring CKD. Proteinuria has also been reported to be related to progression of renal disease in dogs with induced CKD.⁶⁸ A relationship between proteinuria and progression of renal disease has not yet been established in cats.

Proteinuria may promote progressive renal injury in several ways. Some proposed mechanisms include mesangial toxicity, tubular overload and hyperplasia, toxicity from specific proteins such as transferrin/iron, and induction of pro-inflammatory molecules such as monocyte chemoattractant protein-1. Excessive proteinuria may injure renal tubules via toxic or receptor-mediated pathways or via an overload of lysosomal degradative mechanisms. Abnormally filtered proteins accumulate in the renal proximal tubular lumens where, after endocytosis into proximal tubular cells, they contribute to renal tubulointerstitial injury through a complex cascade of intracellular events. These events include upregulation of vasoactive and inflammatory genes such as the endothelin-1 (ET-1) gene, the monocyte chemoattractant protein 1 (MCP-1) gene which encodes for an inflammatory peptide involved in macrophage and T-lymphocyte recruitment, and the RANTES (regulated on activation, normal T-cell expressed and secreted) that encodes for a chemotactic molecule for monocytes and memory T-cells.⁷⁵ Formed in excessive amounts, these molecules are secreted toward the basolateral side of tubular cells and incite an inflammatory reaction. In addition, complement components escaping through glomerular capillary walls may initiate interstitial injury. Small lipids bound to filtered proteins may also be liberated during resorption. Inflammatory or chemotactic properties of these lipids may promote tubulointerstitial disease. Finally, inspissation of filtered proteins due to tubular reabsorption of water in the distal nephron may lead to formation of casts that obstruct nephrons.

TUBULOINTERSTITIAL DISEASE IN GLOMERULOPATHIES

In humans, primary glomerular diseases are typically associated with varying degrees of tubulointerstitial lesions. Remarkably, it is the intensity of the accompanying or evolving injury in the tubulointerstitium, rather than injury in glomeruli, that is the most reliable overall predictor of decline in renal function.⁷⁶ In contrast, primary tubulointerstitial diseases as a group are the more indolent and slowly progressive of all human nephritides. While the etiopathogenesis of canine and feline nephropathies is often uncertain, current evidence suggests that a substantial portion of canine CKD results from primary glomerulopathies, while the majority of feline CKD appears to be of tubulointerstitial origin.^{11,77} The indolent course of CKD commonly observed in cats may be related to the tubulointerstitial origin of their disease, while many dogs experience a more aggressive decline in renal function as a consequence of the glomerular origin of their primary renal disease.

Glomerular diseases have the capacity to incite tubulointerstitial disease. While the mechanisms underlying the development of tubulointerstitial disease in this setting are incompletely understood, multiple factors have been hypothesized to contribute.⁷⁶ As described above, proteinuria is an important factor.⁷⁸ Additional factors include tubular ischemia related to decreased postglomerular blood flow; loss of tolerance with subsequent tubulointerstitial

damage secondary to immune mechanisms of glomerular injury; seeping of inflammatory mediators from inflamed glomeruli; renal deposition of calcium phosphate; and enhanced tubular ammoniogenesis leading to complement-mediated injury of the tubulointerstitium.⁷⁶ There is evidence that an active immunologic process may be involved in the tubulointerstitium of patients with glomerulonephritides beginning early in the course of disease. In some instances this process appears to represent an extension of the inflammation in glomeruli.⁷⁶ In some models of renal disease, corticosteroids or other immunosuppressive therapy can ameliorate the tubulointerstitial damage without effect on glomeruli.⁷⁹

INTRARENAL PRECIPITATION OF CALCIUM PHOSPHATE

Phosphate retention begins early in the course of CKD and has been implicated in promoting progressive renal injury in several species, including dogs and cats.^{56,69,80} A role for phosphorus in promoting progressive CKD is based on the observation that dietary phosphorus restriction limited renal-related mortality in dogs and renal mineralization in cats. Phosphorus may promote progression of CKD, at least in part, by precipitation with calcium in the renal interstitium. This renal mineralization may then initiate an inflammatory reaction, resulting in renal interstitial fibrosis and tubular atrophy.

OTHER FACTORS

Lipids and Progression

Experimental studies in rodents indicate that hyperlipidemia may promote progression of renal disease.⁸¹ This association is based on the observation that cholesterol loading enhanced glomerular injury, while reducing lipid levels with drugs such as lovastatin slowed the rate of progressive injury. Factors responsible for these effects are incompletely understood. Exposing glomerular and tubular cells to low-density lipoprotein and its oxidized variant stimulates their proliferation, induces injury and apoptosis, and stimulates them to produce extracellular matrix contributing to fibrosis.¹⁹ An additive effect of hyperlipidemia and proteinuria has been described in humans with CKD.⁸² Although hypercholesterolemia is common in dogs and cats with CKD, the clinical applicability of these findings in other species is unclear. Evidence that lipid reduction is beneficial in humans with CKD is conflicting. However, a meta-analysis of 13 prospective controlled studies indicated that lipid reduction was associated with a lower rate of decline in kidney function and decreased proteinuria.⁸³

Metabolic Acidosis

Metabolic acidosis has been theorized to enhance progression of CKD by activation of the alternative complement pathway as a result of enhanced renal ammoniogenesis.⁷⁶ In human patients with CKD, reducing renal ammoniogenesis and renal tubular peptide catabolism was accompanied either by reduced renal tubular injury or by tubular hyperfunction. However, recent studies in rats have failed to confirm a role for acidemia and enhanced renal ammoniogenesis in renal injury and progression of CKD.⁸⁴ Longer-term studies have suggested that effects initially attributed to enhanced renal ammoniogenesis may have been a transient and/or related to the timing of therapeutic intervention in the previous study. These researchers concluded that metabolic acidosis neither causes nor exacerbates chronic renal injury. Further, the renal protective effect of alkali therapy is unproven in humans with CKD. Studies performed by us in cats with induced CKD have likewise failed to identify an adverse effect of chronic acidosis on renal structure or function.

Chronic Hypoxia

It has been hypothesized that chronic oxygen deprivation to the tubulointerstitial compartment contributes to scarring in the tubulointerstitium.⁸⁵ Chronic hypoxia is thought to result from compromise of blood flow to the interstitial capillary network downstream from inflamed glomeruli. Concurrently, the peritubular capillary network downstream from other vasodilated glomeruli may be damaged subsequent to transmission of systemic blood pressures to this normally low-pressure capillary network. The resultant tubulointerstitial hypoxia is hypothesized to promote fibrosis by regulating gene expression of a broad spectrum of molecules including growth factors, hormones, vasoactive compounds, and enzymes. For example, *in vitro* studies have indicated that hypoxia is a profibrotic stimulus for tubular epithelial cells, interstitial fibroblasts, and renal microvascular endothelial cells. Hypoxia has been shown to induce a wide variety of growth factors, including many implicated in the pathogenesis of progressive renal disease, such as TGF- β 1 and platelet derived growth factor.

The apparent beneficial role for ACE inhibitors in minimizing progressive renal diseases is consistent with the proposed role for chronic hypoxia. In theory, ACE inhibition could protect the kidneys by enhancing interstitial oxygen delivery through dilating the efferent arterioles, reducing vascular resistance, and improving microvascular flow through the interstitium.

DIAGNOSTIC EVALUATION

Patients with CKD should be evaluated to determine their diagnosis (type of CKD), severity, complications, comorbid conditions (concurrent diseases unrelated to CKD), and risk for continued loss of kidney function.³ Morphologic diagnoses usually require evaluation of kidney biopsy samples. However, unless the benefit of results of renal biopsies (e.g. the results are likely to substantially change the prognosis or treatment) outweigh the associated risks, we do not recommend them. Currently, this decision must be made on a case by case basis; however, it is essentially never justified to biopsy small kidneys from a patient with CKD unless neoplasia or infection are highly suspected (when fine-needle biopsy will usually suffice).

Severity of CRD is classified on the basis of the level of renal function. Serum creatinine concentration is the most commonly used measure of severity of renal dysfunction and is the basis for staging CKD (table 2). In order to optimize accuracy of staging of CRD, serum creatinine concentrations used to stage CRD should be evaluated when patient is well hydrated. Multiple measurements are desirable to establish accuracy and stability of renal dysfunction. However, renal function may be more accurately measured using plasma clearances of iohexol, inulin, or other substances excreted exclusively by glomerular filtration.⁸⁶⁻⁹⁰ Plasma clearance studies are indicated in at least 3 settings. First, they provide an accurate measure of renal dysfunction in stages 1 and 2 patients where serum creatinine determinations may be insensitive. Second, they provide a basis for dosage adjustments for drugs that are potentially toxic and are excreted primarily by the kidneys. Third, they are an excellent means of assessing progression of CKD. Because body muscle mass commonly declines as CKD progresses through stages 3 and 4, endogenous production of creatinine from muscle creatine may decline confounding interpretation of serial serum creatinine values.

Table 6 – Complications and Comorbid Conditions in CKD

Complications of CKD	Comorbid Conditions
Anemia	Cardiac disease
Arterial hypertension	Degenerative joint disease
Dehydration	Dental and oral diseases
Hyperparathyroidism	Hyperthyroidism (cats)
Hyperphosphatemia	Nephroliths and ureteroliths
Hypocalcemia and hypercalcemia	Urinary tract infections
Hypokalemia	
Malnutrition	
Metabolic acidosis	
<u>Uremic signs</u>	

Appropriate management of complications and comorbid conditions may improve patient quality of life as well as short-term and long-term survival (table 6). Diagnostics necessary to identify complications and comorbid conditions associated with CKD are outlined in table 7. The prevalence of complications of CKD is mainly related to the level of renal function as reflected in the stage of CKD. Chronic kidney disease is typically characterized by alterations in a variety of kidney functions in addition to impaired GFR. These may include impairment of the 1) filtration barrier for plasma proteins (resulting in albuminuria and proteinuria), 2) reabsorption or secretion of water or specific solutes, and 3) various endocrine functions (anemia due to erythropoietin deficiency, calcitriol deficiency and renal secondary hyperparathyroidism). These functional derangements are the basis of most complications of CKD.

Comorbid conditions are concurrent diseases other than CKD. Because patients with CKD are typically middle-aged to older they often have a substantial number of comorbid conditions. Comorbid conditions of particular frequency and concern for dogs and cats with CKD include urinary tract infections, urolithiasis, urinary obstruction, degenerative joint diseases, dental and other oral diseases, and cardiac disease. In addition, hyperthyroidism and upper urinary tract uroliths are common and important comorbid condition in cats with CKD. In a survey of 91 cats with CKD, we found that 25% had upper urinary tract stones. Comorbid conditions may have an important impact on prognosis and treatment.

Table 7 – Problem Specific Database for Patients with CKD

1. Medical history including medication review
2. Physical examination including retinal examination
3. Complete urinalysis including urine sediment examination
4. Quantitative urine culture
5. Complete blood count
6. Urine protein:creatinine ratio
7. Serum urea nitrogen concentration
8. Serum creatinine concentration
9. Serum (or plasma) electrolyte and acid-base profile including:
 - a. Sodium, potassium, and chloride concentrations
 - b. Blood gas analysis or total serum CO₂ concentrations
 - c. Calcium, phosphorus and albumin concentrations
10. Arterial blood pressure
11. Kidney-bladder-urethra survey radiographs
 - a. Kidneys - size, shape, location, number
 - b. Uroliths or masses affecting kidneys, ureters or urethra
 - c. Urinary bladder - size, shape, location, uroliths
12. Consider:
 - a. Additional imaging studies as indicated (rule-out: urinary obstruction, renal uroliths, pyelonephritis, renal cystic disease, perinephric pseudocysts, and renal neoplasia):
 - i. Renal ultrasound
 - ii. Intravenous urography
 - b. Determining glomerular filtration rate
 - i. Plasma clearance of iothexol, inulin, creatinine, or other
 - ii. Classical clearance methods or scintigraphic methods
 - c. Determining parathyroid hormone and ionized calcium levels for managing renal secondary hyperparathyroidism, especially if calcitriol therapy is being considered
 - d. Skeletal radiographs for evidence of renal osteodystrophy, measurement of carbamylated hemoglobin concentration, or parathyroid gland ultrasonography when the distinction between acute and chronic kidney disease remains unresolved
 - e. Renal biopsy
 - f. Prior to initiating therapy, consider freezing aliquots of serum (or plasma) and urine for additional diagnostics that may be desired later.

The level of kidney function tends to decline over time for most patients with CKD. It is important to assess the risk for loss of kidney function so that therapy may be designed to minimize progressive decline in GFR can be initiated. The risk of progression of CKD is affected by diagnosis and by modifiable and nonmodifiable factors. Some of these factors can be assessed even before the decline in GFR. Therapies designed to slow progression of CKD may be specific for the diagnosis (e.g. antibiotics for bacterial pyelonephritis), while others are supportive (e.g. dietary intervention, antihypertensive therapy and angiotensin converting enzyme inhibitors).

TREATMENT OF CKD

Overview of Treatment

Treatment of CKD should generally include specific therapy, prevention and treatment of complications of decreased kidney function, management of comorbid conditions, and therapy designed to slow loss of kidney function.³ To this end, a clinical action plan should be developed for each patient based on their diagnosis, stage of CKD, existing complications and comorbid conditions, and risk factors for progression of their CKD.

Specific therapy for CKD is based on a renal diagnosis. Treatment is directed at the etiopathogenic processes responsible for the patient's primary renal disease. Because the renal lesions of CKD are irreversible, they cannot be completely reversed or eliminated by specific therapy. Nonetheless, progression of renal lesions may be slowed or stopped by therapy designed to eliminate active renal diseases. Specific therapies are described in the chapters of this text on glomerular diseases, bacterial infections, familial renal diseases, and renal tubular disease. Unfortunately, a renal diagnosis amenable to specific therapy is not obtained for most patients.

Treatment directed at the complications of decreased kidney function is often termed conservative medical management. It consists of supportive and symptomatic therapy designed to correct deficits and excesses in fluid, electrolyte, acid-base, endocrine, and nutritional balance thereby minimizing the clinical and pathophysiologic

consequences of reduced renal function. Conservative medical management also includes therapy designed to limit the progressive loss of renal function.

The goals of conservative medical management of patients with chronic primary CKD are to: (1) ameliorate clinical signs of uremia, (2) minimize disturbances associated with excesses or losses of electrolytes, vitamins, and minerals, (3) support adequate nutrition by supplying daily protein, calorie, and mineral requirements, and (4) modify progression of CKD.⁹¹ These goals are best achieved when recommendations regarding conservative medical management are individualized to patient needs based on clinical and laboratory findings. Because CRF is progressive and dynamic, serial clinical and laboratory assessment of the patient, and modification of the therapy in response to changes in the patient's condition, is an integral part of conservative medical management.

Dietary Therapy

DIETARY MODIFICATIONS IN CKD

Diet therapy has been a mainstay in the management of canine and feline CKD for decades and continues to be the most commonly recommended treatment for these patients. In the past, the emphasis has been on reducing protein content. While protein content continues to play an important role in diet formulation, other diet modifications are also important in managing CKD patients. Diets recommended for dogs and cats with CKD are modified from typical maintenance diets in several ways including reduced protein, phosphorus, and sodium content, increased B-vitamin content and caloric density, and a neutral effect on acid-base balance. Feline CKD diets are typically supplemented with additional potassium. Canine CKD diets may have an increased omega-3 to omega-6 polyunsaturated fatty acid (PUFA) ratio. Diets may also have added fiber designed to enhance gastrointestinal excretion of nitrogenous wastes. Of these diet modifications, only phosphate, omega-3 PUFA, and protein have been extensively examined.

Diet Phosphate

Renal diets are limited in phosphorus content in order to limit phosphorus retention, hyperphosphatemia, renal secondary hyperparathyroidism, and progression of renal disease. Phosphate balance results largely from the interaction between dietary intake and renal excretion. Ingested phosphate is cleared from blood by glomerular filtration, and then total excretion is adjusted by modifying proximal tubular reabsorption. As renal function declines, renal tubular reabsorption of phosphorus declines (increasing renal excretion) in an attempt to compensate for the reduction in glomerular filtration, thereby maintaining phosphorus balance. However, if phosphorus intake continues unabated, the renal adaptive capacity soon becomes overwhelmed and phosphorus retention and hyperphosphatemia develop.

While phosphorus retention and hyperphosphatemia probably do not cause clinical signs, they may promote renal secondary hyperparathyroidism and renal mineralization that enhances progressive decline in renal function. Dietary phosphorus restriction has been shown to enhance survival and a slow decline in renal function in dogs with induced CKD.⁵⁶ In cats, dietary phosphorus restriction has been shown to limit renal mineralization.

Available evidence supports a recommendation for dietary phosphate restriction for dogs and cats in stages 3 and 4 CKD. Because protein is a major source for phosphate, it is usually necessary to limit dietary protein in order to limit diet phosphate content.

The goals of phosphate management vary according to the patient's stage of CKD. In stage 2 dogs and cats, serum phosphorus should be maintained below 5.0 mg/dl. In stage 3 CKD, serum phosphorus should be maintained below 5.5 mg/dl. In stage 4 CKD, serum phosphorus should be maintained below 6.0 mg/dl. Achieving these stage-based goals may require a combination of diet therapy and phosphorus binders (see below).

Omega-3 PUFA

Dietary supplementation with omega-3 PUFA have been shown to be beneficial in dogs with induced CKD. Compared to dogs fed diets high in saturated fats or omega-6 PUFA, dogs consuming a diet supplemented with omega-3 PUFA had lower mortality, better renal function, fewer renal lesions, less proteinuria, and lower cholesterol levels.⁹² In dogs fed the omega-3 PUFA diet, renal function actually increased and remained above baseline over 20 months of study. Lesions of glomerulosclerosis, tubulointerstitial fibrosis, and interstitial inflammatory cell infiltrates were also diminished in dogs fed the omega-3 PUFA diet. A variety of effects attributed to omega-3 PUFA supplementation may have contributed to the favorable renal effects observed, including their tendency to reduce hypercholesterolemia, suppress inflammation and coagulation (by interfering with the production of proinflammatory, procoagulant prostanoids, thromboxanes, and/or leukotrienes), lower blood pressure, favorably influence renal hemodynamics, provide antioxidant effects, or limit intrarenal calcification. A subsequent study supported possible roles for altered lipid metabolism, glomerular hypertension and hypertrophy, and urinary eicosanoid metabolism in the beneficial renal effects of omega-3 PUFA.⁹³

Available evidence supports a recommendation for dietary supplementation with omega-3 PUFA for dogs in stages 3 and 4 CKD. The optimum quantity of omega-3 PUFA supplementation and ratio of omega-3 to omega-6

PUFA appropriate for renal diets have not been conclusively established. Additional omega-3 PUFA supplementation may not be appropriate for dogs already consuming a renal diet enhanced with omega-3 PUFA. Currently, there is no evidence to support a recommendation for or against omega-3 PUFA supplementation for cats with CKD.

Diet Protein

While the ideal quantity of protein to feed dogs and cats with CKD remains unresolved, there is a general consensus of opinion, that reducing protein intake ameliorates clinical signs of uremia in CKD and is therefore indicated for stage 4 CKD. Blood urea nitrogen can be used as a crude measure of compliance with dietary recommendations because it declines as dietary protein intake is reduced. While not generally regarded as an important uremic toxin, BUN is a surrogate marker for retained non-protein nitrogenous waste products and typically correlates better with clinical signs than serum creatinine concentration.

The concept of reducing dietary protein intake in CKD patients that do not have clinical signs of uremia has been questioned. Limiting protein intake has been advocated for these patients in order to slow progression of CKD. This suggestion derives from studies in rats indicating that dietary protein restriction limits glomerular hyperfiltration and hypertension and slows the spontaneous decline in kidney function that follows reduction in kidney mass.⁶⁵ Studies in humans have supported the concept that protein restriction slows progression of CKD, albeit this effect may be small.⁹⁴ In contrast, multiple studies have failed to confirm a beneficial role for protein restriction in limiting progression of CKD in dogs or cats.⁹¹ When not excessive, limiting protein intake does not appear to have any adverse effects, and it may be easier to initiate treatment with renal diets before the onset of clinical signs of uremia. In addition, protein restriction may delay onset of clinical signs of uremia as renal disease progresses. While a role for protein restriction in slowing progression of canine and feline CKD has not been entirely excluded, available evidence fails to support a recommendation for or against protein restriction in patients with stage 3 CKD.

DIET THERAPY – EVIDENCE FROM CLINICAL TRIALS

The effectiveness of diet therapy in minimizing uremic episodes and mortality in dogs with naturally occurring stage 3 and stage 4 CKD has been established in a double-masked, randomized, controlled clinical trial.¹⁸ The study compared a renal diet to a prototypical canine maintenance diet. The renal diet was characterized by reduced quantities of protein, phosphorus, and sodium compared to the maintenance diet, and was supplemented with omega-3 PUFA. In this study, the risk of developing an uremic crisis was reduced by approximately 75% in dogs fed the renal diet compared to dogs fed an adult maintenance diet, and the median interval before development of uremic crisis in dogs fed the renal diet was twice as long as that observed in dogs fed the maintenance diet. Further, the risk of death irrespective of the cause was reduced by at least two-thirds when dogs were fed the renal diet, and renal death risk was reduced by 70%. Dogs fed the renal diet survived at least 13 months longer than dogs fed the maintenance diet. In addition, owners of dogs fed the renal diet reported significantly higher quality of life scores for their dogs than owners of dogs consuming the maintenance diet. The delay in development of uremic crises and reduced mortality observed in dogs fed renal diet was associated, at least in part, with reduction in the rate progression of CKD.

The effectiveness of diet therapy in cats has been tested in a prospective study comparing a renal diet characterized by protein and phosphorus restriction to no diet change.⁶³ Cats that would not accept the renal diet, either due to pet or owner issues, continued to eat their regular diet. Therefore, this study was neither randomized nor blinded, but nonetheless yielded results similar to those observed in the canine study. Cats fed the renal diet (mean survival time = 633 days) survived substantially longer than cats that continued to consume their regular diet (mean survival time = 264 days). In addition, plasma urea nitrogen, phosphorus, and parathyroid hormone concentrations were reduced in cats that consumed the renal diet. Results of more recent randomized controlled clinical trial performed in our clinical trial unit found that feeding a maintenance diet to cats with serum creatinine values between 2.0 and 4.5 mg/dl was associated with a 2-year mortality rate of 22%. In contrast, none of the cats fed the renal diet died over the 2 years of study. This more controlled trial supports the findings of the study described above, confirming the value of renal diets in managing cats with CKD.

INDICATIONS FOR DIET THERAPY

In the past, criteria for timing of dietary intervention in dogs and cats with spontaneous CKD have been based on empirical observations. An often-cited guideline has been to initiate dietary therapy when serum creatinine exceeds 2.5 mg/dl or the SUN exceeds 60-80 mg/dl. More recently, one investigator recommended a staged approach whereby dietary phosphorus restriction and omega-3 PUFA dietary supplementation be implemented in dogs with serum creatinine values below 4.0 mg/dl with dietary protein restriction recommended only in dogs with serum creatinine values exceeding 4.0 mg/dl.⁴ However, the clinical trial data available to date have demonstrated a benefit of dietary intervention in both stage 3 and stage 4 CKD. In a randomized, controlled clinical trial in dogs

with naturally occurring CKD, diet therapy significantly reduced the risk of uremic crises and death in dogs with serum creatinine concentrations between 2.0 and 3.0 mg/dl.¹⁸ These studies did not selectively determine the benefits of modifying individual dietary components, but rather report the results of a “diet effect.” While studies on individual dietary components have been reported in dogs and cats with induced CKD, the potential interactions between components have not been examined, nor have the results of these studies been confirmed in clinic patients.

Currently available data supports recommending therapy with appropriately modified diets in dogs and cats in stages 3 and 4 CKD. The value of diet therapy in stages 1 and 2 CKD has not been established, therefore there is no evidence to support a recommendation for or against diet therapy in these patients. In cats, clinical trials have confirmed the value of renal diets beginning in the middle of CKD Stage 2 (serum creatinine concentrations 2.0 mg/dl and higher).

Drugs – Medication Review and Dose Modification

A review of current medications should be performed at each clinic visit, including dosage adjustment based on level of kidney function, detection of potential adverse effects on kidney function or complications of CKD, detection of drug interactions, and, where indicated, therapeutic drug monitoring.³ Ensure that all current medications are still necessary and that new medications have specific indications and do not pose a risk of drug interaction.

Because the kidneys are responsible for elimination of many drugs from the body, renal drug clearance is reduced as renal function declines causing the half-life of the drug to be prolonged. In addition, distribution, protein binding, and hepatic biotransformation of drugs may be altered. For example, two protein binding defects are seen in CKD.⁴⁹ One group of primarily acidic drugs shows decreased binding leading to increases in free, active drug fractions in plasma (e.g. theophylline, methotrexate, diazepam, digoxin, and salicylate). The effect of this change in binding is that lower doses of drugs are required to achieve therapeutic levels, but conventional doses may result in toxic levels. Basic drugs, such as propranolol or cimetidine, have increased binding leading to a decrease in free drug levels, thus diminishing the therapeutic effect. Increased total drug levels may be required to achieve the desired therapeutic effect with these drugs. However, these effects may be complicated by decreased renal clearance of the drugs. Further, accumulation of active drug metabolites may augment drug potency or toxicity.

The sum effect of these changes is that for many drugs normally excreted by the kidneys, there is a tendency for drug to accumulate in patients with CKD. Excessive drug accumulation promotes an increased rate of adverse drug reactions and nephrotoxicity. If drugs requiring renal excretion must be administered to patients with CKD, dosage regimens should be adjusted to compensate for decreased organ function. However, dosage adjustments may not be appropriate for drugs that are administered to a physiologic endpoint or effect such as antihypertensive agents.⁹⁵

Because drug accumulation in patients with reduced kidney function is primarily a result of reduced renal drug clearance, dosage adjustments should be made according to changes in drug clearance. Net renal excretion of a drug is a composite of glomerular filtration, tubular secretion, and tubular reabsorption. Generally it is assumed that these 3 factors all decline in parallel. Therefore, drug clearance may be estimated by measuring GFR, either by plasma disappearance rate (e.g. iothexol disappearance rate) or classical clearance studies. Drug dosage may then be adjusted according to the percentage reduction in GFR (i.e. the ratio of patient GFR to normal GFR), also known as the dose fraction (K_f):

$$K_f = (\text{patient GFR} / \text{normal GFR})$$

Dosage regimens can be adjusted by increasing the normal dosage interval or decreasing the normal dose in direct proportion to K_f .⁹⁶ The interval extension method is particularly useful for drugs with wide therapeutic ranges and long plasma half-lives in patients with renal impairment. Interval lengthening will result in wide swings of the plasma drug concentrations from peak to trough levels. If the range between the toxic and therapeutic levels is too narrow, either toxic or subtherapeutic plasma concentrations may result. For drugs excreted 100 percent unchanged by the kidneys, a precise increase in dosage interval may be calculated by dividing the normal dosing interval by K_f :

$$\text{modified dose interval} = (\text{normal dose interval} / K_f)$$

For example, if a drug is normally administered every 8 hours and the patient's GFR is 25% of normal (i.e. $K_f = 0.25$), then the appropriate dosing interval is $(8 \text{ hrs} \div 0.25)$ or 32 hrs. The calculated dose interval should be rounded to a convenient time schedule.

Alternatively, the size of the individual doses can be reduced while maintaining the time interval between doses normal. Decreasing the individual doses reduces the difference between peak and trough plasma concentrations. This effect is important for drugs with narrow therapeutic ranges and short plasma half-lives in patients with renal dysfunction and is recommended for drugs for which a relatively constant blood level is desired. Dose reduction may be determined by multiplying the normal dose by K_f :

$$\text{modified dose reduction} = (\text{normal dose} \times K_f)$$

For example, if the normal dosage is 10 mg/kg given every 8 hours and the patient's GFR is 25% of normal (i.e. $K_f = 0.25$), then the appropriate dosage is (10 mg/kg \times 0.25) or 2.5 mg/kg given every 8 hours. Even using the reduced dosage, normal interval method, the first dose of drug should be administered at the usual dosage to initiate therapeutic drug concentrations in tissues and blood.

There have been no controlled clinical trials to establish the efficacy of the two methods for drug-dose alteration in patients with CKD. Prolonging the dose interval is usually more convenient and less expensive. A combination of interval prolongation and dose size reduction may also be convenient and effective.

Table 8- Drug Dosage Modifications for Patients with Renal Insufficiency and Failure

Drug	Route(s) of Excretion*	Nephrotoxic?	Dosage Adjustment in Renal Failure†
Amikacin	R	yes	Pr
Amoxicillin	R	no	D/I
Amphotericin B	O	yes	Pr
Ampicillin	R,(H)	no	D/I
Cephalexin	R	no	C _{Cr}
Cephalothin	R,(H)	no(?)	C _{Cr} or D/I
Clindamycin	H,(R)	no	N
Chloramphenicol	H,(R)	no	N,A
Cyclophosphamide	H,(R)	no	N
Corticosteroids	H	no	N
Dicloxacillin	R,(H)	no	N
Digoxin	R,(O)	no	Pr
Doxycycline	GI,(R)	?	N
Enrofloxacin	R	no	I
Furosemide	R	no(?)	N
Gentamicin	R	yes	Pr
Heparin	O	no	N
Kanamycin	R	yes	Pr
Neomycin	R	yes	C/I
Nitrofurantoin	R	no	C/I
Orbaloxacin	R	no	I
Penicillin	R,(H)	no	D/I
Propranolol	H	no	N
Streptomycin	R	yes	C _{Cr}
Sulfisoxazole	R	yes	C _{Cr}
Tetracycline	R,(H)	yes	C/I
Tobramycin	R	yes	Pr
Trimethoprim/	R	yes	C _{Cr} ,A

Sulfamethoxazole

* Routes of excretion: R=Renal; H=Hepatic; GI=Gastrointestinal; O=Other (minor route in parentheses)

† Dosage modification:
 N - normal
 D/I - half dose or double dosage interval (in severe renal dysfunction)
 C_{Cr} - adjust according to C_{Cr} (see text)
 Pr - precise dosage modification (see text - adjust according to K_f)
 C/I - contraindicated
 A - avoid in advanced renal failure

Dosage of antimicrobial drugs may be modified according to 3 general patterns, depending on the fraction of the drug eliminated by the kidneys (table 8): (1) doubling the dosing interval or halving the drug dosage in patients with severe reduction in renal function, (2) increasing the dosage interval according to ranges of creatinine clearance values, and (3) precise dosage modification as described above. Drugs in the first category are relatively nontoxic. The second class includes drugs requiring dosage modification according to GFR values because they are more likely to be toxic. For drugs in this class, dosing interval is increased two-fold when GFR is between 1.0 and 0.5 ml/min/kg, three-fold when GFR is between 0.5 and 0.3 ml/min/kg, and four-fold when GFR is less than 0.3 ml/min/kg. Drugs in the third class include relatively toxic antimicrobial drugs that are excreted solely by glomerular filtration (particularly aminoglycoside antibiotics). They require precise dosage modification according to K_f. For these drugs, increased interval, fixed dosage regimens appear to result in less nephrotoxicity than reduced

dose, fixed interval methods. A combination of dosage reduction and interval extension has been recommended for animals with markedly reduced kidney function (GFR less than 0.7 ml/min/kg).

Although GFR is the preferred measure of renal dysfunction for modifying drug therapy, serum creatinine concentration is a more universally available measure of renal dysfunction. A regression equation relating serum creatinine concentration to glomerular filtration rate in dogs has been established.⁹⁷

Although the relationship between serum creatinine concentration and GFR is not linear, the reciprocal of serum creatinine concentration may be used to approximate GFR when serum creatinine concentration is less than 4 mg/dl. This rule of thumb will overestimate GFR when serum creatinine concentration exceeds 4 mg/dl. Despite increased expense and effort involved, it is recommended that GFR be used as the basis for modifying drug dosage schedules whenever possible. This recommendation is particularly relevant when a potentially nephrotoxic drug must be administered.

Patients with preexisting renal disease and CKD may also be predisposed to nephrotoxicity. For this reason, nephrotoxic drugs and drugs requiring renal excretion should generally be avoided in patients with CKD. Where possible, less nephrotoxic drugs should be chosen. If nephrotoxic drugs are unavoidable, therapeutic drug monitoring or serial evaluation of renal function is essential.

So-called "complementary medications" (sometimes called herbal medicines, naturopathic remedies and phytomedicines) are becoming increasingly popular. The potential for interactions with prescribed medications or simple adverse consequences in patients with reduced kidney function should be considered for patients receiving these medications. Herbal products which should be avoided in patients with renal dysfunction include aristolochic acid, barberry, buchu, Chinese herbal drugs, juniper, licorice, and noni juice.⁹⁵

Phosphorus Retention, Hyperphosphatemia and Renal Secondary Hyperparathyroidism

Serum phosphorus concentrations represent the net balance between dietary intake and renal excretion of phosphorus. Therefore, maintaining serum phosphorus concentrations within the normal range as renal function is lost requires modification of phosphorus intake. In theory, optimum control of hyperphosphatemia would be achieved by reducing dietary phosphorus intake "in proportion" to the decrease in glomerular filtration rate.

Without treatment, phosphorus retention, hyperphosphatemia and renal secondary hyperparathyroidism occurs in most dogs and cats with stage 3 or stage 4 CKD.^{38,98} Although hyperphosphatemia has been linked to pruritus, conjunctivitis, renal osteodystrophy, and soft-tissue calcification in humans, hyperphosphatemia *per se* is rarely linked to clinical signs in dogs and cats with CKD. Rather, minimizing phosphorus retention and hyperphosphatemia is an important therapeutic goal in patients with CKD because it appears to limit renal secondary hyperparathyroidism and prolong survival.^{56,98}

The first step in correcting hyperphosphatemia is to restore hydration and correct prerenal hyperphosphatemia. Minimizing long-term phosphorus retention and hyperphosphatemia may be accomplished by limiting dietary phosphorus intake, oral administration of agents that bind phosphorus within the lumen of the intestines, or a combination of these methods. The usual approach is to start with diet therapy, and add phosphorus binding agents if diet therapy alone fails to normalize serum phosphorus concentrations. Diet therapy with or without phosphate binding agents normalizes serum phosphorus levels in most patients. However, phosphorus restriction alone appears to be insufficient to normalize serum PTH levels in some patients.^{38,98} In such patients, a combination of limiting phosphorus intake combined with administration of calcitriol has been recommended.³⁸ Nagode and colleagues have suggested that normalization of PTH levels using calcitriol therapy may provide clinical benefits that cannot be achieved by phosphorus restriction alone including amelioration of many clinical signs associated with CKD. We have been unable to completely substantiate these claims, but did find that calcitriol therapy significantly prolonged survival in dogs with stages 3 and 4 CKD.

DIETARY PHOSPHORUS RESTRICTION

Dietary phosphorus restriction is an important and effective intervention for normalizing phosphorus balance. It may be effective in normalizing serum phosphorus concentrations in most stage 3 and some stage 4 CKD patients. It will also decrease the dosage of intestinal phosphorus binding agents needed to bind dietary phosphorus in patients with more severe hyperphosphatemia. Dietary phosphorus restriction is clearly indicated for patients with hyperphosphatemia. However, because phosphorus retention and hyperparathyroidism may occur before serum phosphorus concentrations exceed normal limits and because fasting serum phosphorus concentrations may not accurately reflect overall phosphorus balance, phosphorus restriction may be indicated before the onset of overt hyperphosphatemia.⁹⁹

Because proteins are a major source of dietary phosphorus, manufactured and homemade renal diets are usually restricted in both protein and phosphorus content. Typical commercial dog foods contain approximately 1 to 2 percent phosphorus on a dry matter basis and provide about 2.7 mg/kcal or more phosphorus. Modified protein diets designed for dogs with kidney disease may contain as little as 0.13 to 0.28 % phosphorus on a dry matter basis

and provide about 0.3 to 0.5 mg/kcal of phosphorus. Typical commercial cat foods contain from 1 to 4 percent phosphorus on a dry matter basis and provide about 2.9 mg/kcal or more phosphorus. Modified protein diets designed for cats with CKD may contain as little as 0.5 % phosphorus on a dry matter basis and provide about 0.9 mg/kcal of phosphorus.

Phosphorus retention in CKD appears to occur in multiple compartments. As dietary phosphorus restriction reduces serum phosphorus levels, phosphorus leaches out of tissues delaying the overall reduction in serum phosphorus concentration. Thus, the overall efficacy of dietary phosphorus restriction in reducing serum phosphorus concentrations may not occur until the patient has been consuming the phosphorus-restricted diet for several weeks. In a study in cats with renal insufficiency/failure, the effect of restricting dietary phosphorus intake was apparent after 28 to 49 days.⁹⁸ Samples obtained for determinations of serum phosphorus concentration should be collected after a 12-hour fast to avoid postprandial effects. Sample hemolysis should be avoided because red blood cells contain substantial quantities of phosphorus.

As described previously (see diet therapy), the goal of phosphate therapy is based on the patient's stage of CKD. While PTH levels generally decline as serum phosphorus levels decline, achieving the therapeutic goal for serum phosphate concentration may not always result in normalization of PTH concentration. In a recent clinical study of cats with chronic renal insufficiency/failure, dietary phosphorus restriction was associated with a normal serum phosphorus concentration in 12 of 13 cats while PTH concentration was normalized in only 8 of these 13 cats.⁹⁸ It is unclear whether further reducing serum phosphorus concentration within the normal range or using normalization of PTH levels as the preferred therapeutic endpoint would be of any clinical benefit.

Hypercalcemia was reported to develop in two cats managed with dietary phosphorus restriction.⁹⁸ The significance of the relationship, if any, between dietary phosphorus restriction and hypercalcemia in these two cats is unclear.

Unfortunately, as CKD becomes more advanced, dietary phosphorus restriction alone may be insufficient to prevent hyperphosphatemia. When hyperphosphatemia persists despite dietary phosphorus restriction, administration of intestinal phosphorus binding agents should be considered.

INTESTINAL PHOSPHORUS BINDING AGENTS

Phosphorus binding agents should be used in conjunction with dietary phosphorus restriction when dietary therapy alone fails to reduce serum phosphorus concentrations to the normal range. Dietary phosphorus intake should be reduced before initiating therapy with intestinal phosphorus binding agents in order to minimize the quantity of phosphorus that must be bound. High dietary phosphorus content may greatly limit the effectiveness of phosphorus-binding agents, or substantially increase the dosage required to achieve the desired therapeutic effect.¹⁰⁰ Administration of 1500 to 2500 mg of aluminum carbonate to dogs with moderate CKD failed to consistently correct hyperphosphatemia when dogs were fed diets containing greater than 1.0% phosphorus on a dry matter basis.¹⁰¹

Currently available phosphorus binding agents include aluminum-based and calcium-based exchange compounds that liberate varying amounts of their associated cation (e.g. aluminum, calcium) as dietary phosphorus is bound. Factors which may influence selection of a specific phosphorus binding agent include availability, palatability, and the associated cation. Aluminum-based binding agents have generally been preferred for dogs and cats because they are effective, inexpensive and seemingly have few side-effects. However, concern about the potential toxic effects of aluminum in humans has caused many aluminum-containing drugs to be removed from the market. Encephalopathies, microcytic anemia, and bone disease (particularly osteomalacia) related to aluminum toxicity have been extensively reported in humans patients treated with these drugs. The potential for toxicity of aluminum salts in dogs and cats has been confirmed, but there is little evidence that use of these drugs leads to clinically important aluminum toxicity in dogs and cats. Calcium-based drugs have the potential to promote hypercalcemia, particularly when administered between meals or used in combination with calcitriol.

Aluminum-containing intestinal phosphorus binding agents include aluminum hydroxide, aluminum carbonate, and aluminum oxide. Initial doses of 30 to 100 mg/kg/day have been recommended for these aluminum-based phosphorus-binding agents. They are available over-the-counter in liquid, tablet or capsule forms from most pharmacies as antacid preparations. In humans, capsules and tablets are less effective than liquids, but liquid preparations may be unpalatable to some dogs and cats. Sucralfate, a complex polyaluminum hydroxide salt of sulfate used primarily for treatment of gastrointestinal ulcerations may also be effective in binding phosphorus within the intestine.

Calcium-based phosphorus binding agents include calcium acetate, calcium carbonate, or calcium citrate. Because calcium-based products may promote clinically significant hypercalcemia, it is recommended that serum calcium concentrations be monitored intermittently when using these drugs. They should not be used in hypercalcemic patients. When indicated, they may be used between meals as a source of additional dietary calcium.

Calcium supplementation may increase the efficacy of phosphorus restriction in normalizing renal secondary hyperparathyroidism.

Reduced dosages of calcium carbonate and calcium acetate may be used concurrent with aluminum-based binding agents to limit risks of both hypercalcemia and aluminum toxicity. However, calcium citrate may promote absorption of aluminum and should therefore not be used in concert with aluminum-based binding agents. Calcium acetate is the most effective calcium-based phosphorus-binding agent as well as the agent least likely to induce hypercalcemia because it releases the least amount of calcium compared to the amount of phosphorus it binds.¹⁰⁰ Initial doses of 60 to 90 mg/kg/day have been recommended for calcium acetate and 90 to 150 mg/kg/day for calcium carbonate. Some calcium carbonate preparations may not be effective because they fail to dissolve well in the gastrointestinal tract; this may be investigated by examining the stool or obtaining radiographs of the abdomen for evidence of radiodense tablets that have failed to dissolve.

The most recent addition to the phosphorus binding armamentarium is the cationic polymer agent sevelamer hydrochloride (Renagel® Tablets and Capsules, Genzyme Corp.). The primary advantage of this drug is that it does not promote hypercalcemia or absorption of aluminum. However, it is more expensive than older phosphorus binding agents. In addition, concerns have been raised over its potential for inducing vitamin-K deficiency and hemorrhage. In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, K, and folic acid levels when given at doses of 6-100 times the recommended human dose. In clinical trials in humans, there was no evidence of reduction in serum levels of vitamins; however, patients in this study were receiving vitamin supplements. There is scant information on the safety, effectiveness or dosage of sevelamer in dogs and cats. On the basis of extrapolating the recommended dosage from humans, an initial dose of 30 and 135 mg/kg per day divided and given with meals may be considered. Because the contents of Renagel expand in water, the manufacturer recommends that tablets and capsules should be swallowed intact and should not be crushed, chewed, broken into pieces, or taken apart prior to administration. Sevelamer reportedly lowers total and low-density lipoprotein cholesterol concentrations and elevated high-density lipoprotein cholesterol levels in humans.¹⁰² Consideration should be given to monitoring clotting ability using the prothrombin time if this drug is used in dogs or cats with CKD.

Intestinal phosphorus binding agents render ingested phosphorus and the phosphorus contained in saliva, bile, and intestinal juices unabsorbable. Because the primary goal is limiting absorption of phosphorus contained in the diet, administration of phosphorus binding agents should be timed to coincide with feeding. These agents are best administered with or mixed into the food, or just prior to each meal. It is particularly important that calcium-based phosphorus-binding agents be administered with meals both to enhance the effectiveness of phosphorus binding and to minimize absorption of calcium and the risk of hypercalcemia.

Dosage of phosphorus binding agents should be individualized to achieve the desired serum phosphorus concentration. The effectiveness of therapy should be assessed by serial evaluation of serum phosphorus concentrations at about 2 to 4-week intervals. Dosage of calcium-based phosphorus binding agents should be decreased if serum calcium concentrations exceed normal limits; additional aluminum-based agents should be used in these patients if hyperphosphatemia persists.

Dehydration

Fluid balance in patients with polyuric CKD is maintained by compensatory polydipsia. If water consumption is insufficient to compensate for polyuria, dehydration is the result. This may occur as a consequence of lack of intake or lack of access to fresh, clean, unadulterated water. Cats and some dogs with CRF fail to consume sufficient water to prevent chronic or recurrent dehydration. In addition, acute gastrointestinal fluid losses resulting from renal or non-renal causes may lead to extracellular fluid volume depletion.

Dehydration and volume depletion promote renal hypoperfusion and prerenal azotemia that may exacerbate the clinical and laboratory abnormalities of chronic renal insufficiency/failure. In addition to prerenal azotemia, dehydration may be associated with electrolyte disturbances such as hyperphosphatemia, hyperkalemia, and metabolic acidosis. Clinical signs characteristic of dehydration include decreased appetite, lethargy, and constipation. In some patients, prerenal azotemia may precipitate uremic crisis. Further, if dehydration and decreased renal blood flow are allowed to persist, additional ischemic renal damage may occur.

Patients that develop recurrent episodes of signs consistent with dehydration are candidates for intermediate- to long-term subcutaneous fluid therapy to be administered at home by the owner. The principal benefits of subcutaneous fluid therapy include improved appetite and activity and reduced constipation. The decision to recommend administration of subcutaneous fluids should be made on a case-by-case basis. Not every patient with chronic renal insufficiency/failure requires or will benefit from fluid therapy. While a substantial number of cats with CKD appear to benefit from subcutaneous fluid therapy, proportionately fewer dogs require fluid therapy. In addition, home administration of subcutaneous fluids is not appropriate for all owners. While it is inexpensive, it

does require time and may cause stress on the owner-pet relationship. It also has the potential to promote hypokalemia, hypertension and fluid overload. While there is a risk of subcutaneous infections, this appears to be an uncommon complication when owners are taught proper technique.

Normal saline or lactated Ringer's solution are the fluids most commonly used for home subcutaneous fluid therapy. They are well tolerated by most cats and dogs and appear to be reasonable choices for most patients. However, chronic administration of lactated Ringer's solution or normal saline as the principal maintenance fluid source may cause hypernatremia because they fail to provide sufficient electrolyte-free water. Ideally, fluids selected for chronic parenteral administration should provide free water as well as electrolytes for maintenance. A solution containing 0.45% saline and 2.5% glucose supplemented with 20 meq/L of potassium chloride meets these requirements. Unfortunately, fluids containing dextrose may be irritating when administered subcutaneously, and their use should be discontinued if the patient indicates discomfort when they are given. A typical cat or small dog receives approximately 75 to 150 ml of fluids given daily or as needed. Chronic subcutaneous fluid therapy can result in fluid overload in some patients, particularly when fluid volumes in excess of those recommended here are used. We have seen several cats given large quantities of fluid (200 to 400 ml/day) present with severe dyspnea due to pleural effusion. This condition can usually be avoided by reducing the volume of fluids administered.

Response to long-term subcutaneous fluid therapy should be monitored by serially assessing hydration status, clinical signs, hematocrit, total serum protein concentrations, blood pressure, and serum urea nitrogen, creatinine, phosphorus, potassium, total CO₂, sodium and chloride concentrations.

Hypokalemia and Potassium Depletion

Potassium depletion and hypokalemia are common in cats with CKD. Estimates of the prevalence of hypokalemia in this population of cats are in the range of 20 to 30%.^{2,8,9} Total body potassium depletion is likely to be even more common than hypokalemia.⁶¹ In contrast, hypokalemia is an uncommonly recognized complication of canine CKD. The mechanisms underlying development of hypokalemia in cats with CKD remain unclear, but inadequate potassium intake coupled with increased urinary and/or fecal losses have been hypothesized to play a role. While increasing the potassium content of renal diets has reduced the incidence of overt clinical signs of hypokalemia, hypokalemia remains a common laboratory finding in cats with renal insufficiency/failure. The antihypertensive agent amlodipine may promote hypokalemia in cats with chronic renal insufficiency/failure.¹⁰³

Hypokalemia and potassium depletion may affect the kidneys or muscles of cats with CKD. Diets low in potassium and high in acid content have been implicated in impairing renal function and promoting development of lymphoplasmacytic tubulointerstitial lesions in cats.^{32,59-62} Potassium depletion may result in reduced renal blood flow and GFR as a consequence of angiotensin II and thromboxane-mediated renal vasoconstriction. In addition, hypokalemia may promote polyuria by impairing renal responsiveness to antidiuretic hormone, and by stimulating the brain thirst centers through increased levels of angiotensin II. Hypokalemic polymyopathy, characterized by generalized muscle weakness and cervical ventroflexion, is a well-recognized complication of chronic renal insufficiency/failure in cats.

Oral supplementation of potassium has been recommended for cats with renal insufficiency/failure in order to treat or prevent renal and muscular consequences of potassium depletion and hypokalemia. While there is a consensus of opinion that cats with hypokalemia should receive potassium supplementation, the justification for "prophylactic" potassium supplementation in normokalemic cats is not well established. While potassium supplementation is unlikely to be medically harmful to polyuric, normokalemic cats, administration of an oral medication may impose an unnecessary burden on both the cat and the cat owner. Patient acceptance may be a limitation due to the unpleasant flavor of potassium salts.

Oral replacement is the safest and preferred route for administering potassium. Parenteral therapy is generally reserved for patients requiring emergency reversal of hypokalemia or for patients that cannot or will not accept oral therapy. Potassium chloride may be added to fluids administered subcutaneously up to 30 meq/L.

Potassium may be supplemented orally as the gluconate or citrate salts. Potassium chloride is not recommended because of its lack of palatability and acidifying nature. Potassium gluconate may be administered orally as tablets, flavored gel, or in a palatable powder form (Tumil-K, Daniels Pharmaceuticals, Inc.). Depending on the size of the cat and severity of hypokalemia, potassium gluconate is given initially at a dose of 2 to 6 mEq per cat per day. Acidosis is a major risk factor for development of hypokalemia and therefore should be rectified early in the management of hypokalemia. Potassium citrate solution (Polycitra®-K Syrup, Baker Norton) is an excellent alternative that has the advantage of providing simultaneous alkalization therapy. Potassium citrate is initially given at a dose of 40 to 60 mg/kg/day divided into 2 or 3 doses. If muscle weakness is present, it usually resolves within 1 to 5 days after initiating parenteral or oral potassium supplements. Potassium dosage should thereafter be adjusted based on the clinical response of the patient and serum potassium determinations. Serum potassium concentration should initially be monitored every 7 to 14 days and the dosage adjusted accordingly to establish the

final maintenance dosage. In patients with hypokalemic polymyopathy, it may be necessary to monitor serum potassium concentrations every 24 to 48 hours during the initial phase of therapy. It is unclear whether all cats require long-term potassium supplementation; however, preliminary evidence suggests that such therapy is likely to be required by at least some older cats with chronic renal insufficiency/failure.

Routine supplementation of low oral doses of potassium (2 meq/day) has been recommended for all cats with chronic renal insufficiency/failure.⁵⁸ This recommendation appears to be based on the as yet unproved hypothesis that in some cats with CKD, hypokalemia and potassium depletion might promote a self-perpetuating cycle of declining renal function, metabolic acidosis, and continuing potassium losses. It is proposed that supplementation may stabilize renal function before potassium depletion exacerbates the disease. Some investigators have observed positive responses to potassium supplementation in several normokalemic cats that had chronic renal insufficiency/failure. However, results of a recent clinical trial suggested that in cats with chronic renal insufficiency/failure that initially had normal serum potassium concentrations daily supplementation for 6 months with 4 meq of potassium gluconate was not demonstrably superior to providing sodium gluconate in restoring muscle potassium stores.⁶¹ However, there were only a small number of cats enrolled in this clinical trial. In addition, median muscle potassium content did increase in the potassium supplemented cats from 328 to 402 meq/kg, a value close to the value of 424 meq/L established for normal cat muscle. Thus, while the value of providing supplemental potassium to cats with chronic renal insufficiency/failure having normal serum potassium concentrations has not been established, it is clear that muscle potassium and probably total body potassium stores are likely to be reduced in cats with chronic renal insufficiency/failure, increasing the risk for developing hypokalemia. Further, there is evidence from this study that chronic supplementation of 2 to 4 meq/day of potassium is unlikely to be associated with significant adverse events. Based on current data, a recommendation cannot be made for or against routine supplementation of potassium.

Diets that are acidifying and restricted in magnesium content may promote hypokalemia. Therefore, they should therefore generally be avoided in cats with CKD. Intensive fluid therapy during uremic crises, particularly with potassium deficient fluids, may promote hypokalemia in cats or dogs that were not previously hypokalemic. Therefore, serum potassium concentrations should be monitored during fluid therapy and maintenance fluids should be supplemented with potassium chloride to prevent iatrogenic hypokalemia (concentrations of 13 to 20 meq/L are appropriate for maintenance fluids). Potassium given intravenously should not be administered at a rate exceeding 0.5 meq/kg/hour.

Metabolic acidosis

Alkalinization therapy designed to correct metabolic acidosis plays an important role in management of patients with chronic renal insufficiency/failure. Potential benefits of alkalinization therapy in these patients include: 1) ameliorating signs of uremic acidosis, including anorexia, lethargy, nausea, vomiting, muscle weakness, and weight loss, 2) minimizing the catabolic effects of metabolic acidosis on protein metabolism,⁵³ 3) enhancing the patient's capacity to adapt to additional acid stress resulting from such factors as diarrhea, dehydration, or respiratory acidosis, 4) limiting skeletal damage (demineralization and inhibited skeletal growth) resulting from bone buffering, and 5) rectifying adverse effects of severe acidosis on the cardiovascular system (impaired myocardial contractility and enhanced venoconstriction).¹⁰⁴

Although data are unavailable for dogs, a recent study in cats with chronic renal insufficiency/failure indicated that metabolic acidosis occurred in less than 10% of cats with stage 3 CKD, but approaches 50% of cats in uremic crisis.² Based on this data, it appears that only a minority of cats with clinically stable chronic renal insufficiency/failure are likely to benefit from routine alkalinization therapy. Thus, the decision to intervene with alkalinization therapy should be based on a laboratory assessment of the patient's acid-base status. Unfortunately, there is no clinical data providing an obvious intervention threshold for treating metabolic acidosis in dogs and cats. However, in studies performed at our research center, we have been unable to demonstrate any adverse clinical effects of mild to moderate chronic metabolic acidosis in cats with induced chronic renal insufficiency/failure. In absence of clear clinical data, we recommend considering alkalinization therapy for dogs and cats with stable chronic renal insufficiency/failure when blood gas analysis confirms plasma bicarbonate values remain below 15 mmol/L on more than one determination. However, for patients with metabolic acidosis associated with a blood pH below 7.10, immediate parenteral intervention with sodium bicarbonate should be considered to increase the blood pH above 7.20.¹⁰⁴

Because total CO₂ measurements are of questionable accuracy and yet remain the most common tool for establishing acid-base status for most dogs and cats, we recommend that blood gas analysis be performed to confirm metabolic acidosis whenever total CO₂ decline below 15 mmol/L. Low serum or plasma total CO₂ values obtained by autoanalyzer techniques should be confirmed by blood gas analysis because falsely low total CO₂ readings may occur when blood collection tubes are not fully filled or are exposed to air while awaiting analysis.¹⁰⁵ In addition,

there may be a substantial systematic difference between blood bicarbonate concentrations determined by blood gas analysis and serum total CO₂ concentrations determined on autoanalyzers due to inherent differences in the analytical methods. Appropriate reference ranges are equipment- and method-specific.

Treatment options for alkalinization therapy include diet, sodium bicarbonate, and potassium citrate. Most renal diets are neutral to slightly alkalinizing in effect and are an appropriate first step in mitigating metabolic acidosis. When several weeks of diet therapy alone fails to ameliorate the metabolic acidosis, alkalinization therapy should be considered.

Oral sodium bicarbonate is the most commonly used alkalinizing agent for patients with metabolic acidosis of chronic renal insufficiency/failure. Because the effects of gastric acid on oral sodium bicarbonate are unpredictable, the dosage should be individualized for each patient. A suggested initial dose of sodium bicarbonate is 8 to 12 mg/kg body weight given every 8 to 12 hours. Unfortunately, many dogs and cats find sodium bicarbonate distasteful unless given as tablets. Sodium bicarbonate is available as 5 and 10 grain tablets.

Potassium citrate may offer the advantage, especially in cats, of allowing for the simultaneous treatment of both hypokalemia and acidosis with a single drug. Metabolic acidosis when accompanied by potassium depletion or magnesium depletion may respond poorly to alkali therapy alone. However, in that potassium doses required for adequate correction of hypokalemia may exceed the citrate dose required to correct acidosis, there is a risk for excessive alkalinization. Starting doses of 40 to 60 mg/kg every 8 to 12 hours are recommended.

Regardless of the alkalinizing agent chosen, administration of several smaller doses is preferred to a single large dose in order to minimize fluctuations in blood pH. The patient's response to alkalinization therapy should be determined by performing blood gas analysis 10 to 14 days after initiating therapy. Ideally, blood should be collected just prior to administration of the drug. Dosage of the alkalinizing agent should be adjusted to maintain blood bicarbonate concentrations within the normal range. Because urine pH is often insensitive as a means of assessing the need for or response to treatment, it is not recommended for this purpose.

Arterial hypertension

RATIONALE FOR TREATMENT

Chronic kidney disease is the most common recognized cause for arterial hypertension in dogs and cats. In these species, hypertension has been linked to renal, ocular, neurological and cardiac complications. In dogs with naturally occurring chronic renal insufficiency/failure, higher initial blood pressure has been reported to be a risk factor for uremic crisis and mortality.¹⁷ In addition, retinopathy and hypertensive encephalopathy were detected in 3 of 14 dogs with blood pressure values exceeding 180 mmHg in this study. However, firm evidence that pharmacologically lowering blood pressure will prevent or ameliorate the renal and extrarenal complications of arterial hypertension in dogs is lacking.

Lethargy, blindness, retinal hemorrhage and detachment, cerebral hemorrhage, seizures, stupor, and ventricular hypertrophy have been reported in cats with hypertension.¹⁰⁶⁻¹⁰⁸ Although it is likely that elevated blood pressure promotes progressive renal injury in cats, there is as yet no reported evidence confirming this relationship. However, in contrast to dogs, there are studies supporting the value of therapeutic intervention for hypertension in cats. Subcutaneous administration of the antihypertensive drug hydralazine was reported to reduce the prevalence of seizures that developed as a consequence of hypertension following renal transplantation.¹⁰⁷ In a recent study using a surgically induced model of hypertensive renal insufficiency, only 2 of 10 cats receiving the antihypertensive agent amlodipine developed evidence of hypertensive retinal lesions, whereas these lesions developed in 7 of 10 cats receiving placebo.¹⁰⁶

INDICATIONS FOR TREATMENT

Unless there is evidence for hypertension-related organ injury (e.g. retinal lesions or neurological signs) or the systolic blood pressure is greater than 200 mmHg, the decision to initiate anti-hypertensive therapy is not an emergency. Before initiating therapy for arterial hypertension, the patient's blood pressure should be established based on blood pressure determinations performed at three successive clinic visits. Every effort should be made to minimize the risk that measured elevations in blood pressure represent a transient "white coat" effect, rather than a sustained elevation in blood pressure.¹⁰⁹

Patients with blood pressure values exceeding 160/100 mmHg should be considered for treatment. While specific values for diagnosis of arterial hypertension have not been established for dogs and cats, current evidence suggests that concurrent CKD may place them at increased risk for sustaining additional renal injury or developing complications associated with elevated blood pressure.^{17,106-108} Findings in two studies suggested that ocular lesions associated with elevated blood pressure occurred in cats with systolic blood pressure values exceeding about 160 mmHg. Similarly, in study in dogs with naturally occurring chronic renal insufficiency/failure, the risk for uremic crises and increased mortality was reported to be increased in a group of dogs with systolic blood pressure values

above 160 mmHg.¹⁷ However, this cut-off point was arbitrarily chosen in this study and should not be interpreted as the lower limit of hypertension.

GENERAL GOALS AND GUIDELINES FOR TREATMENT

The optimum endpoint for antihypertensive therapy has not been established for dogs and cats with CKD. In the absence of such information, treatment for arterial hypertension should be initiated cautiously with the goal of reducing blood pressure to at least below 160/100 mm Hg. Except in patients with acute, severe ocular or neurological lesions, rapid reduction in blood pressure is not necessary. Particularly in dogs, it may take weeks to months to achieve satisfactory blood pressure control.

Angiotensin converting enzyme inhibitors (ACEI) such as enalapril and benazepril, and calcium channel blocking (CCB) drugs such as amlodipine have potential renoprotective benefits and are therefore appropriate options for renal patients with hypertension.¹¹⁰ Angiotensin converting enzyme inhibitors generally produce a relatively small reduction in blood pressure.^{111,112} However, because of their beneficial role in altering intraglomerular hemodynamics, proteinuria, and the profibrotic effects of the intrarenal renin-angiotensin system, ACEI may have renoprotective effects even in absence achieving adequate blood pressure control. In a recent study, the ACEI enalapril reduced the severity of renal lesions that develop in dogs with surgically reduced renal mass.¹¹¹ Further, in dogs with naturally occurring glomerulopathies, the ACEI enalapril significantly reduced proteinuria and may have been beneficial in stabilizing renal function.²¹ On this basis, they appear to be the preferred antihypertensive agent for dogs with CKD. However, the role of the renin-angiotensin-aldosterone system (RAAS) and ACEI therapy in cats with CKD and hypertension is more controversial.¹¹³⁻¹¹⁶ Evidence that activation of the RAAS is consistently central to the genesis of hypertension in cats is contradictory, and ACEI have not been found to be consistently effective in lowering blood pressure in cats with CKD. Therapy using either benazepril or enalapril may be initiated in dogs or cats with CKD at a dose of 0.5 mg/kg given orally every 24 hours.

Calcium channel blockers preferentially antagonize preglomerular vasoconstriction, which theoretically, should not reduce glomerular hypertension. However, CCB have additional renoprotective properties.¹¹⁰ They may prevent renal injury by limiting renal growth, by reducing mesangial entrapment of macromolecules, and by attenuating the mitogenic effects of diverse cytokines and growth factors (e.g. platelet-derived growth factor and platelet-activating factor). In addition, amlodipine inhibits the *in vitro* proliferation of mesangial cells. However, clinical trials in humans have provided conflicting results as to the renoprotective effect of CCB beyond their antihypertensive effects. Controlled studies on the renoprotective effects of amlodipine in dogs and cats have not been published. However, our clinical experience has been that they are effective antihypertensive agents in dogs and cats with CKD. Because it is usually highly effective, has few side-effects, and has a relative rapid onset, the long-acting dihydropyridine calcium antagonist amlodipine is the antihypertensive of choice for most cats with CKD. Amlodipine is prescribed at a dose of 0.625 mg for cats less than 4 kg, and 1.25 mg for cats greater than 4 kg. In cats with CKD, amlodipine typically reduces systolic blood pressure by about 30 to 50 mmHg within the first one to two months of therapy.^{106,117}

Treatment of anemia of CKD

GENERAL GUIDELINES FOR MINIMIZING ANEMIA

An obvious but often overlooked consideration is minimizing iatrogenic blood loss. Iatrogenic loss is especially likely to occur in hospitalized cats and small dogs because of repeated sampling for diagnostic tests and monitoring. Therefore, the quantities of blood collected from these patients should be recorded and monitored.

Chronic low-grade gastrointestinal blood loss can also result in moderate to severe anemia in patients with chronic renal insufficiency/failure that would otherwise have sufficient endogenous erythropoietin production to maintain their hematocrit values in the low normal range. These patients may lack overt gastrointestinal signs or melena. Iron deficiency and an elevation in BUN/creatinine ratio above what is expected in context of the patient's diet may provide indirect evidence of occult gastrointestinal blood loss. Because of difficulty in confirming gastrointestinal hemorrhage, a therapeutic course with histamine H₂-receptor antagonists and sucralfate may be considered. Improvements in hematocrit and/or appetite indicate a positive response.

Iron deficiency is a relatively common problem in dogs and cats with CRF. In a recent study, the serum iron concentrations of 3 of 6 CRF dogs and 3 of 7 CRF cats were below the reference range; transferrin saturations less than 20%.¹¹⁸ Whether this is related primarily to inadequate intake and absorption of iron or increased losses of iron due to gastrointestinal blood loss is unclear. Unfortunately, iron status can be difficult to assess in dogs and cats. Serum iron levels can be used to screen for both iron deficiency and anemia of chronic inflammatory disease as contributing factors in the diagnostic evaluation of anemia. In dogs, serum iron levels may not reflect body iron stores in that normal values can occur in patients with iron deficiency. However, determining stainable iron content in bone marrow is helpful assessing body iron stores and may detect problems not identified by serum iron levels or transferrin saturation. When low serum iron levels reflect true iron deficiency, bone marrow stainable iron levels

will be low; in those with anemia of chronic inflammatory disease, levels will be normal or high reflecting sequestration. The distinction is important because anemia of chronic inflammatory disease will not improve in response to iron supplements; and may even result in iron overload. It is necessary to identify and remove the concurrent inflammatory disease to treat anemia of chronic inflammatory disease. Transferrin saturation (estimated by dividing serum iron by total iron binding capacity) may be useful for assessing the ability of the mobilizable iron stores (perhaps independent of total tissue iron stores) to meet the demands of erythropoiesis and, thus, is particularly useful in evaluating patients during periods of increased erythropoiesis such as during recombinant human erythropoietin (rHuEPO) therapy.

Oral supplementation with ferrous sulfate is the preferred therapy for treatment of iron deficiency anemia and also for prevention of iron-deficient erythropoiesis in patients starting erythropoietin replacement therapy. Alternatively, iron dextran may be administered by intramuscular injection. However, parenteral administration of iron is associated with a small risk of anaphylaxis, shunting of iron to reticuloendothelial storage, and iron overload. Although serum iron levels and transferrin saturation should be monitored to adjust therapy, starting doses of iron sulfate of 50-100 mg/day for cats and 100-300 mg/day for dogs have been recommended. Oral iron supplements may be associated with gastrointestinal upset and diarrhea, so small divided doses may be preferable.

In addition to iron deficiency, other nutritional abnormalities may contribute to anemia in patients with chronic renal insufficiency/failure. Protein malnutrition, and its attendant changes in plasma amino acid and hormone concentrations, is known to cause suboptimal erythropoiesis and anemia. Similar changes occur in human patients and may reflect mild protein/calorie malnutrition commonly present in advanced CKD. Although they have not been examined in dogs and cats, deficiencies in riboflavin (vitamin B2), cobalamin (vitamin B12), folate, niacin or pyridoxine (vitamin B6) might theoretically induce nutritional anemia. Vitamin status cannot be easily determined in dogs and cats; however, deficiencies should be suspected in patients with persistent anorexia, protein/calorie malnutrition or gastrointestinal malabsorption. In addition, some drugs may predispose the patient to nutritional anemia even when dietary intake is normal. For example, therapy with trimethoprim or methotrexate may interfere with cellular folate metabolism. Hypersegmentation of the polymorphonuclear leukocytes may provide a clinical indication of vitamin B12 or folate deficiency.

Risk of nutritional deficiencies can be minimized through timely initiation of proper diet modifications and, if necessary, use of dietary supplements. In addition to minimizing renal anemia, preventing protein/calorie malnutrition may reduce morbidity. B vitamins, folate and niacin can be provided as an oral supplement often with iron.³³ Care must be taken with multivitamins not to over supplement the fat-soluble vitamins A and D.

Red blood cell life span is decreased in advanced CKD. Proposed mechanisms for this mild hemolytic tendency include a malfunctioning of the membrane $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ pump and impaired regeneration of reduced glutathione needed to prevent hemoglobin oxidation. Cat hemoglobin appears to be especially prone to oxidative stress as evidenced by the frequent observation of Heinz bodies in their red blood cells. Cats with chronic renal insufficiency/failure having large numbers of Heinz bodies tend to be more anemic. Drugs and foods (e.g., onions, propylene glycol, methylene blue, sulfonamides) that promote formation of Heinz bodies should be avoided in uremic pets whenever possible.

Parathyroid hormone (PTH) has been postulated to play a role in the pathogenesis of anemia of CRF. Parathyroid hormone inhibits growth of all bone marrow cell lines in vitro. However, leukopenia and thrombocytopenia are not characteristic of chronic renal insufficiency/failure arguing against an important role for PTH-induced bone marrow suppression. In a clinical series of canine CRF patients with anemia, the authors found no correlation between PTH levels and the degree of anemia.³⁴

It has been postulated that increased serum phosphorus leads to increased intracellular red cell phosphorus. This in turn increases red cell 2,3 DPG levels, a noteworthy finding in anemic CRF patients.³⁴ Increased 2,3 DPG levels cause a rightward shift in the oxyhemoglobin dissociation curve improving tissue oxygenation and decreasing the stimulus for erythropoietin synthesis.

ANABOLIC STEROIDS

Anabolic steroids were at one time the mainstay of therapy for anemia associated with CKD. Although controlled safety and efficacy studies in dogs and cats are lacking, clinical experience with anabolic steroids has been disappointing. With the advent of rHuEPO therapy, androgens have largely fallen out of favor for treatment of renal anemia in human and veterinary medicine. Based on studies in human patients and clinical experience with veterinary patients, androgens appear to work in only a small percentage of patients (usually those mildly affected), have a long delay to onset of action, and may be associated with undesirable side effects. Administration of anabolic steroids for treatment of dogs and cats with anemia of CKD should probably be limited to those patients with symptomatic anemia in which all other factors adversely affecting erythropoiesis (nutritional deficiencies,

blood loss, hemolysis, concurrent disease) have been eliminated and other treatment options (erythropoietin, transfusion) are unavailable or have been exhausted.

BLOOD TRANSFUSION

Transfusions of packed red blood cells or whole blood may be indicated for anemic CKD patients who need rapid correction of their anemia, as in preparation for surgery. For some patients, repeated transfusions can be used for long-term maintenance of hematocrit. However, several drawbacks have limited the use of this therapy in dogs and cats including lack of availability and expense of blood products, increasing risk of transfusion reactions with multiple transfusions, risk of immunosuppression, risk of transfer of infectious agents, and decreased life span of transfused cells in uremic patients. Even for the first transfusion, only compatible blood products (as determined by crossmatching) should be used in both dogs and cats. The post-transfusion target hematocrit should be the low end of the normal range. This should be adequate to reverse the anorexia and fatigue associated with the anemia while minimizing the complications of too rapid an increase in blood volume and viscosity such as circulatory overload, hypertension and seizures.

HORMONE REPLACEMENT THERAPY

Hormone replacement therapy using rHuEPO has become the treatment of choice for anemia of CRF in cats and dogs when hematocrit values decline below about 20% and clinical signs are attributable to the anemia. Administration of rHuEPO causes a dose-dependent increase in hematocrit.¹¹⁸ Correction of hematocrit to low normal takes approximately 2 to 8 weeks depending on the starting hematocrit and dose given. As the anemia is corrected, most clients report that their pets show increases in appetite, body weight, energy level and sociability.¹¹⁸

Initially, erythropoietin is usually administered at a dosage of 50 to 150 units/kg subcutaneously three times weekly. Most dogs and cats should be started at 100 units/kg administered three times weekly. Hematocrit is monitored weekly or biweekly until a target hematocrit of approximately 30 - 40% for cats and 37% to 45% for dogs is achieved.¹¹⁸ When anemia is severe (hematocrit <14%) but not requiring transfusion, daily therapy with 150 units/kg may be preferred for the first week. In the presence of hypertension or when anemia is not severe, a dosage of 50 units/kg three times per week may help to prevent increases in blood pressure and iron-deficient erythropoiesis. When a hematocrit at the low end of the target range is reached, the dosing interval should be decreased to twice weekly. Most animals require 50 -100 units/kg two to three times weekly to maintain their hematocrit in the target range; however, the dose and dosing interval required to maintain individual patients in the normal range is highly variable. Ongoing monitoring of hematocrit will be necessary to allow adjustments in dose and dosing interval. Animals requiring more than 150 units/kg three times weekly should be evaluated for erythropoietin resistance. Because of the lag time between dosage adjustment and effect on hematocrit, patience must be exercised so as not to adjust the dose too frequently. Frequent dose adjustments will result in rapid, unpredictable changes in hematocrit and an inability to find a stable dosing regimen. In general, dosage should not be changed any more often than once monthly. Avoiding iatrogenic polycythemia is especially important.

The basis for individual differences in response to rHuEPO is incompletely understood. Several causes of blunted response or failure to resolve renal anemia with rHuEPO therapy have been identified including: functional or absolute iron deficiency, anti-rHuEPO antibody formation, ongoing gastrointestinal blood loss or hemolysis, concurrent inflammatory or malignant disease, and aluminum overload (not documented in veterinary patients). Owner errors related to drug storage, handling, or administration may account for some instances of poor response to rHuEPO therapy.

The demand for iron associated with stimulated erythropoiesis is high, and human patients without pre-existing iron overload will exhaust iron storage during rHuEPO therapy. The same appears true of dogs and cats. Iron supplementation is therefore recommended for all patients receiving rHuEPO therapy.

Adverse effects related to rHuEPO therapy in dogs and cats may include systemic hypertension, seizures, local reactions at the injection site, and development of antibodies directed at erythropoietin.¹¹⁸ Hypertension may develop or increase in severity with rHuEPO therapy. Increased peripheral vascular resistance secondary to improved oxygen delivery and reversal of the vasodilation induced by chronic hypoxia may contribute to this effect. Increased blood viscosity associated with the increased hematocrit is only a minor contributor.

Seizures have been observed in human, canine, and feline patients being treated with rHuEPO that have no prior history of seizure a disorder.¹¹⁸ In dogs and cats, they have been reported in the setting of moderate to severe azotemia. Although hypertension, anemia, and uremic encephalopathy may be contributory, in humans, seizures are thought to be related to compensatory adaptations to increases in red blood cell mass. Seizures are not thought to be directly related to rHuEPO.

Allergic reactions including cutaneous or mucocutaneous reactions or cellulitis sometimes with fever and arthralgia were uncommonly observed in both dogs and cats early in the course of rHuEPO therapy.¹¹⁸ Lesions generally resolved within a few days and some did not recur when therapy was reinstated.

The most important complication associated with use of rHuEPO is refractory anemia and hypoplasia of the erythroid bone marrow associated with formation of neutralizing anti-rHuEPO antibodies.¹¹⁸ In some affected patients, the severity of anemia was worse than before initiation of rHuEPO treatment. This observation suggested that the anti-rHuEPO antibodies were effective in interfering with the erythropoietin effects of rHuEPO and endogenous erythropoietin. The rHuEPO protein appears to be immunogenic in many, but not all, dogs and cats with antibody titers developing at variable times from several weeks to months after the onset of therapy. After cessation of therapy, antibody titers declined. In the absence of a widely available anti-EPO antibody assay, bone marrow myeloid/erythroid ratios provide the best method to ascertain if rHuEPO resistance is due to antibody formation. After therapy is stopped and antibody titers decline, suppressed erythropoiesis may be reversible and pre-treatment levels of erythropoiesis are attained.

The relatively high prevalence of anti-rHuEPO antibody production prompts the question of when to initiate rHuEPO therapy. Premature initiation of erythropoietin therapy with subsequent development of anti-erythropoietin antibodies may deprive the patient of the clinical benefits of this therapy when clinical signs of anemia eventually do develop and rHuEPO can be of greatest clinical benefit. When hematocrit values are below 20%, anemia likely contributes to adverse clinical signs characteristic of uremia. In addition, degree of azotemia, expected rate of progression of kidney failure, appetite and willingness to eat therapeutic diets, and rate of progression of anemia must all be considered in the risk/benefit analysis of when to start therapy. The advantages and disadvantages of rHuEPO therapy should be discussed with the owners when anemia appears to be contributing to the patient's deteriorating quality of life. Many cat owners consider quality of life to be as or more important than quantity of life.

A potentially less immunogenic and longer-acting form of erythropoietin, *darbepoietin*, may be a suitable alternative to r-HuEPO therapy. Although there is a paucity of information concerning the clinical use of darbepoietin in canine and feline patients, the structural and pharmacologic properties of the drug may prove beneficial in treating animals with hypoproliferative anemias. To date, there have been a few anecdotal reports of the use of darbepoietin in dogs and cats with suspected anti-rHuEPO antibodies as well as well as a first line treatment for anemia of CKD. In theory, darbepoietin should be as effective as rHuEPO in stimulating the production of red blood cells in dogs and cats, and may be less immunogenic. The addition of the 2 N-linked glycosylation sites will hopefully shield more of the polypeptide from the immune system, thus reducing immunogenicity. In addition, the increased biologic activity and prolonged serum half-life should allow for smaller dosages to be given less frequently, resulting in decreased immune stimulation.

Until clinical investigations that establish the appropriate dose and dosing interval of darbepoietin in cats and dogs have been completed, clinical judgment and careful monitoring is required when this drug is used. Amgen, the company that manufactures darbepoietin and one brand of rHuEPO (Epogen®) provides a conversion chart on their website (www.aranesp.com) for switching from rHuEPO to darbepoietin. In general, the recommended frequency of administration of darbepoietin is approximately 1/3 of that used for rHuEPO. For example, if a patient requires thrice weekly dosing of rHuEPO, they may only require one weekly administration of darbepoietin. It is important to note that darbepoietin is supplied in a concentration of µg/ml, while rHuEPO is supplied in IU/ml. A conversion factor of 200IU rHuEPO = 1µg darbepoietin has cautiously been suggested for humans. Using this guideline, the total weekly dosage of rHuEPO in IU should be divided by 200 to obtain the µg dosage of darbepoietin to be administered once weekly.¹⁴ Once the target PCV has been attained, the frequency of administration may be decreased to every other week, or longer, if the PCV is maintained. Dosage adjustments should not be made more frequently than every 4 weeks.

Judicious and frequent monitoring of the PCV is essential when using darbepoietin; it should not be administered to a patient without first checking a PCV. As with rHuEPO, darbepoietin should only be used in patients that are iron replete. Iron supplementation should be provided, or iron stores should be monitored in all patients receiving darbepoietin. Likewise, blood pressure should be carefully monitored in patients treated with any erythropoietic stimulating protein. Adverse effects attributable to treatment with darbepoietin in humans are similar to those reported with rHuEPO, and include hypertension, pain at injection site, infection, myalgia, headache and GI signs.

Darbepoietin alfa is a novel erythropoiesis stimulating protein that may be beneficial in the management of veterinary patients with CKD associated anemia. Structural differences may make darbepoietin less immunogenic, while the longer half-life means that it may be administered less frequently than rHuEPO while maintaining the same level of clinical effectiveness. Clinical trials examining the safety and efficacy of darbepoietin in dogs and cats are required before therapeutic recommendations can be made.

FUTURE TREATMENT DIRECTIONS

Future options for treatment of anemia of CKD may include development of species-specific erythropoietin and gene therapy.¹¹⁹ Although not commercially available, recombinant canine and feline erythropoietin have been developed.¹²⁰ They offer the hope of erythropoietin replacement therapy in dogs and cats without concern for anti-erythropoietin antibody formation. If concern for antibody formation can be eliminated, erythropoietin therapy could be initiated earlier in the course of chronic renal insufficiency/failure. It also has been demonstrated that gene therapy can be used to induce extra-renal production of erythropoietin in cats.¹²¹

Calcitriol therapy

RATIONALE FOR CALCITRIOL THERAPY

An undesirable consequence of reduced renal production of calcitriol is renal secondary hyperparathyroidism. Calcitriol (1,25-dihydroxyvitamin D), the most active metabolite of vitamin D, results from renal hydroxylation of 25-hydroxyvitamin D. Normally, calcitriol inhibits PTH synthesis and release and parathyroid gland growth, an effect mediated by the vitamin D receptor in the parathyroid gland. As functioning renal mass declines, renal production of calcitriol declines. In addition, phosphorus retention also inhibits renal hydroxylation of 25-hydroxyvitamin D to calcitriol and directly stimulates PTH release. By reducing PTH levels, calcitriol therapy minimizes abnormalities associated with renal secondary hyperparathyroidism.

The effectiveness of calcitriol therapy in reducing PTH levels in dogs and cats with CKD is well established.³⁸ Although PTH has been proposed as a potential uremic toxin responsible for many constitutional signs or uremia, studies performed in our center have failed to confirm the clinical benefits of reducing PTH levels on these constitutional signs in dogs and cats. Calcitriol was effective in reducing uremic crises and delaying premature death due to renal causes in dogs with stages 3 and 4 CKD. A favorable effect of calcitriol was not detected in cats with CKD. Hypercalcemia did not appear to be a common complication in these studies. Calcitriol dosing was begun at 2.5 ng/kg/day and adjusted according to changes in ionized calcium and PTH levels.

Despite reported favorable impressions concerning use of calcitriol, its role in managing dogs and cats with CKD should be confirmed by randomized, controlled clinical trials. Routine clinical practice is never "blind," since owners and veterinarians know when active treatment is being received. Interpretation of uncontrolled studies is confounded by the desire of pet owners and clinicians for success, and the placebo effect, which can cause both parties to overestimate efficacy. In addition, calcitriol has the potential to promote hypercalcemia and renal injury if improperly used. A recommendation for or against routine use of calcitriol awaits results of properly designed controlled clinical trials.

GUIDELINES FOR USING CALCITRIOL

The primary goal of calcitriol therapy is to prevent or correct renal secondary hyperparathyroidism and its consequences. However, the decision to use calcitriol must be made with caution because hypercalcemia is a potentially serious complication. Sustained calcitriol-induced hypercalcemia will likely result in reversible or irreversible reduction in GFR. Although hypercalcemia reportedly occurs in 30% to 57% of humans treated with calcitriol, hypercalcemia appears to be an uncommon side effect in dogs treated with dosages in the range of 2.5 to 3.5 ng/kg/day.⁴³ Hypercalcemia is likely to occur when calcitriol therapy was combined with calcium-containing phosphorus binding agents, particularly calcium carbonate.

Serum phosphorus concentrations must be reduced to 6.0 mg/dl or lower before initiating calcitriol therapy (consult the section of this chapter on management of hyperphosphatemia). Serum phosphorus concentrations > 6.0 mg/dl may inhibit the effectiveness of calcitriol therapy and enhance the tendency for calcitriol to promote renal mineralization and injury. In addition, phosphorus restriction and calcitriol therapy are likely additive in reducing plasma PTH activities. Thus, serum calcium and phosphorus concentrations should be carefully monitored in patients receiving calcitriol.

Calcitriol rapidly and effectively suppresses renal secondary hyperparathyroidism. An important advantage of calcitriol over other forms of vitamin D therapy in CKD is that calcitriol does not require renal activation for maximum efficacy. Dogs and cats appear to require much lower dosages of calcitriol than those recommended for humans calculated on the basis of body weight.³⁸ Nagode and colleagues have recommended a dosage of 2.5- to 3.5 ng/kg body weight per day given orally to dogs and cats with CKD. The optimum maintenance dosage for calcitriol must be determined for each patient on the basis of serial evaluation of serum calcium and phosphorus and plasma PTH concentrations. The recommended endpoint of calcitriol therapy is normalization of PTH activity in absence of hypercalcemia. When the dose of calcitriol necessary to normalize PTH levels is associated with hypercalcemia, the daily dose may be doubled and given every other day. This approach is thought to be less likely to induce hypercalcemia because the effect of calcitriol on intestinal calcium absorption is related to the duration of exposure of intestinal cells to calcitriol.

When plasma PTH concentration is markedly elevated or when standard therapy with calcitriol fails to normalize plasma PTH levels, pulse calcitriol therapy has been recommended.³⁸ In this approach, patients are given 20 ng/kg of calcitriol twice per week in the evening on an empty stomach. Pulse therapy is usually used no longer than 1 to 2 months to suppress resistant hyperparathyroidism. If successful, calcitriol is then given at the standard daily dose.

Because it enhances intestinal absorption of calcium and phosphorus, calcitriol should not be given with meals. Custom-made capsules or liquid preparations containing appropriate doses of calcitriol for use in dogs and cats are available from compounding pharmacies. Compounded calcitriol preparations should contain appropriate preservatives to prevent oxidation.

Early detection of hypercalcemia is indicated to limit the extent of renal injury. However, the onset of hypercalcemia after initiation of vitamin D therapy is unpredictable (i.e. it may occur after days to months of treatment). Therefore, continued monitoring of serum calcium, phosphorus, and creatinine concentrations are necessary to detect hypercalcemia, hyperphosphatemia, or deteriorating renal function before irreversible renal damage ensues. Serum calcium, phosphorus, urea nitrogen, and creatinine concentrations should be monitored one week and one month after initiating calcitriol therapy, and monthly to bimonthly thereafter. The product of serum calcium and phosphorus concentrations should not exceed 60; the goal is to attain values between 42 and 52.⁴⁷ Calcitriol's rapid onset (about 1 day) and short duration of action (half-life less than 1 day) permits rapid control of unwanted hypercalcemia. If hypercalcemia develops, it is advisable to stop treatment completely rather than reduce the dose. Therapy may be re-instituted with a reduced dosage when serum calcium concentration returns to normal and serum phosphorus concentration is < 6.0 mg/dl.

Minimizing progression of CKD

All patients with CKD are at risk for progressive CKD. Progression may occur as a consequence of their primary renal disease, in association with a variety of secondary factors that may promote progressive renal disease, or both. An important therapeutic goal for managing patients with CKD is to minimize or prevent progressive loss of renal function. Treatment designed to limit progression of CKD may involve a variety of interventions including diet therapy, controlling hypertension, minimizing proteinuria, and modulating the renin-angiotensin-aldosterone system.

There is clinical and experimental evidence that dietary intervention may be effective in preserving renal structure and function and prolonging survival. In a randomized controlled clinical trial in dogs with naturally occurring CKD, dietary intervention significantly prolonged survival and slowed decline in renal function.¹⁸ Dogs consuming the renal diet survived on average 593 days while dogs consuming a maintenance diet survived on average 188 days. This beneficial effect applied over a range of serum creatinine values encompassing both stages 3 and 4 CKD. Renal function declined in both groups, but the decline was significantly greater in the dogs consuming the maintenance diet. The specific mechanisms underlying the beneficial effects of the diet were not determined. However, it is likely that at least dietary phosphorus restriction and omega-3 PUFA supplementation contributed to the favorable effect.^{18,56,92,93} It is also likely that once the dogs progressed to a more advanced level of renal dysfunction, protein restriction provided an additional period of symptomatic relief, thereby prolonging survival further.

Similarly, in a non-randomized clinical trial, cats fed a renal diet survived significantly longer than cats that continued to consume their usual diet (633 days versus 264 days).⁶³ It was not possible to establish the differences between diets used in this study, but the therapeutic renal diet was reduced in protein and phosphorus content. The renal diet was shown to be beneficial in lowering serum phosphorus and PTH concentrations, and it was suggested that the beneficial effect of the diet may have been related to this effect.⁹⁸

Treatments designed to limit hypertension and proteinuria may also be of value in slowing progression of CKD. Hypertension and proteinuria are a well-established risk factors for progression of renal disease in humans.^{19,123} Similarly, studies at the University of Minnesota Veterinary Medical Center have shown that elevated blood pressure and proteinuria are risk factors for uremic crises and increased mortality in dogs with stages 3 and 4 CKD.¹⁷ The effects of blood pressure and proteinuria on progression of feline CKD have not been established.

Experimental and clinical evidence has confirmed the beneficial effect of blood pressure control on slowing progression of diabetic and non-diabetic nephropathies in humans.^{19,124} In one large clinical trial, the renoprotective effect of anti-hypertensive therapy was further enhanced by maintaining blood pressure below the usual target value.¹²⁵ As a consequence, the "ideal" blood pressure to attain using anti-hypertensive therapy in human patients with CKD remains unresolved. Patient factors such as the presence or absence of proteinuria may also influence the goals of therapy. Anti-hypertensive therapy was most effective in limiting progression of CKD in patients with proteinuria. A greater reduction in blood pressure appears to be necessary for equivalent renoprotection in patients with greater levels of proteinuria.^{19,125} Further, independent of blood pressure control, reducing proteinuria has been shown to slow CKD progression.¹²⁶

Evidence supporting the renoprotective value of anti-hypertensive therapy in dogs and cats with naturally occurring CKD is lacking. However, studies performed in dogs with induced CKD indicate that administration of the ACEI enalapril limited glomerular and systemic hypertension, proteinuria and glomerular and tubulointerstitial lesions.¹¹¹ Interestingly, enalapril was renoprotective in this study despite the fact that the dogs had only mild hypertension and relatively modest proteinuria. Enalapril has also been reported to ameliorate proteinuria and stabilize renal function in dogs with naturally occurring glomerulopathies with protein-to-creatinine ratios greater than 3.0.²¹ Enalapril therapy was associated with a reduction in proteinuria of over 50%. Over the six months of study, serum creatinine increased by more than 0.2 mg/dl in 13 of 14 dog receiving placebo, but only 3 of 16 dogs receiving enalapril. In this study, enalapril significantly reduced systolic blood pressure from a mean of 154+/-25 before therapy to 142+/-19 after 6 months of treatment.

In humans, angiotensin converting enzyme inhibitors are generally considered to be the antihypertensive drugs of choice in patients with CKD, particularly when proteinuria is evident, because they lower both systemic and intraglomerular pressures as well as proteinuria.¹⁹ Further, ACEI are indicated for patients with proteinuric CKD for the purpose of reducing proteinuria, regardless of whether the patient is hypertensive. It appears appropriate to consider ACEI treatment for dogs with CKD when systolic blood pressure values are proven to remain above 160 mmHg and when the urine protein-to-creatinine values exceed 1.0.

Angiotensin converting enzyme inhibitors reduce blood pressure and proteinuria in cats; however, their unique renoprotective value has yet to be established in this species.¹¹² As a consequence, recommendations concerning use of ACEI in cats with CKD remain unresolved. The dihydropyridine calcium-channel blocker amlodipine is the antihypertensive drug of choice for most cats. However, in humans, dihydropyridine calcium-channel blockers appear to be associated with a greater risk of progression of CKD.¹²⁵ While clinical impression suggests this is not the case in cats with CKD, the effect of amlodipine on progressive renal disease has not been critically examined in cats.

Table 9 - Potential Adverse Effects of Angiotensin II on the Kidneys

- Glomerular hypertension
- Impaired glomerular permselectivity
- Mesangial cell proliferation
- Induction of TGF- β thereby increasing production of extracellular matrix
- Increased aldosterone production
- Macrophage activation; activation of inflammation-related transcription factors
- Increased production of plasminogen activator inhibitor-1

Modified from: Rosenberg ME: Chronic kidney disease: Progression. *NephSAP* 2(3):94, 2003.

The renoprotective effects of ACEI cannot be explained entirely by their effects on blood pressure. It is likely that renoprotection results in part from suppressing renal levels of angiotensin II. Angiotensin II may adversely affect the kidneys in several ways (table 9).¹²⁴ Because of the role of angiotensin II in progression of CKD, angiotensin receptor blockers have also been considered for humans with CKD.¹²⁷ Angiotensin receptor blockers and ACEI differ in the mechanism by which they inhibit angiotensin II. The ACEI block conversion of angiotensin I to angiotensin II. However, angiotensin II formation is not completely inhibited because it can also be generated by a non-ACE-dependent pathway such as by the enzyme chymase. Also, because bradykinin is normally degraded by ACE, ACEI therapy is associated with elevated bradykinin levels. Bradykinin is a vasodilator that may have renoprotective effects by stimulating nitric oxide production. Angiotensin receptor antagonists block the type 1 receptor, but leave type 2 receptor effects unopposed, which appears to be important in vasodilation. In rats with nephropathy, angiotensin II antagonism has been reported to normalize proteinuria, eliminate inflammatory cell infiltration, and ameliorate glomerular and tubular structural changes.¹²⁸ A combination of an angiotensin receptor antagonist and ACEI has been suggested as a way to maximize blockade of the renin-angiotensin system by affecting both the bioavailability of angiotensin II and also by affecting its activity at the receptor level.¹²⁹ Each type of drug has been shown to be effective in reducing proteinuria and slowing progression of renal disease. However, in experimental models and in humans, combination therapy has proven more effective than either drug alone.¹²⁷ In humans, there does not appear to be an increase in toxicity or adverse events with combination therapy.¹²⁴ Whether combination therapy is safe, effective, and provides a therapeutic advantage needs to be determined for dogs and cats with CKD.

Blockade of the renin-angiotensin system limits both angiotensin II and aldosterone while retarding progression of renal disease. Recent studies have implicated aldosterone as an important pathogenic factor in this process.^{130,131} Selective blockade of aldosterone, independent of renin-angiotensin blockade, reduces proteinuria and glomerular lesions in rats with experimental CKD. Where blockade of the renin-angiotensin system ameliorates proteinuria and glomerular injury, selective reinfusion of aldosterone restores proteinuria and glomerular lesions despite continued blockade of the renin-angiotensin system. This observation suggests an independent pathogenic role for aldosterone as a mediator of progressive renal disease. Aldosterone appears to promote progressive renal injury through both hemodynamic effects and direct cellular actions.¹³⁰ It appears to have fibrogenic properties in the kidneys, perhaps in part by promoting production of the profibrotic cytokine TGF- β .¹³¹ Experimental studies have shown that the aldosterone-receptor antagonist eplerenone may attenuate proteinuria and renal damage, independent of its effect on blood pressure. While ACEI initially cause an acute reduction in aldosterone concentration, this effect is not sustained. It has been proposed that use of aldosterone-receptor antagonists in addition to ACEI will have additional benefits toward protecting the kidneys.¹³⁰ However, the role of this form of therapy has yet to be established.

Vasopeptidase inhibitors are agents that inhibit both ACE and neutral endopeptidase, an enzyme involved in the breakdown of natriuretic peptides, adrenomedullin, and bradykinin. They decrease angiotensin II production and increase accumulation of the afore-mentioned vasodilators. In experimental renal disease, they appear to have a greater renoprotective effect than ACEI.¹³² Studies on these agents have not been reported in dogs and cats with CKD.

Inflammation is a prominent feature of progressive renal diseases. Future therapies are likely to include novel inhibitors of specific profibrotic or proinflammatory cytokines and growth factors. The immunosuppressive agent mycophenolate mofetil has been shown to be renoprotective in remnant kidney rats.¹³³ Pirfenidone, an anti-fibrotic agent, has been shown to attenuate renal fibrosis.¹³⁴

PATIENT MONITORING

Response to treatment should be monitored at appropriate intervals so that treatment can be individualized to the specific, and often changing, needs of the patient. The database obtained before initiating therapy or after correcting overt an overt uremic crisis should be used as a baseline for comparison of the patient's progress. This evaluation should be repeated at appropriate intervals. Evaluations every 2 to 4 weeks are suggested until the initial response to therapy can be established. However, the frequency of evaluation may vary depending on severity of renal dysfunction, complications present in the patient, and response to treatment. Patients receiving therapy with erythropoietin or calcitriol require frequent monitoring life-long. After the initial response to therapy, if any, has been established, dogs and cats in stages 1 and 2 CKD may require evaluation as infrequently as every 6 to 12 months. However, patients with substantial proteinuria may require monitoring much more frequently depending on the course of their disease. Cats and dogs in stages 3 and 4 CKD should be reevaluated about every 2 to 4 months, depending on the stability of their renal function. Specific recommendations for monitoring are described in the various treatment sections.

Proteinuric Renal Diseases

Clinical significance of proteinuria

Finding isolated proteinuria (i.e. proteinuria which occurs in absence of other signs of inflammation such as hematuria and/or pyuria) gives rise to two important questions: (1) does proteinuria reflect underlying renal disease, and, if so, (2) will the disease eventually cause morbidity or death? Isolated proteinuria does not always indicate renal disease as strenuous exercise, extremes of heat or cold, stress, fever, seizures, or venous congestion have been reported as causes of isolated proteinuria. These causes are termed functional proteinuria. They are characteristically mild and transient, and therefore are considered non-pathologic. Proteinuria may also result from increased plasma concentrations of certain proteins (e.g. hemoglobin, myoglobin, or immunoglobulin light-chain monomers and dimers) which are small enough to pass through the glomerular barrier into urine. Because they overwhelm tubular reabsorptive mechanisms, they are called overload proteinuria. Proteinuria resulting from immunoglobulin fragments should be suspected when protein is detected by turbidometric techniques for urine protein, but not by dipstick methods. However, radiographic contrast agents, penicillins, cephalosporins, or sulfonamide metabolites may cause false positive reactions with turbidometric tests. Myoglobin and hemoglobin may be detected by tests for urine occult blood.

Because transient proteinuria is often of nonrenal origin, persistent proteinuria should be confirmed by repeating the urinalysis after several days. If the second urinalysis confirms proteinuria, further diagnostic inquiry is indicated because persistent proteinuria in absence of an active urine sediment is almost invariably a sign of renal structural disease even when other aspects of renal function are normal. The amount of protein excreted by such patients is of considerable diagnostic significance. Heavy proteinuria associated with hypoalbuminemia is called the nephrotic syndrome and indicates generalized glomerular disease. Urinary excretion of lesser quantities of protein may indicate either glomerular or non-glomerular renal diseases (proteinuria in non-glomerular diseases may result from glomerular hyperperfusion/hypertension or renal tubular dysfunction in which tubular reabsorption of filtered proteins is impaired). Urine protein:creatinine ratios may provide guidance in differentiating glomerular from non-glomerular disease. Ratios greater than 3.0 suggest (but do not conclusively prove) glomerular disease.

The clinical significance of mild persistent isolated proteinuria is uncertain in dogs and cats. Even when proteinuria does signal glomerular disease, it is not always progressive. Spontaneous remissions and even resolution of glomerular disease may occur in dogs and cats. In man, persistent, isolated proteinuria affects from 0.6 to 8.8% of otherwise healthy young adults. Up to 70% of these individuals have abnormal renal biopsies. However, the renal lesions are highly variable and of uncertain clinical significance. About half of these patients continue to have proteinuria, but their prognosis is typically excellent. Some adult humans with isolated proteinuria have been followed for over 40 years without development of serious disease. Nonetheless, humans with persistent proteinuria appear to develop progressive renal failure more often than non-affected individuals.

A conservative approach to patients with isolated mild proteinuria is recommended. Although the ideal frequency of evaluation has not been established, we suggest evaluating these patients every several months to determine persistence or progression of proteinuria. As a minimum, urinalysis and renal function should be monitored; however, important additional information may be gleaned from serial evaluation of urine protein:creatinine ratios. Patients in which pattern of persistent, but stable proteinuria is established may require evaluation less often. Diagnostic inquiry into the various causes of secondary glomerular disease should be considered for patients in which glomerular proteinuria is suspected. Nephrotic syndrome or chronic renal failure may develop in some patients.

The Nephrotic Syndrome may occur in patients with marked proteinuria. It is characterized by: 1) proteinuria, 2) hypoalbuminemia, 3) hyperlipidemia (hypercholesterolemia), and 4) edema.

Patients with evidence of progressive proteinuria should be aggressively evaluated as described in the following table. Renal biopsy may be employed to ascertain a precise morphologic diagnosis in patients with persistent proteinuria. However, data of therapeutic value may not be obtained, and serial assessment of proteinuria

and renal function provides a more accurate prognosis. For these reasons, renal biopsy may or may not be justified patients with asymptomatic persistent proteinuria.

Glomerulonephritis

Glomerular structure and function. The glomerulus is a high-pressure capillary tuft which allows production of a nearly protein-free filtrate. Smaller proteins may pass through the glomerulus, but they are normally reabsorbed by the renal tubules before excretion. Glomerular pore size and electrostatic charges influence passage of large molecules through the glomerular barrier. Protein passage through the glomerular capillary wall is limited by molecular size (<70,000 Dalton may pass) and charge (free passage of anionic compounds is inhibited to a greater degree than passage of neutral or cationic compounds). Various glomerular injuries may disrupt the normal function of the glomerulus leading to proteinuria. Hence, proteinuria is generally accepted as a hallmark of glomerular disease.

Immunopathogenesis of glomerulonephritis. Immune mechanisms are central to the pathogenesis of most types of glomerulonephritis. In such cases, immunoglobulins and complement factors can be demonstrated on glomerular structures. Mediators of immune glomerular injury can be divided into two groups: primary and secondary. Antibody and T cells are primary mediators, whereas complement, other inflammatory cells, and their secretagogues are secondary mediators of the immune response. There are at least 2 mechanisms of antibody mediated injury to the glomerulus: 1) deposition of circulating immune complexes in the glomerular capillary wall, and 2) binding of antibodies directed against antigens present in the glomerular wall resulting in in-situ immune complex formation. However, immune complex disposition within the glomerular capillary alone is regarded as insufficient to cause renal injury. Cell-mediated tissue injury can follow through release of cytokine growth factors or other mediators of inflammation. It is thought that inflammatory cells may directly injure the glomerulus. Cells found in increased quantities in some forms of glomerulonephritis include neutrophils, monocytes, T cells, platelets, and proliferation of resident glomerular cells. Activation of the complement cascade also plays a significant role in glomerular damage.

The location of immune complex deposition profoundly affects the clinical syndrome induced by the glomerular lesion (figure 1). Subepithelial disposition of immune complexes largely places the immune complexes beyond the reach of the cellular immune system, thus limiting cellular infiltration. The inflammatory reaction in this situation is primarily mediated by complement and activation of cytokines (membranous glomerulopathy). Such lesions produce the nephrotic syndrome with, at least initially, limited impact on glomerular filtration rate. When immune complex deposition occurs predominantly in a subendothelial location, cellular infiltration is usually vigorous and associated with glomerular hypercellularity and reduction in glomerular filtration rates (proliferative, Exudative or Membranoproliferative glomerulopathies).

Renal biopsy in glomerulonephritis. In veterinary medicine, only a limited number of histologic forms of glomerulonephritis are commonly reported by veterinary pathologists: membranous, proliferative (mesangiocapillary), and membranoproliferative nephropathies, and glomerulosclerosis. Accurate classification of glomerular diseases requires not only light microscopy, but also electron microscopy and immunofluorescent microscopy (or immunoperoxidase techniques). In human medicine, the pathologic description of the renal lesions is often an essential guide to prognosis and therapy of patients with glomerulonephritis. Similar associations between pathology and prognosis or therapy have not been elucidated in dogs and cats, thus limiting the clinical utility of renal biopsy.

Renal amyloidosis may be associated with profound proteinuria and the nephrotic syndrome in dogs. Infiltration of amyloid into the glomerulus disrupts normal glomerular function leading to proteinuria. In one study, dogs with marked elevations in protein:creatinine ratios were more likely to have amyloidosis than immune-mediated glomerulonephritis. In cats, renal amyloidosis is most often seen in the renal interstitial space and may not result in proteinuria. Amyloidosis may be a primary disorder or secondary to a variety of chronic inflammatory or neoplastic conditions.

Diagnostic approach to dogs and cats with glomerulonephritis. When confronted with a patient with glomerular disease, clinicians not only must evaluate the clinical signs and symptoms of renal disease but must also be vigilant for evidence of a systemic disease that could be causing the renal disease. Many diseases have been

associated with glomerulonephritis in dogs and cats (table 1). It is important to pursue possible diagnostic associations with systemic disease in dogs and cats with glomerulonephritis (table 2).

Complications of glomerulonephritis and proteinuria. Clinically important complications associated with glomerulonephritis and proteinuria include: hypercoagulability, arterial hypertension, and edema. Hypercoagulability may lead to pulmonary or other thromboembolic complications. Hypercoagulability results from urinary loss of clotting inhibitors (particularly antithrombin III), increased hepatic synthesis of fibrinogen and other pro-coagulant factors, and thrombocytosis and enhanced platelet aggregation. Hemoconcentration (due to loss of fluid from the extracellular space associated with hypoalbuminemia), immunopathologic injury (especially membranous nephropathies), and administration of diuretics and corticosteroids may further promote clotting.

Arterial hypertension is thought to result from salt and water retention leading to expansion of the extracellular fluid space. It may be further enhanced by increased peripheral vascular resistance. Inappropriately high levels of angiotensin II have been recognized in some patients with glomerulonephritis and hypertension.

Edema also results from retention of salt and water leading to expansion of the extracellular space. Loss of plasma albumin leads to a reduction in the oncotic pressure of plasma. Starling forces then facilitate increased delivery of fluid from the vascular space into the interstitium.

Treatment of Dogs and Cats with Glomerulonephritis

Elimination of Causative Factors. Elimination of diseases responsible for development of immunologic disturbances and glomerular disease may halt progression of glomerular disease or induce its resolution. For this reason, it is important to attempt to identify infectious and non-infectious agents in dogs and cats suspected of having immune-complex GN. We have observed significant improvement in the severity of proteinuria and hypoalbuminemia in some glomerulonephritic dogs with dirofilariasis following elimination of adult parasites and microfilaria by medical therapy. Likewise, removal of the uterus from dogs with pyometra may be associated with improvement in the subclinical glomerular lesions occasionally associated with that disorder. Similar beneficial effects may occur in other forms of GN. Although elimination of antigens is the most logical and seemingly safest therapeutic approach to GN, it is limited in many instances by the obscurity of the antigenic source, the fact that more than one antigen may be involved, and/or identification of an antigenic source that is currently impossible to eliminate (e.g. feline leukemia virus).

Corticosteroid and Immunosuppressive Therapy. Corticosteroids and immunosuppressive drugs (particularly cyclophosphamide, chlorambucil, cyclosporine A, and others) have been used for treating patients with glomerulonephritis (GN) with the expectation that they will suppress formation of immune-complexes, and ameliorate the glomerular inflammatory reaction initiated by antigen-antibody-complement reactions. One theoretical basis for use of these drugs is the concept that patients with GN have a hyperactive immune system leading to formation of immune-complexes that otherwise would not have been formed. However, naturally occurring immune-complex GN is not consistently associated with hyperactivity of the immune system. To the contrary, at least some patients with immune-complex disease may have suppressed rather than hyperactive immune systems. Formation during moderate antigen excess (a condition most likely to occur with an impaired immune system) produces immune complexes of the size most likely to be deposited in glomeruli and initiate glomerular injury. Failure of the mononuclear-phagocytic system to eliminate circulating immune complexes may also facilitate their glomerular deposition. Moderate antigen excess and failure of the mononuclear-phagocytic system are consistent with an immunosuppressed condition. Therefore, administration of corticosteroids and cytotoxic agents to patients with GN that results from glomerular deposition of circulating immune complexes may be harmful rather than beneficial. However, this line of reasoning may not be valid when immune complexes are formed in situ because glomerular injury does not result from deposition of circulating immune-complexes or lack of their destruction by the mononuclear-phagocytic system.

Although corticosteroids appear an illogical choice for some patients with GN, they are of recognized benefit in treatment of Minimal Change Disease in humans. In addition, some studies indicate that corticosteroids and/or immunosuppressive agents (primarily alkylating agents) may be beneficial in treatment of human patients with membranous GN, membranoproliferative GN, and proliferative GN. Other studies of the effectiveness of corticosteroids and immunosuppressive agents in treatment of membranous and proliferative GN in humans have

provided conflicting results. Therefore their use to treat the aforementioned types of GN remains controversial. The only randomized, controlled clinical trial designed to evaluate immunosuppressive therapy in dogs with GN found no significant advantage of the immunosuppressive drug cyclosporin compared to placebo.

Modifying the Magnitude of Proteinuria. Administration of angiotensin converting enzyme (ACE) inhibitors reduces the magnitude of proteinuria in humans with diabetic nephropathy, primary glomerular disease, and various other renal diseases. Similar observations have been made in dogs with spontaneous glomerulonephritis. Mechanism(s) by which ACE inhibitors may reduce proteinuria include: (1) reduced glomerular hypertension, (2) reduced glomerular hyperpermeability due to reduced angiotensin II formation, (3) anti-inflammatory effects, or (4) anti-platelet effects. Reduction of systemic blood pressure alone probably does not account for the antiproteinuric effect. Studies have suggested that the antiproteinuric effect of ACE inhibitors is most likely the result of amelioration of intraglomerular hypertension by postglomerular arteriolar vasodilation.

Studies have shown that high dietary protein intake may have an adverse effect on the magnitude of proteinuria and hypoalbuminemia in humans. Reducing dietary protein intake in humans with nephrotic syndrome limits proteinuria while stabilizing protein nutrition. We have observed similar effects in some dogs. Changes in the magnitude of albuminuria were detected within 14 days of diet change in humans and dogs.

Based on these findings, it is recommended that protein intake should be limited in dogs and cats with moderate to severe proteinuria. However, the response to limiting protein intake should be monitored. If reducing protein intake reduces the magnitude of proteinuria, and does not adversely affect renal function or serum albumin concentration, such therapy should be continued. However, adverse nutritional effects of protein restriction may not become apparent for weeks or months. Therefore, continued monitoring of renal function, proteinuria, and serum albumin concentration is recommended. Because serum albumin concentration may be an insensitive indicator of protein nutrition, body weight and subjective assessments of protein nutrition such as muscle mass and hair coat condition should also be monitored.

Anticoagulant and Anti-Platelet Therapy. Anticoagulant (heparin, coumadin) and anti-platelet (aspirin, indomethacin, dipyridamole, and others) therapy have been used for treatment of GN in humans because of the apparent role of the coagulation system in development of glomerular lesions. Intraglomerular coagulation and fibrin deposition appears to play a role in many glomerulonephritides. There is also evidence from both experimental GN and spontaneous human GN that platelets may be involved in mediating or amplifying glomerular injury by: 1) promoting proliferation of glomerular mesangial and endothelial cells, and 2) by increasing vascular permeability, thereby facilitating glomerular localization of circulating immune complexes. Platelets may also promote proteinuria through glomerular localization of platelet-derived cationic secretory proteins leading to loss of glomerular fixed anionic charge and enhanced glomerular capillary permeability. Platelet-related antigens have been demonstrated in glomeruli of patients with GN.

Platelets have been described as inflammatory cell fragments which can induce inflammation and release chemotactic and mitogenic substances. Platelet turnover, an indicator of platelet activity, has been found to be increased in several forms of GN. Furthermore, a positive correlation has been reported between intraglomerular-cell proliferation and increased platelet consumption. Evidence supporting a link between increased platelet destruction, proliferation of mesangial cells, and glomerular inflammation is based on observations that platelet-derived factors stimulate proliferation and migration of arteriolar smooth muscle cells and are chemotactic for monocytes and neutrophils.

The efficacy and safety of anti-platelet agents and anticoagulants have not been clinically evaluated in dogs and cats with GN. However, in humans, combination therapy with dipyridamole and aspirin was associated with hemorrhagic complications. Anticoagulant therapy may be associated with a substantial risk of hemorrhagic complications. In one study, 37% of patients given the combination of cyclophosphamide, coumadin, and dipyridamole had significant hemorrhagic complications. Pending results of controlled clinical trials documenting the safety and efficacy of these drugs in treatment of canine and feline GN, treatment with this class of drugs should probably be limited to administration of low doses of aspirin.

Therapy of arterial hypertension. Arterial hypertension is usually treated with salt restriction and antihypertensive drugs. The first drug of choice for hypertension in dogs is an ACE inhibitor (e.g. enalapril or

benazepril). The drug of choice in cats is the calcium channel blocking drug amlodipine besylate. These drugs used singly or in combination are given to reduce blood pressure into the normal range (less than 160/100 mmHg).

Therapy for Edema. Nephrotic edema rarely causes life-threatening complications unless pleural or pericardial effusions occur. Therefore, aggressive, rapid therapy solely for the purpose of cosmetic effects of reducing edema is inadvisable. More aggressive treatment should be reserved for patients with moderate to severe edema that may result in complications such as respiratory embarrassment. Aggressive therapy includes abdominocentesis, colloid administration, and/or intravenous diuretic therapy. For less severe edema, dietary sodium restriction alone or combined with furosemide therapy may be used.

Table 1: Conditions Which Have Been Associated with Glomerulonephritis in Dogs and Cats

- **Infectious, Inflammatory - Dogs:**

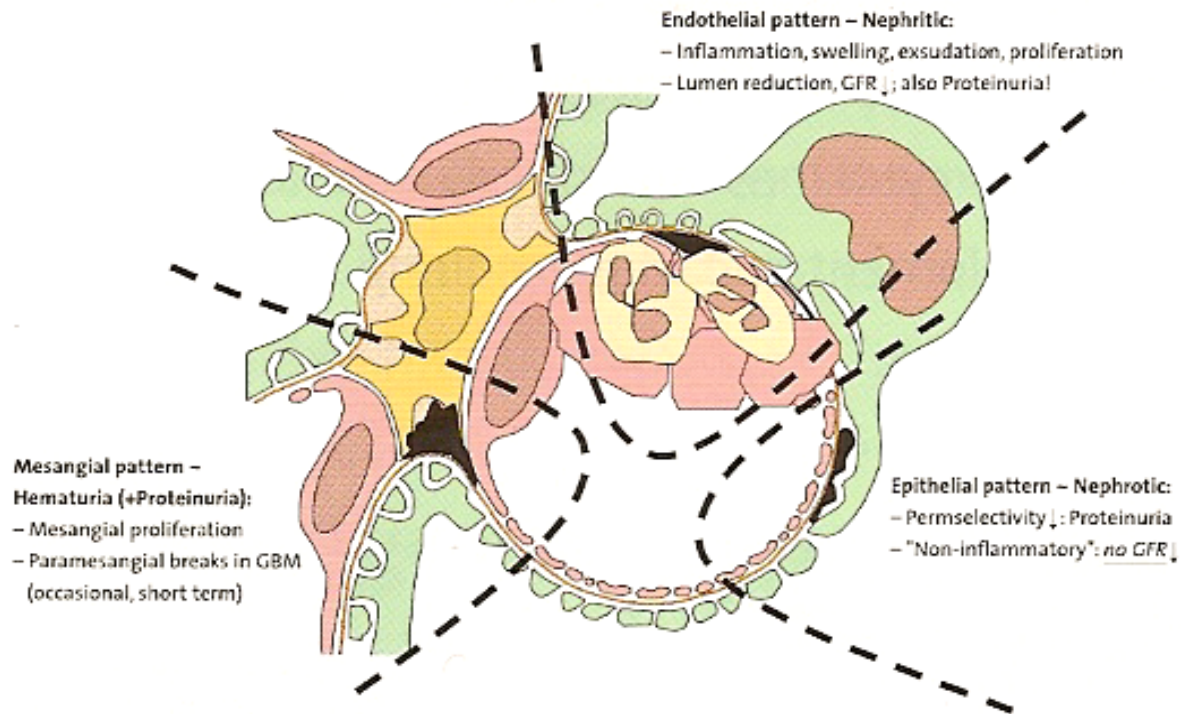
Dirofilariasis	ICH	RM Spotted Fever
Ehrlichiosis	Brucellosis	Trypanasoma
Bacterial endocarditis	Leishmaniasis	Septicemia
Borelliosis	Pyometra	Canine adenovirus-2
- **Non-infectious, inflammatory - Dogs:**
 - Pancreatitis (chronic)
 - Immune-mediated diseases, including SLE
 - Polyarthritis
 - Prostatitis
- **Infectious, Inflammatory - Cats:**
 - Feline Leukemia virus
 - Feline infectious peritonitis
 - Mycoplasmal polyarthritis
 - FIV
- **Non-Infectious, Inflammatory - Cats:**
 - Pancreatitis
 - Immune-mediated diseases, including SLE
 - Polyarthritis
 - Chronic skin disease
- **Neoplasia (various)**
- **Familial**

Samoyeds	Bull Terriers
English Cocker Spaniels	Doberman Pinschers
Newfoundland Dogs	Rottweilers
Burmese Mtn Dog	Wheaten Terrier
Shar Pei (amyloid)	Beagle (amyloid)
Greyhounds	
- **Idiopathic**

Table 2: Diagnostic Evaluation of Patients with Progressive or Marked Proteinuria

1. Medical history and physical examination
2. Urinalysis (including urine sediment examination)
3. Quantitative measure of magnitude of proteinuria (Usual method is urine protein:creatinine ratio)
4. Serum total protein, albumin, and globulin concentrations
5. Renal function tests
 - a. Serum urea nitrogen
 - b. Serum creatinine concentration
 - c. Consider endogenous C_{Cr} for nonazotemic patients
6. Serum cholesterol concentration
7. Complete blood count (including cytologic examination of blood cells)
8. Serum (or plasma) electrolyte and acid-base profile
 - a. Sodium, potassium, and chloride concentrations
 - b. Bicarbonate or total CO_2 concentrations
 - c. Calcium and phosphorus concentrations
9. Serum alanine aminotransferase, alkaline phosphatase, amylase and lipase activities
10. Blood pressure determination to rule out systemic hypertension
11. Consider:
 - a. Freezing aliquots of serum (or plasma) and urine for additional diagnostic determinations which may be desired later (e.g. titers against infectious agents, toxicological studies, etc.).
 - b. Survey radiographs of thorax and abdomen to identify/localize infectious, inflammatory, or neoplastic processes
 - c. Abdominal ultrasonography to evaluate kidneys and to identify/localize infectious, inflammatory, or neoplastic processes
 - d. Rule out immune-mediated diseases:
 - i. FANA
 - ii. Coomb's test
 - iii. LE prep
 - iv. Joint taps
 - v. Serum protein electrophoresis
 - vi. Others?
 - e. Fundic examination - R/O hypertensive lesions, infectious diseases
 - f. Screening for infectious diseases:
 - i. Bacterial endocarditis - Blood cultures, echocardiogram
 - ii. Cats: Rule out FeLV and FIV
 - iii. Rule out Dirofilaria
 - iv. Rule out appropriate infectious disease (based on potential exposure; e.g. Ehrlichiosis, Rocky Mountain Spotted Fever, Borelliosis, etc.)
 - g. Rule out hyperadrenocorticism
 - h. Coagulation studies - particularly Antithrombin III and fibrinogen levels
 - i. Renal biopsy to identify morphologic lesion
 - i. Light microscopy
 - ii. Immunofluorescence microscopy
 - iii. Electron microscopy

Figure 1: Impact of location of glomerular lesion on clinical syndrome



Protecting the Kidneys from Acute Uremic Crisis

Acute uremic crisis usually indicated abrupt decline in kidney function and may occur in several settings, including urinary obstruction, decompensation of chronic kidney disease, acute-on-chronic kidney disease and acute renal failure. Of these, acute-on-chronic kidney disease and acute renal failure are of particular clinical importance in that they are often predictable and, therefore, potentially preventable. Further, they often occur in the clinic setting or in patients under long-term management by a veterinarian. Because these adverse events often occur in setting that we control, it provides us with an opportunity to profoundly alter patient outcomes.

Although the potential for reversibility exists for many patients with ARF, mortality remains high. Two recent retrospective studies have provided evidence that the prognosis of acute renal failure (ARF) in dogs is associated with a poor prognosis. In one study, the survival rate for dogs with hospital-acquired ARF was 40%, while in the other study the survival rate for ARF due to any cause was 24%. Mortality of ARF in humans ranges from 50 to 60% despite the availability of hemodialysis. Even when renal injury is reversible, therapy is often expensive and may be prolonged. These statistics emphasize the importance of prophylaxis. Mortality in ARF may either be because the renal damage was sufficiently severe to be irreversible, or the patient succumbed from the acute consequences of uremia before recovery of the renal lesions could occur.

Preventable ARF typically results from acute tubular necrosis (ATN). Acute tubular necrosis results from either ischemic or nephrotoxic causes. Factors that may promote renal ischemia include: 1) dehydration, 2) intravascular volume contraction, 3) decreased effective circulating volume, 4) altered renal hemodynamics (locally reduced perfusion pressure), 5) NSAIDs, 6) hypercalcemia, 7) renovascular obstruction, abrupt systemic vasodilation, and 8) increased blood viscosity. Important therapeutic nephrotoxins include aminoglycoside antibiotics, amphotericin B and cisplatin, Renal hypoperfusion also promotes nephrotoxic ATN.

Acute renal failure is usually described as having three phases: 1) initiation, 2) maintenance, and 3) recovery. It is before or during the initiation phase that prophylactic therapy is most likely to reduce renal injury and prevent development of established ARF. Therapeutic intervention during the maintenance phase is typically ineffective in reducing existing renal lesions or improving renal dysfunction. However, therapy during this phase may permit the patient to live long enough to survive reversible renal injury. During the recovery phase, renal lesions resolve and function improves, although the patient may experience metabolic instability that can still result in death. It is important to remember that even with incomplete renal functional recovery, sufficient renal function may be restored to allow good quality life .

It is seemingly difficult to experimentally induce ARF in dogs with ischemia and toxins, at least at levels normally experienced in most clinical settings. However, this observation is probably misleading in that most studies use young, healthy dogs which are indeed unlikely to develop ARF. Clinical patients represent a very different population unlike the dogs used in these experimental studies because they often have “risk factors” that predispose them to development of ARF. Many factors appear to increase the risk of a patient developing ARF (table 1). Most of these risk factors can be identified with appropriate patient evaluation, and many, but not all, are amenable to therapeutic intervention. These risk factors do not mean that a given patient will develop ARF, but that the patient has a higher probability of ARF with ischemic or nephrotoxic insult. The risk factors are additive – the more factors any individual has, the greater the likelihood that ARF may result.

Possible Risk Factors for Acute Renal Failure

- Advanced age
- Volume depletion
- Sepsis
- Chronic NSAID admin
- Hypokalemia
- Hypomagnesaemia
- Hypocalcaemia
- Renal disease
- Fever
- Liver disease
- Nephrotoxins
- Metabolic acidosis
- Hyperphosphatemia

The key to prophylaxis is recognizing that ATN is often predictable, therefore it is often preventable. In most patients, a combination of risk factors can be retrospectively identified as having predisposed to ATN. The first step in prophylaxis is assessing and identifying the patients at risk (table 1).

The second step is to modify or eliminate risk factors amenable to intervention. For example, fluid and electrolyte disorders can be corrected appropriate therapy. Infection (sepsis) can be treated with antibiotics. Cardiac

dysfunction may be amenable to supportive intervention. Drug therapy may be altered as to drug selection, dosage, frequency of administration, and duration of therapy. In contrast, advanced age is not a modifiable risk factor, but it can be a marker for which patients needs more extensive evaluation for risk factors. During interventions that may promote risk factors (e.g. anesthesia induced hypotension), monitoring patients closely for perfusion and blood pressure may be effective prophylaxis.

The third step is to monitor patients to detect ATN during the initiation phase of ATN wherein therapeutic intervention has at least some hope for terminating the process of renal injury. Serial renal function tests, urinalyses (especially focusing on proteinuria, hematuria, glucosuria, and cylindruria), or urinary enzyme activities (e.g. GGT) may enhance early detection of renal injury.

When risks cannot be eliminated or corrected, they may sometimes be mitigated. The risk to benefit ratio of interventions should be assessed – should the intervention occur at all? Alternate options for interventions should be considered (e.g. local anesthesia versus general anesthesia for a procedure). Finally, general medial prophylaxis may be considered where no specific prophylaxis is possible.

It appears that the medical prophylaxis most likely to be effective is related to pre-intervention fluid support. Pre-loading patients with fluids before potential ischemic or nephrotoxic interventions has thus far been shown to be the most effective therapy. Other options that have been investigated include diuretics, vasodilators, and some forms of metabolic support. However, none have thus far proven to be superior to support with a saline-based fluid. Usually, fluids should be administered in sufficient volume to induce diuresis.