"Assessment and Management of Proteinuria in Dogs and Cats"

2004 ACVIM Forum Consensus Statement (Small Animal)

DRAFT - July 28, 2004

Consensus Panel Members:

George E. Lees, Chair
Texas A&M University, USA
glees@cvm.tamu.edu

Scott A. Brown
University of Georgia, USA
sbrown@vet.uga.edu

Gregory F. Grauer
Kansas State University, USA
ggrauer@vet.ksu.edu

Jonathan Elliott
Royal Veterinary College, UK
amc@jelliott60.freeserve.co.uk

Shelly L. Vaden
North Carolina State University, USA
shelly_vaden@ncsu.edu

Table of Contents Page(s)

Introduction

Results of recent studies suggest that in dogs and cats, as in human beings, persistent proteinuria is associated with greater frequency of renal morbidity, renal mortality, and all cause mortality [1-3]. Moreover, risk of developing these adverse outcomes increases as the magnitude of proteinuria increases [2]. Existing data supporting these statements are derived mainly from studies of dogs and cats with chronic renal failure; that is, animals with chronic kidney disease (**CKD**) that is already causing azotemia [1,2]. However, some recent data also indicate that proteinuria is associated with an increased risk of all cause mortality even in cats with renal function that is otherwise good (ie, exhibiting adequate urine concentrating ability and not azotemic) when their proteinuria is first discovered [3].

Although data from studies of dogs and cats are sparse, results of recent studies also suggest that when markedly proteinuric dogs and cats are treated with angiotensin converting-enzyme inhibitors having renoprotective effects (ie, that decrease or delay adverse outcomes), a reduction in the magnitude of proteinuria is also observed during treatment [4,5]. This same phenomenon is now well documented in human beings with many different types of renal disease [6-9].

Observation that greater proteinuria is associated with more rapid renal disease progression and that interventions that reduce proteinuria also are renoprotective has fueled speculation and much investigation about the possible role of proteinuria as a direct cause of further glomerular and/or tubulointerstitial injury in subjects with progressive nephropathies (reviewed in [10-12]). At the mechanistic level, the precise role of proteinuria in renal disease progression currently is uncertain, especially in dogs and cats. Moreover, even if proteinuria is harmful, such questions as how much proteinuria?, of what kind?, for how long?, to produce what changes?, cannot be answered with the data that are presently available from studies of dogs or cats. Nevertheless, regardless of proteinuria's role as a ***mediator*** of renal injury, proteinuria is an important ***marker*** both for increased risk of adverse outcomes and for response to renoprotective interventions. The value of proteinuria as a marker of clinically important events in the kidney arises because it can occur and subsequently vary in magnitude because of altered vascular permeability of glomerular capillary walls (ie, possibly marking the presence of immune complexes, vascular inflammation, or intraglomerular hypertension, for example), or impaired tubular handling of filtered proteins (ie, possibly marking the presence of tubulointerstitial dysfunction, or example), or both. For these reasons, we have a strong consensus that veterinarians should give more attention to the detection, evaluation, monitoring, and treatment of dogs and cats with proteinuria.

Our goals herein are to: 1) describe a comprehensive cognitive framework with which to approach this task, and 2) provide veterinarians with specific recommendations for assessing and managing dogs and cats with proteinuria based on data that are currently available. We recognize that ongoing and future research will generate new information that may necessitate modification of the specific recommendations; however, we believe that the cognitive framework will serve to guide the development and implementation of future recommendations. Our sincere hope also is that this consensus statement will invigorate the ongoing quest for greater understanding of the clinical pathophysiology of proteinuria in dogs and cats; its causes, consequences, and diagnosis, as well as of the effects of interventional therapies.

Defining and Classifying Proteinuria

Definition of Proteinuria

Urine obtained from healthy dogs or cats with healthy kidneys typically contains a small amount of protein, but as a diagnostic term, **proteinuria** generally is taken to mean detection of an abnormal (ie, excessive) amount of protein in the urine. Several different methods to detect proteinuria can be used to evaluate dogs and cats. These include semiquantitative tests performed in a conventional urinalysis, determination of urine protein:creatinine ratio, and assay of urine albumin concentration. Each of these methods has its place in veterinary practice; none of the methods entirely replaces the others, and they can be used in a complementary fashion.

Categories of Causes of Proteinuria

Proteinuria has numerous possible causes. The classification scheme for categories of causes of proteinuria that we recommend for use in dogs and cats is slightly adapted from the one published by DiBartola et al (Table 1) [13]. Moreover, we believe that it is important to assiduously follow the definitions of the categories, as listed in the table.

The most important reason why we prefer this classification scheme is that it provides a specific correlate for each step in the diagnostic approach for localization of proteinuria that we recommend. The rationale underlying the recommended diagnostic process for localization of proteinuria in dogs and cats as outlined in Table 1 is explained as follows:

When evidence of an excessive amount of protein is detected by urinalysis, localization of the likely source of the proteinuria involves these sequential steps:

Step 1. to exclude "extra-urinary postrenal" – evaluate urine obtained by cystocentesis

Step 2. to exclude "prerenal" – evaluate the plasma proteins (ie, look for a dysproteinemia that might explain the proteinuria).

If it's not prerenal and it's not extra-urinary, then it is "urinary," and the next action is to evaluate the urine sediment for evidence of inflammation or hemorrhage.

Step 3. to rule-in "urinary postrenal" – find evidence of inflammation or hemorrhage with or without clinical signs of excretory pathway disease (eg, pollakiuria), but without apparent clinical signs of nephritis.

Step 4. to rule-in "pathological, interstitial renal" – find evidence of inflammation associated with the clinical signs of an active nephritis (eg, tender kidneys, fever, renal failure).

If the proteinuria is "urinary" and not associated with urine sediment evidence of inflammation or hemorrhage the remaining possibilities are:

1. "functional renal" – which is low-grade (ie, of low magnitude, mild, or "light") and transient.

2. "pathological, tubular renal" – which also is low-grade, but typically is persistent. In some cases, such proteinuria is accompanied by normoglycemic glucosuria or abnormal electrolyte excretion that demonstrate the presence of multiple tubular reabsorptive abnormalities and help to identify the tubular origin of the proteinuria; however, tubular proteinuria often occurs in the absence of such findings.

3. "pathological, glomerular renal" – which can be of any magnitude ranging from very low-grade (eg, microalbuminuria alone) to very substantial (ie, "heavy"), but also typically is persistent.

Consequently, the final steps in the localization process are:

Step 5. to rule-in "pathological, glomerular renal" if the magnitude of proteinuria is sufficiently high to support this conclusion; that is, UPC $\geq$ 2.0 in dogs and cats.

Step 6. to rule-in "functional renal" if the proteinuria is mild and proves, with follow-up evaluation, to be transient.

Step 7. to rule-in "pathological, glomerular renal" (albeit low-grade) **OR** "pathological tubular renal" if the proteinuria is mild but proves, with follow-up evaluation, to be persistent. These two types of proteinuria cannot be reliably distinguished from one another by conventional testing that is currently available, unless or until the animals with "pathological, glomerular renal" experience an increase in the magnitude of proteinuria that is sufficient to rule-out "pathological tubular renal" proteinuria (eg, UPC $\geq$ 2.0, as in step # 5).

Definition of Persistent Renal Proteinuria

The term, **persistent renal proteinuria** is subsequently used herein to refer to the types of proteinuria identified in steps 5 and 7 above. Additionally, **persistent microalbuminuria** is the mildest form (ie, lowest magnitude) of persistent renal proteinuria that can be detected (ie, in step 7) with the methods that are currently available. Persistent renal proteinuria is the type of proteinuria for which this panel has been asked to make recommendations and is the principal focus of the remainder of this consensus statement.

Detection and Assessment of Persistent Renal Proteinuria

Proteinuria not only must be detected, it must be **assessed** appropriately to determine its implications for the patient. Assessment of proteinuria involves investigation of 3 key elements:

- *Localization* – the process of determining the likely site or mechanism that is causing the proteinuria. The information needed to make this assessment always includes the history, physical exam findings, the results of a complete urinalysis (ie, including a sediment examination) and sometimes a urine culture, as well as results of blood tests that are sufficient (in the context of the other known findings) to exclude dysproteinemia, which actually is an uncommon cause of proteinuria in dogs and cats.

- *Persistence* – determining whether or not proteinuria persists over time requires repeated testing on ≥ 3 occasions, ≥ 2weeks apart. Moreover, comparison of serial values requires appreciation of the range of day-to-day variation that may be observed in animals with generally stable magnitudes of proteinuria.

- *Magnitude* – use of appropriate quantitative methods to obtain reliable indices of the magnitude of urine protein loss is crucial for clinical decision-making and for monitoring trends, including response to treatment if therapy is indicated. Such methods include UPC ratios to assess proteinuria and quantitative (ELISA) assays for albuminuria expressed either as urine albumin/creatinine ratios or as concentrations (mg/dL) in urine samples diluted in a standardized fashion (eg, to specific gravity, 1.010) to assess microalbuminuria.

Implications of Persistent Renal Proteinuria

General Implications

Persistent renal proteinuria, as defined above, indicates the existence of chronic kidney disease (CKD). However, the entire spectrum of CKD in dogs and cats that is identified in this way has a wide range of possibilities in its clinical course. A substantial number of dogs and cats experience morbidity or mortality attributable to CKD that progresses at a sufficiently rapid rate to cause clinical illness during their lifetimes. Illness caused by such **progressive CKD** usually is due to manifestations of renal failure but can be manifested as hypertension alone. In addition, a larger, but not yet well defined, number of seemingly healthy dogs and cats have CKD that is either non-progressive or so slowly progressive that it never generates recognizable morbidity or mortality (ie, before death due to other causes). That is, some animals have **stable, subclinical CKD** that generates no apparent adverse consequences for their health despite the fact that renal lesions persist for the remainder of their lives. Another important, but also not yet well defined, group of animals with CKD are those that have seemingly stable, subclinical CKD for extended periods that can be quite long but are nonetheless subsequently followed by further renal disease progression that may occur intermittently (ie, sporadically) or steadily once it becomes evident.

Based on the apparent clinical course of disease, animals with CKD identified by finding persistent renal proteinuria can be categorized as follows:

1. those with **apparently progressive CKD**, defined by either:
   a. finding that the condition has already reached an advanced stage, or
   b. serial evaluations having demonstrated worsening trends.
2. those with **temporarily stable, subclinical CKD**, defined by:
   a. extended periods (eg, ≥ 6 months) without apparent disease progression, followed by:
   b. intermittently (ie, sporadically) or steadily worsening trends.
3. those with **indefinitely stable, subclinical CKD**, defined by:
   a. extended periods (≥ 6 months) without apparent disease progression, followed by:
   b. death or euthanasia for reasons unrelated to renal disease or failure.

When the progressive nature of an animal's CKD is not already self-evident, monitoring the animal's renal disease status over time is crucial. Such monitoring is only able to distinguish

animals that ***are progressing during the monitoring period*** from those that are not progressing. That is, in animals with currently stable, subclinical CKD, monitoring will not foretell the future. However, adequate monitoring of animals with stable, subclinical CKD should detect worsening trends in a timely manner if and when they occur, and thus should permit eventual differentiation of animals with temporarily versus indefinitely stable, subclinical CKD.

At least two possible scenarios for animals with temporarily stable, subclinical CKD can be proposed. Such animals might actually be experiencing ongoing renal damage (ie, lesions are progressing) that merely is hidden from detection during this period. This is a plausible scenario, especially if ongoing damage is being contemporaneously offset by compensatory structural and functional changes in the relatively undamaged portions of their kidneys. On the other hand, such animals might actually have stable (ie, essentially unchanging) renal lesions for extended periods that end because of reactivation of old or superimposition of new processes of renal injury. This also is a plausible scenario, especially: (a) when the durations of periods of apparent stability are protracted, or (b) when the functional consequences of the renal lesions are especially mild (eg, causing microalbuminuria alone or mild proteinuria in animals with adequate urine concentrating ability and well-preserved excretory function). Regardless of such possibilities, there currently is no way to reliably tell these two scenarios apart at any one moment in time, and treatment errors (ie, either failing to give treatment that might be helpful, or giving treatment that is unnecessary and could be harmful) will occur if therapeutic decisions are then formulated based on incorrect assumptions about which scenario actually prevails. In this setting of uncertainty, monitoring is the key to minimizing such errors. Detection of progressively worsening trends, such as a rising magnitude of proteinuria, should prompt further action, but demonstration of stable or improving indices of disease severity, including magnitude of proteinuria, is an indication for nothing more than continued monitoring.

Persistent microalbuminuria is the mildest detectable form of abnormal renal handling of protein. Microalbuminuria usually is attributable to altered glomerular permselectivity; however, impaired tubular handling of the albumin that traverses the normal glomerular filtration barrier also can cause or contribute to microalbuminuria. Moreover, there currently is no practical way to reliably determine the portion of microalbuminuria, if any, that is due to tubular dysfunction rather than being of glomerular origin.

Because microalbuminuria is the mildest detectable form of abnormal renal handling of protein, it is both the form of persistent renal proteinuria that is most likely to be manifested by animals that actually have indefinitely stable, subclinical CKD, as well as the form of persistent renal proteinuria that is most likely to be first manifested by animals that actually have or will eventually develop progressive CKD. Again, monitoring is the key to eventually differentiating these two categories of animals with microalbuminuria from one another. Progressive increases in magnitude of microalbuminuria are likely to be indicative of active, ongoing renal injury, and should prompt further investigation.

In animals with CKD causing renal failure, magnitude of proteinuria may diminish as the nephropathy approaches its end-stage because there are fewer and fewer remaining nephrons for protein loss to occur through. Therefore, as renal failure progresses, reductions in the magnitude of proteinuria that may be observed do not necessarily mean that the renal disease has improved.

Indeed, if proteinuria really is a mediator renal injury, this lesser magnitude of proteinuria might actually be as damaging (or more damaging) to the remaining nephrons as greater magnitudes of proteinuria had been at earlier stages of the disease.

In many dogs (and probably cats), renal lesions that cause persistent renal proteinuria are incited by mechanisms that are initiated by disease processes located in other organ systems (ie, by diseases that are not primary renal, or even urinary, disorders). Thus, the kidneys can serve as "sentinels" to aid in the detection of such disorders. That is, finding persistent renal proteinuria can alert the animal's veterinarian and owner to the existence of a previously unsuspected threat to the animal's health. Timely discovery of a treatable underlying infectious, inflammatory, or neoplastic condition because of a clinical investigation that is prompted by detecting previously unsuspected persistent renal proteinuria or microalbuminuria is an important potential benefit of screening apparently healthy animals for proteinuria.

In animals with serious, life-threatening illnesses (eg, in dogs and cats in intensive care units), transient microalbuminuria or mild proteinuria may occur as an indication of endothelial injury throughout the circulation, including in the kidneys [14]. That is, whenever there is a disruption in endothelial architecture to the point that the vessels may leak, small amounts of albumin may appear in the urine, albeit only transiently if the animal survives and recovers from its illness.

Strength of Evidence Levels

For the purposes of this document, the strength of evidence that is available to support specific statements regarding the implications of proteinuria in dogs or cats, as well as specific recommendations for therapeutic interventions, has been categorized in 3 levels as described in Appendix I. Evidence categorized as Level 1 is the strongest (ie, most convincing), and evidence categorized as Level 3 is the weakest (ie, least convincing).

Specific Implications in Dogs

In dogs, persistent renal proteinuria with UPC values ≥ 2.0 usually is due to glomerular renal disease (Level 3) [15].

In dogs with renal failure, having a UPC value ≥ 1.0 at initial evaluation is associated with increased risk of uremic morbidity and mortality. Additionally, risk of adverse outcomes increases as the magnitude of proteinuria increases (Level 1) [2].

In dogs, UPC values ≥ 0.5 are evidence of persistent renal proteinuria when they are found repeatedly in ≥ 3 specimens obtained ≥ 2 weeks apart and cannot be attributed to a prerenal or postrenal cause.

In dogs, microalbuminuria is evidence of persistent renal proteinuria when it is found repeatedly in ≥ 3 specimens obtained ≥ 2 weeks apart and cannot be attributed to a postrenal cause.

Specific Implications in Cats

In cats, renal diseases that cause proteinuria with UPC values ≥ 1.0 occur uncommonly, and data sufficient for the formulation of general statements about the implications of proteinuria in such cats are not available. Nonetheless, UPC values ≥ 1.0 in cats should prompt a high index of suspicion for the presence of glomerular disease, but UPC values ≥ 1.0 (but usually still < 2.0) sometimes are observed in cats with progressive renal failure near end-stage.

In cats with renal failure, the risk of all cause mortality progressively increases as UPC at initial diagnosis increases across the full spectrum of possible UPC values, including UPC values within the normal reference range. That is, the lower the UPC value, the better the prognosis. In one study, having a UPC value ≥ 0.43 at initial evaluation was associated with an increased risk of all cause mortality (Level 2) [1].

In nonazotemic cats, the risk of all cause mortality also increases as UPC or albuminuria at initial evaluation increases, even within the conventional normal reference range. In one study, proteinuria was associated with reduced survival of nonazotemic cats. The median UPC for cats that died was 0.30, while the median UPC for cats that were censored (ie, were alive at the end of the study or were lost to follow up) was 0.16 (Level 2) [3].

In cats, studies comparing the implications of albuminuria (measured with a species-specific immunoassay) and proteinuria (measured by conventional UPC ratios) have thus far shown little difference between the two; however, the UPC cutoffs needed to differentiate cats with good outcomes from cats with adverse outcomes are much lower than the UPC cutoffs that currently are widely used in cats [1,3].

In cats as in dogs, the current conventional definition of persistent renal proteinuria is either UPC ≥ 0.5 or microalbuminuria found repeatedly in ≥ 3 specimens obtained ≥ 2 weeks apart that cannot be attributed to a prerenal or postrenal cause. However, there are some data suggesting that the upper limit of the normal reference range for UPC noncastrated male cats should be as high as < 0.6. Nevertheless, the recent observations (as cited above) of reduced survival in cats being associated with magnitudes of proteinuria that are within the currently accepted normal reference range for healthy animals have generated new uncertainties about cutoff values for proteinuria that should be used to define the health status of cats.

When and How to Test for Proteinuria

Urine testing that will detect proteinuria, if it is present, should be a component of the clinical evaluations of dogs and cats with any serious illnesses that also prompt their attending veterinarians to perform comprehensive hematological and serum biochemical evaluations (ie, urinalyses should be done when CBCs and serum chemistry panels are performed to evaluate dogs and cats with undiagnosed illnesses). In addition, animals with chronic illnesses that are known to often become complicated by proteinuric renal disease should be tested for proteinuria at ≤ 6-month intervals while such disorders are being managed for extended periods.

Urine testing that will detect proteinuria, if it is present, should be a component of routine clinical evaluations of apparently healthy dogs and cats in any circumstances that also prompt their attending veterinarians to perform comprehensive hematological and serum biochemical evaluations (ie, urinalyses should be done when CBCs and/or serum chemistry profiles are performed as routine health evaluations of apparently healthy dogs and cats).

At a minimum, urine tests for proteinuria should consist of a complete urinalysis that includes conventional semiquantitative evaluations of protein. Because false-positive dipstick colorimetric test reactions commonly occur in well-concentrated or highly alkaline (pH ≥ 7.5) dog and cat urine specimens [16], satisfactory test methods are either a dipstick colorimetric test, with positive reactions confirmed by a SSA turbidometric test [17], or a SSA turbidometric test alone. Alternatively, an ERD test (E.R.D.-Screen™ Urine Test, Heska, Ft. Collins, CO) or a quantitative ELISA assay could be used to confirm the presence of albuminuria in the face of a positive dipstick result (see microalbuminuria section below), All positive reactions, regardless of the urine specific gravity, should prompt a follow-up evaluation of some kind. Reliance on dipstick tests alone is not recommended due to the low specificity of positive reactions (ie, high frequency of false-positive results).

- Strong positive reactions (≥ 1+; confirmed by SSA) are an indication to proceed with determination of UPC ratio either immediately or at least after repeated testing in 2-4 weeks verifies persistence of the positive reactions.
- Weak positive reactions (trace; confirmed by SSA) are an indication at least for repeated testing in 2-4 weeks to check for persistence of the proteinuria, with determination of UPC ratio if the positive reactions do persist.
- Negative reactions (by dipstick alone, by SSA alone, or by SSA performed in an attempt to verify a positive dipstick reaction) are sufficient to exclude the existence of all forms of proteinuria except microalbuminuria (see below).

For animals in which proteinuria is documented or suspected, determinations of UPC ratios should be performed to guide clinical decision-making and to monitor trends, including response to treatment when therapeutic interventions are indicated. However, the variation in UPC values observed in dogs with stable proteinuria suggests that serial UPC ratios probably need to differ by as much as 40%, especially in the lower ranges of abnormality, to conclude with a high level of confidence that the prevailing magnitude of proteinuria has actually changed (increased or decreased). The variation of UPC ratios observed in cats with values within the normal reference range suggests that serial UPC ratios need to differ by as much as 90% (ie, nearly double) to conclude with a high level of confidence that a cat's magnitude of proteinuria has increased.

Urine testing that will detect microalbuminuria, if it is present, is recommended under the following circumstances:

- When conventional evaluations for proteinuria are negative in dogs and cats with serious illnesses, and especially in those with chronic illnesses that are known to often become complicated by proteinuric nephropathies.
- When conventional evaluations for proteinuria are negative in apparently healthy dogs that are ≥ 6 years old and cats that are ≥ 8 years old, and use of the most sensitive test that might detect an abnormality is desired by the veterinarian or animal owner.

- When conventional evaluations for proteinuria produce equivocal or conflicting results.
- When dogs or cats that are known to be at risk for developing a glomerular renal disease (eg, individuals in breeds or families that are genetically predisposed to such disorders) are being prospectively monitored to detect onset of the disease as early as possible.

Dogs that have a "high positive" reaction for urine albumin using the semiquantitative test method that is commercially available frequently also have a UPC $\geq$ 0.5, so finding such a "high positive" reaction is an indication to proceed with UPC determinations.

Response to Persistent Renal Proteinuria

General Principles

Appropriate responses to persistent renal proteinuria are the following series of escalating steps that depend on the magnitude of proteinuria and patient status (Figure 1).

- Monitor (lowest level) - which refers to repeating one or more tests that have been done previously in order to detect changes with passing time. The main purpose of monitoring is to detect worrisome trends (ie, changes that should prompt further action) in a timely manner.

- Investigate (higher level) - which refers to performing new or additional tests (ie, that would not otherwise be done) in order to discover an underlying systemic disease or to define the animal's renal disease more exactly.

- Intervene (highest level) - which refers to prescribing dietary changes and/or use of pharmacologic agents in order to at least attempt to beneficially modify the course of disease and/or improve the animal's health.

Implementation of this **escalating responses** approach should be **sequential and inclusive**. That is, one should only monitor (ie, not investigate or intervene) in circumstances that are the least compelling. However, in other more compelling circumstances, one should investigate as well as monitor (ie, but not intervene). Such a step-addition might be immediate or sequential, depending on the situation. Further, one should intervene as well as investigate and monitor in the most compelling circumstances, and once again, this step-addition might be immediate or sequential, depending on the situation. Importantly, correct implementation of this escalating approach precludes intervention without appropriate investigation and monitoring, as well as investigation (especially invasive tests) without sufficient evidence, which might arise from monitoring, to justify the risk to the animal and/or the cost to the owner.

Specific Recommendations (Figure 2)

Persistent renal proteinuria should always prompt action, but appropriate actions depend on the prevailing magnitude of proteinuria and the clinical status of the patient. The categories of possible actions are:

- *Prospective monitoring* – that is meant to promptly detect worsening trends in animals that appear to have stable, subclinical CKD because they are nonetheless at risk to have (or to develop) progressive CKD that may then require therapeutic intervention (ie, that would not otherwise be indicated) or to evaluate response to therapy.

- *Diagnostic investigation* – that is meant to detect any diagnosable, treatable infectious, inflammatory or neoplastic disease that might be the underlying cause of the animal's renal disease.

- *Therapeutic intervention* – that is meant to be renoprotective (ie, to slow the rate of renal disease progression) and using reduction of the magnitude of proteinuria as one index of therapeutic response. The treatment strategies to be considered are to feed an appropriate diet (one with reduced quantity/high quality protein with n-3 fatty acid supplementation) and/or to administer an ACEI drug.

Prospective monitoring sufficient to accomplish timely detection of any worsening trends is recommended for:

- Nonazotemic dogs and cats with persistent microalbuminuria.

- Nonazotemic dogs and cats with persistent renal proteinuria and UPC values ≥ 0.5.

Note: When an underlying infectious, inflammatory or neoplastic condition is already apparent (ie, previously diagnosed and/or now clinically evident) in dogs or cats in this category, prospective monitoring should be combined with appropriate treatment for the underlying condition, when possible.

Diagnostic investigation that is focused on finding a potentially treatable underlying disease and adequate continued monitoring is recommended for:

- Nonazotemic dogs and cats with rising magnitudes of persistent microalbuminuria

- Nonazotemic dogs and cats with persistent renal proteinuria and UPC values ≥ 1.0.

After appropriate investigation and specific treatment of any underlying disease that is identified, therapeutic intervention accompanied by adequate monitoring is recommended for:

- Dogs with CKD causing azotemia and UPC values ≥ 0.5.

- Cats with CKD causing azotemia and UPC values ≥ 0.4.

- Nonazotemic dogs or cats with persistent renal proteinuria and UPC values ≥ 2.0.

Strength of Evidence Levels for Recommended Interventions

Recommendations for responding to proteinuria are provided herein despite the fact that few data with which to address these important clinical questions are available. Indeed, only one recommendation is even partially supported by results of a randomized, controlled clinical trial.

The recommendation to treat nonazotemic dogs with persistent renal proteinuria and UPC values ≥ 2.0 is based mainly on the results of a randomized, placebo-controlled trial of enalapril therapy for dogs with glomerulonephritis reported by Grauer et al (Level 1) [4]. However, all dogs entered into that trial had UPC values ≥ 3.0, so the recommendation to initiate treatment if UPC values are ≥ 2.0 is supported only by expert opinion (Level 3). Additionally, all the dogs in that trial were fed a renal diet and given low-dose aspirin therapy. Therefore, whether or not the benefits of enalapril therapy that were observed in that trial were in any way dependent on either of these concomitant treatments is uncertain.

The recommendation to treat azotemic dogs with persistent renal proteinuria and UPC values ≥ 0.5 is based mainly on the results of experimental studies, albeit in the target species (Level 2). In a study of dogs with the remnant kidney model of chronic renal failure (CRF) that also had mild proteinuria, enalapril therapy reduced proteinuria and modulated progressive renal injury [18]. Additionally, in studies of dogs with the remnant kidney model of CRF, dietary supplementation with omega-3 polyunsaturated fatty acids reduced proteinuria and slowed renal disease progression, whereas supplementation with omega-6 polyunsaturated fatty acids increased proteinuria and enhanced progression [19,20].

All other recommendations in this consensus statement are provided as expert opinion (Level 3). Currently, there are no citable data available regarding a renoprotective reduction of proteinuria (ie, administration of a treatment that decreased proteinuria and improved outcome) in cats. Similarly, no data are available regarding renoprotective reduction of microalbuminuria in either dogs or cats.

Final Caveats

This consensus statement is focused on detection and treatment of animals with persistent renal proteinuria, which is but one of many possible manifestations of CKD in dogs and cats that are important to evaluate and treat appropriately. Although veterinarians caring for animals with renal disease may need to pay greater attention to proteinuria, they also should not lose sight of the proven importance of attending to other problems that often arise in dogs and cats with renal disease or renal failure. Providing details about the proper management of these other problems is beyond the scope of this consensus statement; however, they are individually and collectively no less important to address than is proteinuria. Indeed, depending on the specific circumstances of individual cases, proteinuria might well be relatively unimportant compared with one or more other problems. Although this is not intended to be an all-inclusive list, some of the other issues that often deserve attention include feeding an appropriate diet, controlling hyperphosphatemia and hypertension, as well as combating anemia, metabolic acidosis, and inadequate appetite.

References

[1] Syme HM, Elliott J. Relation of survival time and urinary protein excretion in cats with renal failure and/or hypertension (abst). J Vet Intern Med 2003; 17:405.

[2] Jacob F, Polzin D, Osborne C, Neaton J, Kirk C, Allen T et al. Association of initial proteinuria with morbidity and mortality in dogs with spontaneous chronic renal failure (abst). J Vet Intern Med 2004; 18:417.

[3] Walker D, Syme HM, Markwell P, Elliott J. Predictors of survival in healthy, non-azotaemic cats (abst). J Vet Intern Med 2004; 18:417.

[4] Grauer GF, Greco DS, Getzy DM, Cowgill LD, Vaden SL, Chew DJ et al. Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. J Vet Intern Med 2000; 14(5):526-533.

[5] Grodecki KM, Gains MJ, Baumal R, Osmond DH, Cotter B, Valli VE et al. Treatment of X-linked hereditary nephritis in Samoyed dogs with angiotensin converting enzyme (ACE) inhibitor. J Comp Pathol 1997; 117(3):209-225.

[6] Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med 1996; 334(15):939-945.

[7] Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999; 354(9176):359-364.

[8] Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet 1997; 349(9069):1857-1863.

[9] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; 329(20):1456-1462.

[10] Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med 1998; 339(20):1448-1456.

[11] Keane WF. Proteinuria: its clinical importance and role in progressive renal disease. Am J Kidney Dis 2000; 35(4 Suppl 1):S97-105.

[12] Zoja C, Benigni A, Remuzzi G. Cellular responses to protein overload: key event in renal disease progression. Curr Opin Nephrol Hypertens 2004; 13(1):31-37.

[13] DiBartola SP, Chew DJ, Jacobs G. Quantitative urinalysis including 24-hour protein excretion in the dog. J Am Anim Hosp Assoc 1980; 16:537-546.

[14] Turman CA, Vaden SL, Harris TL, Jensen WA. The prevalence of microalbuminuria in dogs and cats in an intensive care unit (abst). J Vet Intern Med 2004; 18:417-418.

[15] Center SA, Wilkinson E, Smith CA, Erb H, Lewis RM. 24-Hour urine protein/creatinine ratio in dogs with protein-losing nephropathies. J Am Vet Med Assoc 1985; 187(8):820-824.

[16] Grauer GF, Moore LE, Smith AR, Jensen WA. Comparison of conventional urine protein test strip method and a qualtitative ELISA for the detection of canine and feline albuminuria (abst). J Vet Intern Med 2004; 18:418-419.

[17] Moore FM, Brum SL, Brown L. Urine protein determination in dogs and cats: comparison of dipstick and sulfasalicylic acid procedures. Vet Clin Pathol 1991; 20(4):95-97.

[18] Brown SA, Finco DR, Brown CA, Crowell WA, Alva R, Ericsson GE et al. Evaluation of the effects of inhibition of angiotensin converting enzyme with enalapril in dogs with induced chronic renal insufficiency. Am J Vet Res 2003; 64(3):321-327.

[19] Brown SA, Brown CA, Crowell WA, Barsanti JA, Allen T, Cowell C et al. Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. J Lab Clin Med 1998; 131(5):447-455.

[20] Brown SA, Brown CA, Crowell WA, Barsanti JA, Kang CW, Allen T et al. Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. J Lab Clin Med 2000; 135(3):275-286.

Table 1 – Categories of Causes of Proteinuria Based on the Site and/or Mechanism of the Underlying Abnormality

Prerenal (*Definition: due to abnormal plasma content of proteins that traverse glomerular capillary walls having normal permselectivity properties*).

Normal proteins that are not normally present free in the plasma; eg,

Myoglobin

Hemoglobin

Abnormal proteins; eg, immunoglobulin light chains (Bence-Jones proteins)

Renal (*Definition: due to abnormal renal handling of normal plasma proteins*)

Functional (*Definition: proteinuria that is due to altered renal physiology* during or in response to certain transient phenomena; eg, strenuous exercise, fever, etc.). The key distinction here is that the proteinuria is not attributable to presence of renal lesions. The hallmarks of this type of proteinuria are that it is mild and transient; that is, it promptly resolves when the condition that is generating it resolves.

Pathological (*Definition: proteinuria that is attributable to structural or functional lesions within the kidneys*, regardless of their magnitude or duration).

Glomerular (*Definition: due to lesions altering the permselectivity properties of the glomerular capillary wall*).

Tubular (*Definition: due to lesions that impair the tubular recovery of plasma proteins that ordinarily traverse glomerular capillary walls having normal permselectivity properties*). These plasma proteins traffic into the urine from glomerular capillaries. They consist mainly of low molecular weight proteins, but may also include small amounts of moderate molecular weight proteins (eg, albumin).

Interstitial [*Definition: due to inflammatory lesions or disease processes (ie, acute interstitial nephritis) causing exudation of proteins into the urinary space.* These proteins traffic into the urine from peritubular capillaries.

Postrenal (*Definition: due to entry of protein into the urine after it enters the renal pelvis*).

Urinary [*Definition: due to entry of proteins derived from hemorrhagic and/or exudative processes affecting the walls of the urine excretory pathway; renal pelvis, ureter, urinary bladder, and urethra (including into the urethra from the prostate gland in males)*].

Extra-urinary (*Definintion: due to entry of proteins derived from secretions or from hemorrhagic and/or exudative processes affecting the genital tract and/or external genitalia during voiding or in the process of collecting urine for analysis*).

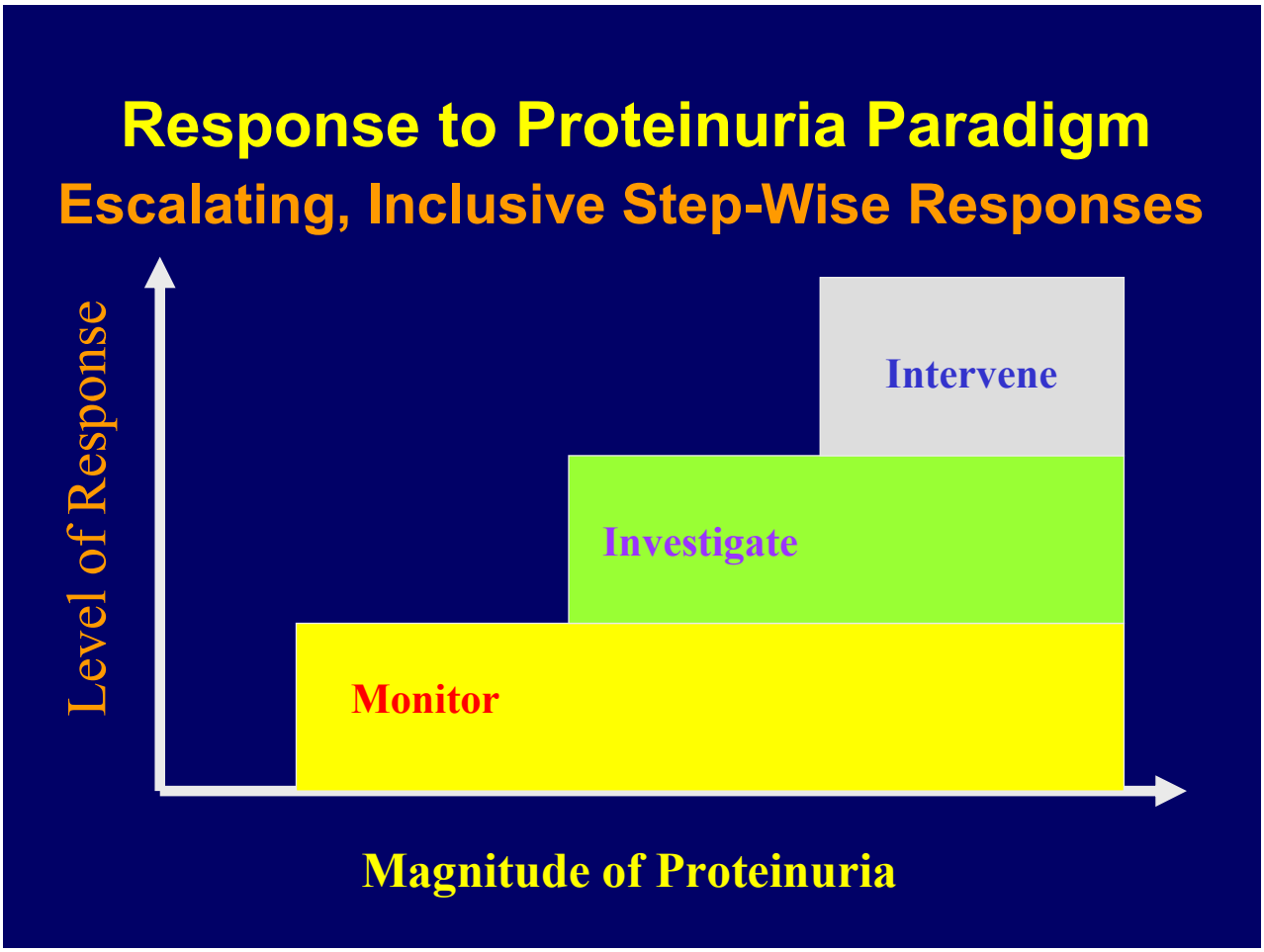
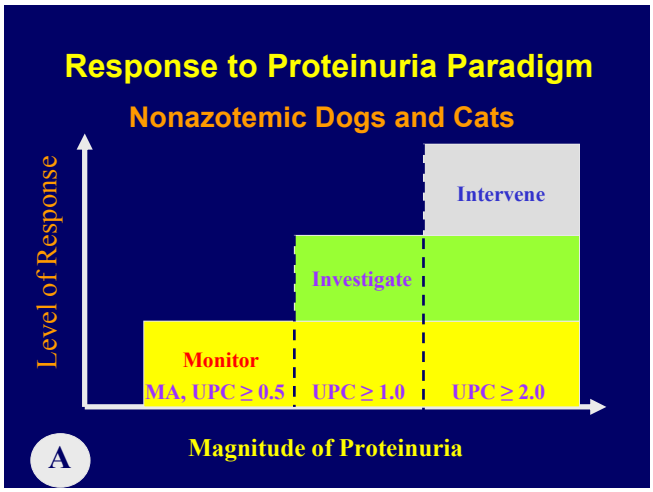
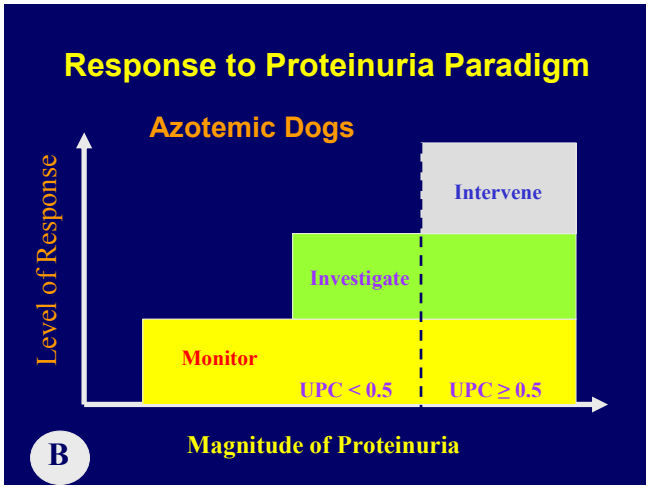


Figure 1 – Schematic representation of the recommended paradigm for responding to proteinuria with a series of escalating, inclusive step-wise responses.





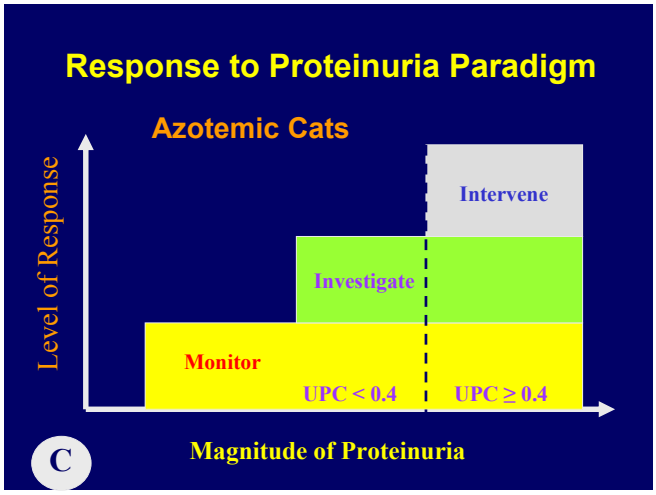


Figure 2 – Recommended cutoffs for the magnitude of proteinuria that should prompt specific escalating responses to proteinuria depending on patient status; (A) in nonazotemic dogs and cats, (B) in azotemic dogs, and (C) in azotemic cats. MA, microalbuminuria; UPC, urine protein-to-creatinine ratio.

Appendix I – Strength of Evidence Levels Used to Annotate Statements Regarding Specific Implications of Proteinuria and Specific Recommendations for Therapeutic Interventions.

Level 1 (best evidence)

Based on data obtained from:

- At least one properly randomized controlled clinical trial

Level 2

Based on data obtained from:

- At least one well-designed clinical trial without randomization
- Cohort or case-controlled analytic studies
- Studies using acceptable laboratory models or simulations in the target species, preferably from more than one center
- Multiple time series
- Dramatic results in uncontrolled experiments

Level 3

Based on:

- Opinions of respected authorities on the basis of clinical experience
- Descriptive studies
- Studies in other species
- Pathophysiological justification
- Reports of expert committees

Initially adapted from: McGowan J, Chesney PJ, Crossley KB, LaForce FM. Guidelines for the use of systemic glucocorticosteroids in the management of selected infections. Working Group on Steroid Use, Antimicrobial Agents Committee, Infectious Diseases Society of America. *J Infect Dis* 1992;165:1-13, by Dr. David J. Polzin, as in Polzin DJ. Treating feline renal failure: an evidence-based approach. *Proceedings of the 20th ACVIM Forum*, Dallas, Texas, May 29 – June 1, 2002, pp 588-590.