

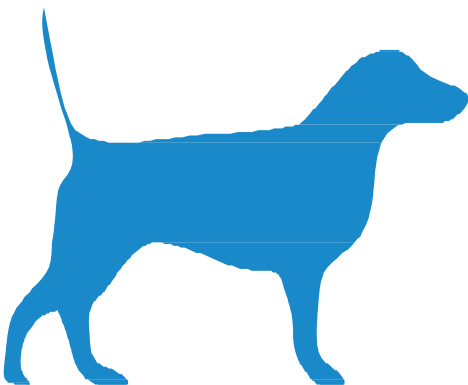
Treatment Recommendations for CKD in Dogs (2023)

All treatments for chronic kidney disease (CKD) need to be tailored to the individual patient. The following recommendations are useful starting points for the majority of dogs at each stage. Serial monitoring of these patients is ideal and treatment should be modified according to the response to treatment. Note that staging of disease is undertaken **following diagnosis of CKD** – an increased blood creatinine or symmetric dimethylarginine (SDMA) concentration alone is not diagnostic of CKD.

Treatment recommendations fall into two broad categories, namely:

1. Those that slow progression of CKD and thereby preserve remaining kidney function for longer
2. Those that seek to improve the quality of life of the dog, reducing signs of CKD

In general, there are few clinical extra-renal signs at the early stages of CKD (Stages 1 and 2) and the therapeutic emphasis is on slowing progression. From Stage 3 onwards, extra-renal signs become more common and more severe. By Stage 4, treatments that are symptomatic and improve quality of life assume greater importance, and become more relevant than those designed to slow progression of CKD. Some of the treatment recommendations are not authorized for use in all geographical regions and some may not be authorized for use in dogs. Such recommended dose rates are therefore empirical. It is the treating veterinarian's duty to make a risk:benefit assessment for each dog prior to administering any treatment.





Treatment recommendations for Dogs with CKD

Stage 1 Canine patients:

1. Discontinue all potentially nephrotoxic drugs if possible.
2. Identify and treat any pre-renal or post-renal abnormalities.
3. Rule out any treatable conditions like pyelonephritis and ureteral obstruction with radiographs and/or ultrasonography.
4. Measure blood pressure and urine protein to creatinine ratio (UP/C).

Management of dehydration:

In these patients, urine concentrating ability may be somewhat impaired and therefore ensure:

- They have fresh water available at all times for drinking
- If become ill for any reason that leads to fluid losses, correct clinical dehydration with isotonic polyionic replacement fluid solutions (e.g. lactated Ringer's) IV or SQ, promptly as needed

Systemic hypertension:

The blood pressure above which progressive renal injury may be induced is unknown. Our goal is to reduce systolic blood pressure to <160 mm Hg and minimize the risk of extra-renal target organ damage (CNS, retinal, cardiac problems/damage). If there is no evidence of such damage but systolic blood pressure persistently exceeds 160 mm Hg, treatment should be instituted.

'Persistence' of increase in systolic blood pressure should be judged on multiple measurements made over the following time-scales in these blood pressure substages:

- Hypertensive (moderate risk of future target organ damage) – systolic blood pressure 160 to 179 mm Hg, persistence demonstrated over 1 to 2 weeks
- Severely hypertensive (high risk of future target organ damage) – systolic blood pressure \geq 180 mm Hg persistence demonstrated over 1 to 2 weeks

If evidence of target organ damage exists, dogs should be treated without the need to demonstrate persistently increased systolic blood pressure. Reducing blood pressure is a long term aim when managing the patient with CKD and a gradual and sustained reduction should be the goal, avoiding any sudden or severe decreases leading to hypotension.

It is recognized that some breeds (such as sight hounds) tend to have higher blood pressure (see Appendix 1) and that this may influence interpretation.

A logical stepwise approach to managing hypertension is as follows:

1. Dietary sodium (Na) reduction – there is no evidence that lowering dietary Na will reduce blood pressure. If dietary Na reduction is attempted, it should be accomplished gradually and in combination with pharmacological therapy.
2. Angiotensin converting enzyme inhibitor (ACEI, such as benazepril) therapy at standard dose rate.



3. Double the dose of ACEI (in some dogs, increasing the dose may improve the antihypertensive effect).
4. Combine ACEI and calcium channel blocker (CCB, such as amlodipine) treatment, especially if severely hypertensive.
5. Combine ACEI and CCB with angiotensin receptor blocker (ARB, such as telmisartan) and/or hydralazine if additional treatment is required.

Note: Take care not to introduce ACEI/CCB with or without ARB to unstable dehydrated dogs as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected.

Monitoring response to antihypertensive treatment:

Hypertensive dogs normally require lifelong therapy and frequently require adjustments in treatment. Serial monitoring is essential. After stabilization, monitoring should occur at least every 3 months.

Systolic blood pressure <120 mm Hg and/or clinical signs such as weakness or tachycardia indicate hypotension, which is to be avoided.

Blood creatinine concentration – reducing blood pressure may lead to small and persistent increases in creatinine concentration (<45 $\mu\text{mol/l}$ or 0.5 mg/dl increase) and/or SDMA (< 2 $\mu\text{g/dl}$), but a marked increase suggests an adverse drug effect. Progressively increasing concentrations indicate progressive kidney damage/disease.

Proteinuria:

Dogs in Stage 1 with UP/C >0.5 should be investigated for disease processes leading to proteinuria (see 1 and 2 below) Those with confirmed and persistent renal proteinuria should be treated with antiproteinuric measures (see 3, 4, 5 and 6 below).

Those with borderline proteinuria (UP/C 0.2 to 0.5) require close monitoring (see 1 and 6 below). The goal of treatment is nuanced. Treatment should be aimed to have the reduction in proteinuria to the lowest UPC possible without doing harm (see point 6).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Consider kidney biopsy (for dogs in stages 1 to 3, not stage 4) as a means of identifying underlying disease (see Appendix 2 and/or consult experts if unsure of indications for kidney biopsy).
3. Administer an angiotensin receptor blocker (ARB) and feed a clinical renal diet.
4. Combination of an ACEI and diet with an angiotensin receptor blocker (ARB) if proteinuria is not controlled should be done judiciously and cautiously, ideally under consultation with a veterinary nephrologist (see note 1 below).
5. Administer clopidogrel (1.1-3 mg/kg orally every 24 hours) if serum albumin is <20 g/l (2.0 g/dl). If clopidogrel is not available, low-dose acetylsalicylic acid (2 to 5 mg/kg once daily) is an acceptable alternative (see note 2 below).



6. Monitor response to treatment / progression of disease:

- stable blood creatinine concentration, decreasing UP/C and/or increasing serum albumin (if previously low) = good response.
- a UPC of < 0.5 is not achievable for many dogs with primary glomerular disease. For these dogs the goal should be a 50% reduction in UPC from baseline
- serially increasing blood creatinine concentration and/or increasing UP/C = disease is progressing.

Ordinarily therapy will be maintained lifelong unless the underlying disease has been resolved in which case dose reduction whilst monitoring UP/C might be considered.

Note 1:

ACEI or ARB use is contraindicated in any dog that is clinically dehydrated and/or is showing signs of hypovolemia. Correct dehydration before using these drugs otherwise glomerular filtration rate may drop precipitously. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected. Further detailed recommendations for diagnosis and management of glomerular disease in dogs can be found in the IRIS Consensus Statements published in Journal of Veterinary Internal Medicine in 2013 (supplement to volume 27).

Note 2:

Dogs with PLN are at risk of thrombosis however it is not possible to predict the risk for thrombosis in the individual patient as serum albumin, antithrombin and degree of proteinuria are poorly associated with thrombotic risk. Tests such as thromboelastography, thrombin generation and markers of activated clotting can be used to document hypercoagulability, however, identification of a hypercoagulable state has not been shown to correlate to risk of developing thrombosis. Prothrombin and partial thromboplastin times (PT, PTT) also cannot be used to predict thrombotic risk. Antithrombotic therapy is indicated in dogs with PLN (CURATIVE Guidelines DOI: 10.1111/vec.12801). Clopidogrel (1-4mg/kg orally once daily) administration may be more effective than low dose acetylsalicylic acid (1-5mg/kg orally once daily) for thromboprophylaxis



Stage 2 Canine patients:

All of the above listed for Stage 1 (listed here again for convenience), plus any additional steps indicated below.

1. Discontinue all potentially nephrotoxic drugs if possible.
2. Identify and treat any pre-renal or post-renal abnormalities.
3. Rule out any treatable conditions like pyelonephritis and ureteral obstruction with radiographs and/or ultrasonography.
4. Measure blood pressure and urine protein to creatinine ratio (UP/C).
5. Consider feeding a clinical renal diet: this may be accomplished more easily early in the course of CKD, before inappetence develops.

Management of dehydration:

These canine patients have decreased urine concentrating ability and therefore ensure:

- They have fresh water available at all times for drinking.
- If they become ill for any reason leading to fluid losses, correct clinical dehydration/hypovolemia with isotonic, polyionic replacement fluid solutions (e.g., lactated Ringer's) IV or SQ promptly as needed

Systemic hypertension:

The blood pressure above which progressive renal injury may be induced is unknown. Our goal is to reduce systolic blood pressure to <160 mm Hg and minimize the risk of extra-renal target organ damage (CNS, retinal, cardiac problems/damage). If there is no evidence of this but systolic blood pressure persistently exceeds 160 mm Hg, increasing the risk of such damage, treatment should be instituted.

'Persistence' of increase in systolic blood pressure should be judged on multiple measurements made over the following time-scales in these blood pressure substages:

- Hypertensive (moderate risk of future target organ damage) – systolic blood pressure 160 to 179 mm Hg – persistence demonstrated over 1 to 2 weeks
- Severely hypertensive (high risk of future target organ damage) – systolic blood pressure ≥ 180 mm Hg persistence demonstrated over 1 to 2 weeks

If evidence of target organ damage exists, dogs should be treated without the need to demonstrate persistently increased systolic blood pressure. Reducing blood pressure is a long term aim in a patient with CKD and a gradual and sustained reduction should be the goal, avoiding any sudden decreases or hypotension.



It is recognized that some breeds (such as sight hounds) tend to have higher blood pressure (see Appendix 1) and that this may influence interpretation.

A logical stepwise approach to managing hypertension is as follows:

1. Dietary sodium (Na) reduction – there is no evidence that lowering dietary Na will reduce blood pressure. If dietary Na reduction is attempted, it should be accomplished gradually and in combination with pharmacological therapy.
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3. Double the dose of ACEI (in some patients, increasing the dose may improve the antihypertensive effect).
4. Combine ACEI and calcium channel blocker (CCB, such as amlodipine) treatment, especially if severely hypertensive.
5. Combine ACEI and CCB with angiotensin blocker (ARB, such as telmisartan) and/or hydralazine if additional treatment is required.

Note: Take care not to introduce ACEI/CCB with or without ARB treatment to unstable dehydrated dogs as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected.

Monitoring response to antihypertensive treatment:

Hypertensive dogs normally require lifelong therapy and frequently require adjustments in treatment dosages. Serial monitoring is essential. After stabilization, monitoring should occur at least every 3 months.

Systolic blood pressure <120 mm Hg and/or clinical signs such as weakness or tachycardia indicate hypotension, which is to be avoided.

Blood creatinine concentration – reducing blood pressure may lead to small and persistent increases in creatinine (<45 $\mu\text{mol/l}$ or 0.5 mg/dl increase) and/or SDMA (< 2 $\mu\text{g/dl}$), but a marked increase suggests an adverse drug effect. Progressively increasing concentrations indicate progressive kidney damage/disease.

Proteinuria:

Dogs in Stage 2 with UP/C >0.5 should be investigated for the disease processes leading to proteinuria (see 1 and 2 below). Those with confirmed and persistent renal proteinuria should be treated with anti-proteinuric measures (see 3, 4, 5 and 6 below). The goal of treatment is nuanced. Treatment should be aimed to have the reduction in proteinuria to the lowest UPC possible without doing harm (see point 6).

Those with borderline proteinuria (0.2 to 0.5) require close monitoring (see 1 and 6 below).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Consider kidney biopsy (for dogs in stages 1 to 3, not stage 4) as a means of identifying underlying disease (see Appendix 2 and/or consult experts if unsure of indications for kidney biopsy).
3. Administer an angiotensin receptor blocker (ARB) and feed a clinical renal diet.



4. Combination of an ACEI and diet with an ARB if proteinuria is not controlled should be done judiciously and cautiously, ideally under consultation with a veterinary nephrologist (see note 1 below).

5. Administer clopidogrel (1.1-3 mg/kg orally every 24 hours) if serum albumin is <20 g/l (2.0 g/dl). If clopidogrel is not available, low-dose acetylsalicylic acid (2 to 5 mg/kg once daily) is an acceptable alternative (see note 2 below).

6. Monitor response to treatment / progression of disease:

- stable blood creatinine concentration, decreasing UP/C and/or increasing serum albumin (if previously low) = good response.
- a UPC of < 0.5 is not achievable for many dogs with primary glomerular disease. For these dogs the goal should be a 50% reduction in UPC from baseline.
- serially increasing blood creatinine concentrations and/or increasing UP/C and/or increasing serum albumin (if previously low) = disease is progressing.

Ordinarily therapy will be maintained lifelong unless the underlying disease has been resolved in which case dose reduction whilst monitoring UP/C might be considered.

Note 1: ACEI or ARB use is contraindicated in any animal that is clinically dehydrated and/or showing signs of hypovolemia. Correct dehydration before using these drugs otherwise glomerular filtration rate may drop precipitously. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected. Further detailed recommendations for diagnosis and management of glomerular disease in dogs can be found in the IRIS Consensus Statements published in Journal of Veterinary Internal Medicine in 2013 (supplement to volume 27).

Note 2: Dogs with PLN are at risk of thrombosis however it is not possible to predict the risk for thrombosis in the individual patient as serum albumin, antithrombin and degree of proteinuria are poorly associated with thrombotic risk. Tests such as thromboelastography, thrombin generation and markers of activated clotting can be used to document hypercoagulability, however, identification of a hypercoagulable state has not been shown to correlate to risk of developing thrombosis. Prothrombin and partial thromboplastin times (PT, PTT) also cannot be used to predict thrombotic risk. Antithrombotic therapy is indicated in dogs with PLN (CURATIVE Guidelines DOI: 10.1111/vec.12801). Clopidogrel (1-4mg/kg orally once daily) administration may be more effective than low dose acetylsalicylic acid (1-5mg/kg orally once daily) for thromboprophylaxis.



Reduction of phosphate intake:

Evidence suggests that chronic reduction of phosphate intake to maintain plasma phosphate concentration below 1.5 mmol/l (but not less than 0.9 mmol/l; <4.6 mg/dl but >2.7 mg/dl) is beneficial to patients with CKD. The following measures can be introduced sequentially in an attempt to achieve this:

1. Dietary phosphate restriction (i.e., clinical renal diet therapy).
2. If plasma phosphate concentration remains above 1.5 mmol/l (4.6 mg/dl) after dietary restriction, give enteric phosphate binders (such as aluminum hydroxide, aluminum carbonate, calcium carbonate, calcium acetate, lanthanum carbonate) to effect, starting at 30-60 mg/kg/day in divided doses to be mixed with each meal (mixed with the food). The dose required will vary according to the amount of phosphate being fed and the stage of CKD. Treatment with phosphate binders should be to effect (as outlined above), with signs of toxicity limiting the upper dose rate possible in a given patient. Monitor serum calcium and phosphate concentrations every 4-6 weeks until stable and then every 12 weeks. Microcytosis and/or generalized muscle weakness suggests aluminum toxicity if using an aluminum containing binder – switch to another form of phosphate binder should this occur. Hypercalcemia should be avoided – combinations of aluminum and calcium containing phosphate binders may be necessary in some cases.

Additional treatments for stage 2 patients aimed at improving their quality of life:

Treat suspected nausea with anti-emetics such as maropitant or ondansetron. Treat decreased appetite/weight and/or muscle loss with appetite stimulants such as capromorelin or mirtazapine. If muscle loss is marked, consider staging based on serum SDMA concentration rather than creatinine and following treatment recommendations for SDMA stage (see below).

Consider omeprazole in dogs with suspected gastric bleeding (eg melena, iron deficiency) or vomiting-induced esophagitis.

Where there is a discrepancy between creatinine and SDMA:

If serum or plasma SDMA is >35 µg/dl in a patient whose creatinine is between 1.4 and 2.8 mg/dl (IRIS CKD stage 2 based on blood creatinine), this patient, should be staged and treated as an IRIS CKD Stage 3 patient.



Stage 3 Canine patients:

The range of presentations for dogs in Stage 3 is wide, from no clinical signs to quite marked extra-renal signs. The treatments mentioned so far for Stages 1 and 2 aimed at slowing progression of CKD also apply in Stage 3 and may be all that is required for dogs with no or mild clinical signs. But treatments designed to improve the quality of life are more important as extra-renal signs become increasingly evident. These include treatments to address dehydration, nausea and vomiting, anemia and acidosis.

Treatment recommendations include all of the above listed for Stage 1 and 2 (listed again here for convenience) plus any additional steps indicated below.

1. Discontinue all potentially nephrotoxic drugs if possible.
2. Identify and treat any pre-renal or post-renal abnormalities.
3. Rule out any treatable conditions like pyelonephritis and ureteral obstruction with radiographs and/or ultrasonography.
4. Measure blood pressure and urine protein to creatinine ratio (UP/C).
5. Feed a clinical renal diet.

Management of dehydration:

These patients have decreased urine concentrating ability and therefore

- correct clinical dehydration/hypovolemia with isotonic, polyionic replacement fluid solutions (e.g., lactated Ringer's) IV or SQ promptly as needed.
- have fresh water available at all times for drinking
- In addition, some of these dogs may require maintenance fluids administered routinely to maintain hydration (see below)

Systemic hypertension:

The blood pressure above which progressive renal injury may be induced is unknown. Our goal is to reduce systolic blood pressure to <160 mm Hg and minimize the risk of extra-renal target organ damage (CNS, retinal, cardiac problems/damage). If there is no evidence of this but systolic blood pressure persistently exceeds 160 mm Hg, increasing the risk of such damage, treatment should be instituted.

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- Hypertensive (moderate risk of future target organ damage) – systolic blood pressure 160 to 179 mm Hg, persistence demonstrated over 1 to 2 weeks
- Severely hypertensive (high risk of future target organ damage – systolic blood pressure \geq 180 mm Hg measured, persistence demonstrated over 1 to 2 weeks

If evidence of target organ damage exists, dogs should be treated without the need to demonstrate persistently increased systolic blood pressure. Reducing blood pressure is a long term aim when managing the patient with CKD and a gradual and sustained reduction should be the goal, avoiding any sudden or severe decreases leading to hypotension.

Some breeds (such as sight hounds) tend to have higher blood pressure (see Appendix) and that this may influence interpretation.

Treatment Recommendations for CKD in Dogs (2023)



A logical stepwise approach to managing hypertension is as follows:

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3. Double the dose of ACEI (in some patients, increasing the dose may improve the antihypertensive effect).
4. Combine ACEI and calcium channel blocker (CCB, such as amlodipine) treatment, especially if severely hypertensive.
5. Combine ACEI and CCB with angiotensin receptor blocker (ARB, such as telmisartan) and/or hydralazine if additional treatment is required.

Note: Take care not to introduce ACEI/CCB with or without ARB treatment to unstable dehydrated dogs as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected. The risk is higher in CKD stages 3 and 4.

Monitoring response to antihypertensive treatment:

Hypertensive dogs normally require lifelong therapy and may require treatment adjustments. Serial monitoring is essential. After stabilization, monitoring should occur at least every 3 months.

Systolic blood pressure <120 mm Hg and/or clinical signs such as weakness or tachycardia indicate hypotension, which is to be avoided.

Blood creatinine concentration – reducing blood pressure may lead to small and persistent increases in blood creatinine (<45 $\mu\text{mol/l}$ or 0.5 mg/dl increase) and/or SDMA (< 2 $\mu\text{g/dl}$), but a marked increase suggests an adverse drug effect. Progressively increasing creatinine concentrations indicate progressive kidney damage/disease.

Proteinuria:

Dogs in Stage 3 with urine protein to creatinine ratio (UP/C) >0.5 should be investigated for disease processes leading to proteinuria (see 1 and 2 below). Those with confirmed and persistent renal proteinuria should be treated with anti-proteinuric measures (see 3, 4, 5 and 6 below). The goal of treatment is nuanced. Treatment should be aimed to have the reduction in proteinuria to the lowest UPC possible without doing harm (see point 6).

Those with borderline proteinuria (0.2 to 0.5) require close monitoring (see 1 and 6 below).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Consider kidney biopsy (for dogs in stages 1 to 3, not stage 4) as a means of identifying underlying disease (see Appendix 2 and/or consult experts if unsure of indications for kidney biopsy).
3. Administer an angiotensin receptor blocker (ARB) and feed a clinical renal diet.
4. Combination of an ACEI and diet with an ARB if proteinuria is not controlled, should be done judiciously and cautiously, ideally under consultation with a veterinary nephrologist (see note 1 below).

Treatment Recommendations for CKD in Dogs (2023)



5. Administer clopidogrel (1.1- 3 mg/kg orally every 24 hours) if serum albumin is <20 g/l (2.0 g/dl). If clopidogrel is not available, low-dose acetylsalicylic acid (2 to 5 mg/kg once daily) is an acceptable alternative (see note 2 below).

6. Monitor response to treatment / progression of disease:

- stable blood creatinine concentration, decreasing UP/C and/or increasing serum albumin (if previously low) = good response.
- a UPC of < 0.5 is not achievable for many dogs with primary glomerular disease. For these dogs the goal should be a 50% reduction in UPC from baseline
- serially increasing blood creatinine concentration and/or increasing UP/C = disease is progressing.

Ordinarily therapy will be maintained lifelong unless the underlying disease has been resolved in which case dose reduction whilst monitoring UP/C might be considered.

Note 1: ACEI or ARB use is contraindicated in any animal that is clinically dehydrated and/or is showing signs of hypovolemia. Correct dehydration before using these drugs otherwise glomerular filtration rate may drop precipitously. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected. The risk is higher in CKD stages 3 and 4. Further detailed recommendations for diagnosis and management of glomerular disease in dogs can be found in the IRIS Consensus Statements published in Journal of Veterinary Internal Medicine in 2013 (supplement to volume 27).

Note 2: Dogs with PLN are at risk of thrombosis however it is not possible to predict the risk for thrombosis in the individual patient as serum albumin, antithrombin and degree of proteinuria are poorly associated with thrombotic risk. Tests such as thromboelastography, thrombin generation and markers of activated clotting can be used to document hypercoagulability, however, identification of a hypercoagulable state has not been shown to correlate to risk of developing thrombosis. Prothrombin and partial thromboplastin times (PT, PTT) also cannot be used to predict thrombotic risk. Antithrombotic therapy is indicated in dogs with PLN (CURATIVE Guidelines DOI: 10.1111/vec.12801). Clopidogrel (1-4mg/kg orally once daily) administration may be more effective than low dose acetylsalicylic acid (1-5mg/kg orally once daily) for thromboprophylaxis



Reduction of phosphate intake:

Evidence suggests that chronic reduction of phosphate intake to maintain a plasma phosphate concentration below 1.5 mmol/l (but not less than 0.9 mmol/l; <4.6 mg/dl but >2.7 mg/dl) is beneficial to patients with CKD.

A more realistic post-treatment target for dogs at Stage 3 is <1.6 mmol/l (5.0 mg/dl).

The following measures can be introduced sequentially in an attempt to achieve this:

1. Dietary phosphate restriction (i.e., clinical renal diet therapy).
2. If plasma phosphate concentration remains above 1.6 mmol/l (5.0 mg/dl) after dietary restriction, give enteric phosphate binders (such as aluminum hydroxide, aluminum carbonate, calcium carbonate, calcium acetate; lanthanum carbonate) to effect, starting at 30-60 mg/kg/day in divided doses to be mixed with each meal (mixed with the food). The dose required will vary according to the amount of phosphate being fed and the stage of kidney disease. Treatment with phosphate binders should be to effect (as outlined above), with signs of toxicity limiting the upper dose rate possible in a given patient. Monitor serum calcium and phosphate concentrations every 4-6 weeks until stable and then every 12 weeks. Microcytosis and/or generalized muscle weakness suggests aluminum toxicity if using an aluminum containing binder – switch to another form of phosphate binder should this occur. Hypercalcemia should be avoided – combinations of aluminum and calcium containing phosphate binders may be necessary in some cases.



Additional recommendations for Stage 3 patients aimed at improving quality of life:

1. Metabolic acidosis:

If metabolic acidosis exists (blood bicarbonate or total CO₂ <18 mmol/l) once the patient is stabilized on the clinical renal diet of choice, supplement with oral sodium bicarbonate (or potassium citrate if hypokalemic) to effect to maintain blood bicarbonate / total CO₂ in the range of 18-24 mmol/l.

2. Consider treatment for anemia if it is affecting the patient's quality of life: typically, this occurs when the PCV is <0.20 l/l (20%). Human recombinant erythropoietin is the most effective treatment but is not approved for veterinary use: darbepoetin is preferable as it is less antigenic than epoetin alfa. Anabolic steroids are of no proven benefit and may be detrimental.

3. Treat vomiting and suspected nausea with anti-emetics such as maropitant or ondansetron. Treat decreased appetite/weight and/or muscle loss with appetite stimulants such as capromorelin or mirtazapine. Consider intermittent omeprazole in dogs with suspected gastric bleeding (eg melena, iron deficiency) or vomiting-induced esophagitis. If pharmacological management of appetite is ineffective and/or supplemental hydration is required long-term, enteral feeding tube should be considered.

4. Give appropriate maintenance fluids parenterally as necessary to maintain hydration (see Footnote).

5. Drugs that rely predominantly on renal function for their clearance from the body should be used with caution in patients in Stage 3 CKD. It may be necessary to adjust the dose of these drugs (depending on their therapeutic indices) to avoid accumulation.

Where there is a discrepancy between creatinine and SDMA:

If serum or plasma SDMA is >54 µg/dl in a dog with a blood creatinine concentration of between 2.8 and 5 mg/dl (IRIS CKD Stage 3 based on creatinine), the patient should be staged an IRIS CKD Stage 4 patient and receive the recommended treatments for Stage 4 patients.



Stage 4 Canine patients:

Most dogs with Stage 4 CKD exhibit many extra-renal signs. Although it is still advisable to try to slow progression of CKD, treatments to improve quality of life become more important, especially management of dehydration, acidosis, vomiting, nausea and inappetence, weight loss and anemia. Treatment recommendations therefore include all of the above listed for Stages 1, 2 and 3, (listed again here for convenience) plus any additional steps indicated below.

1. Discontinue all potentially nephrotoxic drugs if possible.
2. Identify and treat any pre-renal or post-renal abnormalities.
3. Rule out any treatable conditions like pyelonephritis (any urinary tract infection should be regarded as a potential pyelonephritis and treated appropriately) and ureteral obstruction with radiographs and/or ultrasonography.
4. Measure blood pressure and urine protein to creatinine ratio (UP/C).
5. Clinical renal diet therapy.

Management of dehydration:

These patients have decreased urine concentrating ability and therefore

- correct clinical dehydration/hypovolemia with isotonic, polyionic replacement fluid solutions (e.g., lactated Ringer's) IV or SQ, promptly as needed.
- have fresh water available at all times for drinking.
- In addition, some of these dogs may require maintenance fluids administered routinely to maintain hydration (see below)

Systemic hypertension:

The blood pressure above which progressive renal injury may be induced is unknown. Our goal is to reduce systolic blood pressure to <160 mm Hg and minimize the risk of extra-renal target organ damage (CNS, retinal, cardiac problems/damage). If there is no evidence of this but systolic blood pressure persistently exceeds 160 mm Hg, increasing the risk of such damage, treatment should be instituted.

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If evidence of target organ damage exists, dogs should be treated without the need to demonstrate persistently increased systolic blood pressure. Reducing blood pressure is a long term aim when managing the patient with CKD and a gradual and sustained reduction should be the goal, avoiding any sudden or severe decreases leading to hypotension.

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3. Double the dose of ACEI (in some patients, increasing the dose may improve the antihypertensive effect).
4. Combine ACEI and calcium channel blocker (CCB, such as amlodipine) treatment, especially if severely hypertensive.
5. Combine ACEI and CCB with an angiotensin receptor blocker (ARB, such as telmisartan) and/or hydralazine if additional treatment is required.

Note: Take care not to introduce ACEI/CCB with or without ARB treatment to unstable dehydrated dogs as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected. The risk is higher for CKD stages 3 and 4 patients.

Monitoring response to antihypertensive treatment:

Hypertensive dogs normally require lifelong therapy and may require treatment adjustments. Serial monitoring is essential. After stabilization, monitoring should occur at least every 3 months.

Systolic blood pressure <120 mm Hg and/or clinical signs such as weakness or tachycardia indicate hypotension, which is to be avoided.

Blood creatinine concentration – reducing blood pressure may lead to small and persistent increases in creatinine (<45 $\mu\text{mol/l}$ or 0.5 mg/dl increase) and/or SDMA (< 2 $\mu\text{g/dl}$), but a marked increase suggests an adverse drug effect.

Progressively increasing creatinine concentrations indicate progressive kidney damage/disease.



Proteinuria:

Dogs in Stage 4 with urine protein to creatinine ratio (UP/C) >0.5 should be investigated for the disease processes leading to proteinuria (see 1 and 2 below). Those with confirmed and persistent renal proteinuria should be treated with anti-proteinuric measures (see 3, 4, 5 and 6 below). The goal of treatment is nuanced. Treatment should be aimed to have the reduction in proteinuria to the lowest UPC possible without doing harm (see point 6).

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3. Administer an angiotensin receptor blocker (ARB) and feed a clinical renal diet.
4. Combination of an ACEI and diet with ARB if proteinuria is not controlled, should be done judiciously and cautiously, ideally under consultation with a veterinary nephrologist (see note 1 below).
5. Administer an angiotensin receptor blocker (ARB) and feed a clinical renal diet. If clopidogrel is not available, low-dose acetylsalicylic acid (2 to 5 mg/kg once daily) is an acceptable alternative (see note 2 below).
6. Monitor response to treatment / progression of disease:
 - stable blood creatinine concentration, decreasing UP/C and/or increasing serum albumin (if previously low) = good response.
 - a UPC of < 0.5 is not achievable for many dogs with primary glomerular disease. For these dogs the goal should be a 50% reduction in UPC from baseline
 - serially increasing blood creatinine concentrations and/or increasing UP/C = disease is progressing.

Ordinarily therapy will be maintained lifelong unless the underlying disease has been resolved in which case dose reduction whilst monitoring UP/C might be considered.

Note 1: ACEI or ARB use is contraindicated in any animal that is clinically dehydrated and/or is showing signs of hypovolemia. Correct dehydration before using these drugs otherwise glomerular filtration rate may drop precipitously. The risk benefit analysis of combining ACEI with ARBs needs to be made on an individual dog basis and careful monitoring is required to ensure any deterioration in kidney function is detected. The risk is higher in CKD stages 3 and 4. Further detailed recommendations for diagnosis and management of glomerular disease in dogs can be found in the IRIS Consensus Statements published in Journal of Veterinary Internal Medicine in 2013 (supplement to volume 27).



Note 2: Dogs with PLN are at risk of thrombosis however it is not possible to predict the risk for thrombosis in the individual patient as serum albumin, antithrombin and degree of proteinuria are poorly associated with thrombotic risk. Tests such as thromboelastography, thrombin generation and markers of activated clotting can be used to document hypercoagulability, however, identification of a hypercoagulable state has not been shown to correlate to risk of developing thrombosis. Prothrombin and partial thromboplastin times (PT, PTT) also cannot be used to predict thrombotic risk. Antithrombotic therapy is indicated in dogs with PLN (CURATIVE Guidelines DOI: 10.1111/vec.12801). Clopidogrel (1-4mg/kg orally once daily) administration may be more effective than low dose acetylsalicylic acid (1-5mg/kg orally once daily) for thromboprophylaxis

Reduction of phosphate intake:

Evidence suggests that chronic reduction of phosphate intake to maintain a plasma phosphate concentration below 1.5 mmol/l (but not less than 0.9 mmol/l; <4.6 mg/dl but >2.7 mg/dl) is beneficial to patients with CKD.

A more realistic post-treatment target for dogs at Stage 4 is <1.9 mmol/l (6.0 mg/dl).

The following measures can be introduced sequentially in an attempt to achieve this:

1. Dietary phosphate restriction (i.e. clinical renal diet therapy).
2. If plasma phosphate concentration remains above 1.9 mmol/l (6.0 mg/dl) after dietary restriction, give enteric phosphate binders (such as aluminum hydroxide, aluminum carbonate, calcium carbonate, calcium acetate, lanthanum carbonate) to effect, starting at 30-60 mg/kg/day in divided doses to be mixed with each meal (mixed with the food). The dose required will vary according to the amount of phosphate being fed and the stage of kidney disease. Treatment with phosphate binders should be to effect (as outlined above), with signs of toxicity limiting the upper dose rate possible in a given patient. Monitor serum calcium and phosphate concentrations every 4-6 weeks until stable and then every 12 weeks. Aluminum toxicity has been reported in a small number of dogs with stage 4 CKD. Clinical signs included muscle weakness, encephalopathy and microcytosis. If aluminium toxicity is suspected, serum aluminium levels can be measured and, if required, alternative phosphate binders recommended. Hypercalcemia should be avoided – combinations of aluminum and calcium containing phosphate binders may be necessary in some cases.

Treatment Recommendations for CKD in Dogs (2023)



Further treatments aimed at improving quality of life (applicable to Stages 3 & 4)

1. Metabolic acidosis:
If metabolic acidosis exists (blood bicarbonate or total CO₂ <18 mmol/l) once the patient is stabilized on the clinical renal diet of choice, supplement with oral sodium bicarbonate (or potassium citrate if hypokalemic) to effect to maintain blood bicarbonate / total CO₂ in the range of 18-24 mmol/l.
2. Consider treatment for anemia if it is affecting the patient's quality of life: typically this occurs when the PCV is <0.20 l/l (20%) Human recombinant erythropoietin is the most effective treatment but is not approved for veterinary use: darbepoetin is preferable as it is less antigenic than epoetin alfa. Anabolic steroids are of no proven benefit and may be detrimental.
3. Treat vomiting and suspected nausea with anti-emetics such as maropitant, or ondansetron. Treat decreased appetite/weight and/or muscle loss with appetite stimulants such as capromorelin or mirtazapine. Consider intermittent omeprazole in dogs with suspected gastric bleeding (e.g. melena, iron deficiency) or vomiting-induced esophagitis. If pharmacological management of appetite is ineffective and/or supplemental hydration is required long-term, enteral feeding tube should be considered.
4. Give fluids parenterally as necessary to maintain hydration (see Footnote).
5. Drugs that rely predominantly on renal function for their clearance from the body should be used with caution in patients in Stage 4 CKD. It may be necessary to adjust the dose of these drugs (depending on their therapeutic indices) to avoid accumulation.

Further recommendations for Stage 4 patients:

6. Intensify efforts to prevent protein / calorie malnutrition. Consider feeding tube intervention (such as percutaneous gastrostomy tube).
 7. Intensify efforts to prevent dehydration. Feeding tubes can be used to administer fluids as well as food.
 8. Consider dialysis and/or renal transplantation.
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Appendix 1

Adapted Blood Pressure Substaging

For most dogs, the IRIS blood pressure substages are as follows:

- Severely hypertensive (high risk of future target organ damage) – systolic blood pressure ≥ 180 mm Hg
- Hypertensive (moderate risk of future target organ damage) – systolic blood pressure 160 to 179 mm Hg
- Prehypertensive (low risk of future target organ damage) – systolic blood pressure 140 to 159 mm Hg
- Normotensive (minimal risk of future target organ damage) – systolic blood pressure < 140 mm Hg

It is recognized that some breeds, particularly sight hounds, tend to have higher blood pressure than many other breeds.

When dealing with these “high-pressure” breeds the classification of risk for future target organ damage might be adjusted as follows:

- High risk >40 mm Hg above breed-specific reference range
- Moderate risk 20-40 mm Hg above breed-specific reference range
- Low risk 10-20 mm Hg above breed-specific reference range



Appendix 2

Reasons for Undertaking Renal Biopsy

1. Renomegaly
2. CKD in a young patient
3. Persistent and severe proteinuria (UP/C>2.0) in an IRIS CKD Stages 1 and 2 patient
4. Worsening proteinuria in a CKD patient
5. Acute kidney injury, where renal biopsy may provide a prognostic indicator



Footnote

Maintenance fluids to maintain hydration status are low in sodium (30-40mmol/l) and ideally have added potassium (about 13 mmol/l) to ensure daily requirements for fluid and electrolytes are met (e.g. Normosol-M® or 5% Dextrose plus 0.18% NaCl with added KCl).



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