IRIS International Renal Interest Society

Treatment Recommendations for CKD In Cats (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 cats at each stage. Serial monitoring of these patients is ideal and treatment should be adapted according to the response to treatment. Note that staging of disease is undertaken **following diagnosis of CKD** – an increased blood creatinine or SDMA concentration alone is not diagnostic of CKD.

Treatment recommendations fall into two broad categories, namely:

1. Those that slow progression of CKD and so preserve remaining kidney function for longer
2. Those that address the quality of life of the cat, addressing the clinical signs of CKD

In general, at the early stages of CKD (stages 1 and 2), there are few clinical extra-renal signs of the disease and the therapeutic emphasis is on slowing progression. From stage 3 onwards, extra-renal signs become more common and more severe. The importance of administering treatments which address the clinical signs of CKD and improve the cat's quality of life assume greater importance and exceeds the importance of treatments designed to slow progression by stage 4.

Some of the treatment recommendations are not authorized for use in all geographical regions and some may not be authorized for use in cats. Such recommended dose rates are therefore empirical. It is the treating veterinarian's duty to make a risk:benefit assessment for each patient prior to administering any treatment.

Treatment recommendations for Cats with Chronic Kidney Disease

Stage 1 Feline 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 polyioinic 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 to 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, increasing the risk of this occurring, treatment should be instituted.

'Persistence' of increased 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 measured over 1 to 2 weeks
- Severely hypertensive (high risk of future target organ damage) – systolic blood pressure ≥ 180 mm Hg measured over 1 to 2 weeks.

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

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. Calcium channel blocker (CCB), such as amlodipine (0.125 to 0.25 mg/kg once daily) or angiotensin receptor blocker (ARB), telmisartan (2 mg/kg once daily).

3. Double the dose of amlodipine (0.25 to 0.5 mg/kg once daily) if this is treatment selected. Note telmisartan label does not advise a dose increase from 2 mg/kg once daily.
4. Combine amlodipine and telmisartan if either drug alone does not lead to adequate control of blood pressure.

Note: Take care not to introduce CCB/RAAS inhibitor treatment to unstable dehydrated cats as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated.

Monitoring response to antihypertensive treatment:

Hypertensive cats 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 concentration (<45 µmol/l or 0.5 mg/dl increase) or SDMA concentration (<2.0 µg/dl), but a marked increase suggests an adverse drug effect. Progressively increasing concentrations indicate progressive kidney damage/disease.

Proteinuria:

Cats in Stage 1 with UP/C >0.4 should be investigated for disease processes leading to proteinuria (see 1 and 2 below) and treated with anti-proteinuric measures (see 3 and 4 below).

Those with borderline proteinuria (UP/C 0.2 to 0.4) require close monitoring (see 1 and 4 below).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Consider kidney biopsy as a means of identifying underlying disease (see Appendix and consult experts if unsure of indications for kidney biopsy).
3. Administer an RAAS inhibitor (ACEI or ARB) and feed a clinical renal diet.
4. Monitor response to treatment / progression of disease:
   - stable blood creatinine concentration and decreasing UP/C = good response.
   - 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:

a. The use of an RAAS inhibitor is contraindicated in any cat that is clinically dehydrated or is showing signs of hypovolemia. Correct dehydration before using these drugs otherwise glomerular filtration rate may drop precipitously.

b. Cats with proteinuria and hypoalbuminemia likely share the same thromboembolic

risk as dogs (although evidence is lacking in the published literature), but aspirin is difficult to use in cats to achieve a selective antiplatelet effect. If thromboembolic therapy is deemed necessary, clopidogrel (10 to 18.75 mg/day is the drug of choice. Aspirin (1 mg/kg every 72 h) is an alternative (but see above).

c. Cats with serum phosphate within the IRIS target (4.5 mg/dl or 1.5 mmol/l) may be at increased risk of developing hypercalcemia when renal diets are introduced. Measurement of FGF23 may help to identify cats which would benefit from dietary phosphate restriction where plasma phosphate is in the target range. FGF23 >400 pg/ml in the absence of hypercalcaemia, anemia or marked inflammatory disease is an indication to start dietary phosphate restriction. Monitor serum calcium and if total calcium exceeds 12 mg/dl (3 mmol/l) switch the cat to a less phosphate restricted diet.

d. If borderline proteinuria persists, antiproteinuric treatment could be offered, because the association between progression of CKD and proteinuria includes the borderline category. However, there is at present no evidence that intervention with anti-proteinuric drugs slows progression.

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Stage 2 Feline patients:

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

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 patients often have decreased urine concentrating ability 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 polyioinic 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 to 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 increased 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 measured over 1 to 2 weeks.
- Severely hypertensive (high risk of future target organ damage) – systolic blood pressure ≥180 mm Hg over 1 to 2 weeks.

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

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. Calcium channel blocker (CCB) such as amlodipine (0.125 to 0.25 mg/kg once daily) or angiotensin receptor blocker (ARB), telmisartan (2 mg/kg once daily).

3. Double the dose of amlodipine (0.25 to 0.5 mg/kg once daily). if this is treatment selected. Note telmisartan label does not advise a dose increase from 2 mg/kg once daily.
4. Combine amlodipine and telmisartan if either drug on its own does not lead to adequate control of blood pressure

Take care not to introduce CCB/RAAS inhibitor treatment to unstable dehydrated cats as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated.

Monitoring response to antihypertensive treatment:

Hypertensive cats 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 µmol/l or 0.5 mg/dl increase) or SDMA concentration (<2.0 µg/dl), but a marked increase suggests an adverse drug effect. Progressively increasing creatinine concentrations indicate progressive kidney damage/disease.

Proteinuria:

Cats in Stage 2 with UP/C >0.4 should be investigated for disease processes leading to proteinuria (see 1 and 2 below) and treated with anti-proteinuric measures (see 3 and 4 below).

Those with borderline proteinuria (0.2 to 0.4) require close monitoring (see 1 and 4 below).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Consider kidney biopsy as a means of identifying underlying disease (see Appendix and/or consult experts if unsure of indications for kidney biopsy).
3. Administer an RAAS inhibitor (ACEI or ARB) and feed a clinical renal diet.
4. Monitor response to treatment/progression of disease:
   - stable blood creatinine concentration and decreasing UP/C = good response.
   - serially increasing 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 while monitoring UP/C might be considered.

Note:

a. Use of an RAAS inhibitor 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.

b. Cats with proteinuria and hypoalbuminemia likely share the same thromboembolic risk as dogs, (although evidence is lacking in the published literature), but aspirin is difficult to use in cats to achieve a selective antiplatelet effect.

   If thromboembolic therapy is deemed necessary, clopidogrel (10 to 18.75 mg/day is the drug of choice. Aspirin (1 mg/kg every 72 h) is an alternative (but see above).

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c. Cats with serum phosphate within the IRIS target may be at increased risk of developing hypercalcemia when renal diets are introduced. Measurement of FGF23 may help to identify cats which would benefit from dietary phosphate restriction where plasma phosphate is in the target range. FGF23 >400 pg/ml in the absence of hypercalcaemia, anemia or marked inflammatory disease is an indication to start dietary phosphate restriction. Monitor serum calcium and if total calcium exceeds 12mg/dl (3mmol/l) switch the cat to a less phosphate restricted diet.

d. If borderline proteinuria is persistent, antiproteinuric treatment could be offered. The rationale for doing so is that there is an association between progression of CKD and proteinuria which extends into the borderline category. There is no evidence that intervention with anti-proteinuric drugs slows progression, however.

Reduction of phosphate intake:

Many cats in Stage 2 will have normal plasma phosphate concentrations but will have increased plasma FGF23 concentration. 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.

Measurement of FGF23 may help to identify cats which would benefit from dietary phosphate restriction if plasma phosphate is within the IRIS target range. FGF23 >400 pg/ml in the absence of hypercalcaemia, anemia or marked inflammatory disease is an indication to start dietary phosphate restriction.

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 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. Once serum phosphate is in the target range for stage 2 (<1.45 mmol/l or 4.5 mg/dl) measurement of serum FGF23 may assist in determining whether further phosphate restriction would be beneficial to the cat. If FGF23 is >700 pg/ml, further phopshate restriction should be applied (e.g. by increasing the dose of phosphate binder) provided there is no evidence of hypercalcaemia, marked anemia or severe inflammatory disease (all of which can increase FGF23 independently of mineral bone disturbance). Excellent control of mineral bone disturbance would be indicated by serum FGF23 of <500 pg/ml. Microcytosis and/or generalized muscle weakness and neurological signs suggest aluminum toxicity if using an aluminum containing binder – switch to another form of phosphate binder should this occur. It should be noted, however, unlike the dog, aluminum toxicity has not been reported in the cat and it is possible to measure blood aluminum levels to confirm suspected cases. Hypercalcemia should be avoided – combinations of aluminum and calcium containing phosphate binders may be necessary in some cases.

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Additional recommendations for Stage 2 patients:

If the patient is hypokalemic, then potassium gluconate or potassium citrate should be supplemented to effect (typically 1-2 mmol/kg/day).

Treat vomiting / decreased appetite / nausea / weight and/or muscle loss with an antiemetic /appetite stimulant / antinausea agent (such as maropitant, ondansetron, oral or transdermal mirtazapine, or capromorelin).
If there is marked muscle loss, measure serum SDMA and base staging and treatment recommendations on SDMA rather than creatinine as it is not affected by muscle wasting. In addition, evaluate for concurrent diseases leading to vomiting and weight loss.

Evidence suggests oral mirtazapine (1.88 mg/cat every 48 h for 3 weeks) reduces vomiting, improves appetite and leads to weight gain in cats showing signs of inappetence and vomiting in this stage. Maropitant (1 mg/kg daily for 2 weeks) reduced vomiting but did not lead to weight gain/ improved appetite. Further investigations are needed on the use of these and other drugs to determine whether they are useful for managing gastrointestinal disturbances in cats with CKD and uremia when administered longer term.

Where there is a discrepancy between creatinine and SDMA:

If serum or plasma SDMA is persistently >25 µg/dl in a cat with serum creatinine between 1.6 and 2.8 mg/dl (IRIS CKD Stage 2 based on creatinine), stage and treat this cat as and IRIS CKD Stage 3 patient.

Stage 3 Feline patients:

The range of presentations for cats in Stage 3 is likely to be wide, from no clinical signs to quite marked extra-renal clinical signs. The main treatments mentioned so far for stages 1 and 2 are aimed at slowing progression of CKD also apply in stage 3 and may be the only therapies needed for cats with no or mild extra-renal signs. However, treatments designed to improve the quality of life of the cat become more important, the more extra-renal signs are present. These include treatments to address dehydration, nausea and vomiting, anemia and acidosis.

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

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. 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 as needed.
- have fresh water available at all times for drinking.
- In addition, some of these cats 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 to 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 extra-renal target organ 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 measured over 1 to 2 weeks.

- Severely hypertensive (high risk of future target organ damage) – systolic blood pressure ≥180 mm Hg measured over 1 to 2 weeks.

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

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. Calcium channel blocker (CCB) such as amlodipine (0.125 to 0.25 mg/kg once daily) or angiotensin receptor blocker (ARB), telmisartan (2 mg/kg once daily)
3. Double the dose of amlodipine (0.25 to 0.5 mg/kg once daily) if this is treatment selected. Note telemisartan label does not advise a dose increase from 2 mg/kg once daily.
4. Combine amlodipine and telmisartan if either drug on its own does not lead to adequate control of blood pressure.

Note: Take care not to introduce CCB/RAAS inhibitor treatment to unstable dehydrated cats as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated

Monitoring response to antihypertensive treatment:

Hypertensive cats 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 concentration (<45 µmol/l or 0.5 mg/dl increase) or SDMA concentration (<2.0 µg/dl), but a marked increase suggests an adverse drug effect. Progressively increasing concentrations indicate progressive kidney damage/disease.

Proteinuria:

Cats in Stage 3 with urine protein to creatinine ratio (UP/C) >0.4 should be investigated for disease processes leading to proteinuria (see 1 and 2 below) and treated with anti-proteinuric measures (see 3 and 4 below).

Those with borderline proteinuria (0.2 to 0.4) require close monitoring (see 1 and 4 below).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Consider kidney biopsy as a means of identifying underlying disease (see Appendix and/or consult experts if unsure of indications for kidney biopsy).
3. Administer an RAAS inhibitor (ACEI or ARB) and feed a clinical renal diet.
4. Monitor response to treatment / progression of disease:
   - stable blood creatinine concentration and decreasing UP/C = good response.
   - serially increasing 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:

a. Use of an RAAS inhibitor 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.

b. Cats with proteinuria and hypoalbuminemia likely share the same thromboembolic risk as dogs, (although evidence is lacking in the published literature), but aspirin is difficult to use in cats to achieve a selective antiplatelet effect. If thromboembolic therapy is deemed necessary, clopidogrel (10 to 18.75 mg/day is the drug of choice. Aspirin (1 mg/kg every 72 h) is an alternative (but see above).

c. Cats with serum phosphate within the IRIS target may be at increased risk of developing hypercalcemia when renal diets are introduced. Monitor serum calcium and if total calcium exceeds 12mg/dl (3mmol/l) switch to a less phosphate restricted diet.

d. If borderline proteinuria is persistent, antiproteinuric treatment could be offered. The rationale for doing so is that there is an association between progression of CKD and proteinuria which extends into the borderline category. However, there is at present no evidence that intervention with anti-proteinuric drugs slows progression.

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 plasma phosphate concentration for cats 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 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 IRIS stage. 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. Once serum phosphate is in the target range for stage 3 (<1.6 mmol/l or 5 mg/dl) measurement of serum FGF23 may assist in determining whether further phosphate restriction would be beneficial to the cat. If FGF23 is >700 pg/ml, further phosphate restriction should be applied (e.g. by increasing the dose of phosphate binder) provided there is no evidence of hypercalcaemia, marked anemia or severe inflammatory disease (all of which can increase FGF23 independently of mineral bone disturbance).

Microcytosis and/or generalized muscle weakness and neurological signs suggest aluminum toxicity if using an aluminum containing binder– switch to another form of phosphate binder should this occur. It should be noted, however, unlike the dog, aluminum toxicity has not been reported in the cat and it is possible to measure blood aluminum levels to confirm suspected cases. Hypercalcemia should be avoided – combinations of aluminum and calcium containing phosphate binders may be necessary in some cases.

Additional recommendations for Stage 2 and 3 patients:

1. If the patient is hypokalemic, then potassium gluconate or potassium citrate should be supplemented to effect (typically 1-2 mmol/kg/day).

Additional recommendations for stage 3 patients

2. If metabolic acidosis exists (blood bicarbonate or total CO_2 <16 mmol/l) once the patient is stabilized on the diet of choice, supplement with oral sodium bicarbonate, (or potassium citrate if hypokalemic) to effect to maintain blood bicarbonate / total CO in the range of 16-24 mmol/l.

3. Treat vomiting / decreased appetite / nausea / weight and/or muscle loss with an antiemetic /appetite stimulant / antinausea agent (such as maropitant, ondansetron or oral or transdermal mirtazapine or capromorelin). Evidence suggests mirtazapine (1.88 mg/cat every 48 h for 3 weeks) reduces vomiting, improves appetite and leads to weight gain in cats showing signs of inappetence and vomiting in this stage. Maropitant (1 mg/kg daily for 2 weeks) reduced vomiting but did not lead to weight gain/ improved appetite. Further investigations are needed on the use of these and other drugs to determine whether they are useful for managing gastrointestinal disturbances in cats with CKD and uremia when administered longer term. 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 persistently >35 µg/dl in a cat with serum creatinine between 2.8 and 5 mg/dl (IRIS CKD stage 3 based on creatinine) stage and treat the cat as an IRIS CKD Stage 4 patient.

Stage 4 Feline patients:

Most cats with stage 4 CKD have many extra-renal signs present. Although it is still important to administer treatments which slow progression of CKD, the importance of improving quality of life for these cats is greater at this stage. Therapies directly addressing clinical signs and aimed at improving quality of life include management of dehydration, acidosis, vomiting and nausea and anemia.

Treatments include all of the steps listed for listed for Stages 1, 2 and 3 (listed again for convenience) plus any additional steps indicated.

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 ensure:

- 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, these cats 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 to 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 measured over 1 to 2 weeks.
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If evidence of target organ damage exists, cats should be treated without the need to demonstrate persistently increased systolic blood pressure. Reducing blood pressure is a long term aim in managing the patient with CKD and a gradual and sustained reduction should be the goal, avoiding any sudden or severe decreases leading to hypotension.

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. Calcium channel blocker (CCB) such as amlodipine (0.125 to 0.25 mg/kg once daily) or angiotensin receptor blocker (ARB), telmisartan (2 mg/kg once daily)..
3. Double the dose of amlodipine (0.25 to 0.5 mg/kg once daily) if this is treatment selected. Note telemisartan label does not advise a dose increase from 2 mg/kg once daily.
4. Combine amlodipine and telmisartan if either drug on its own does not lead to adequate control of blood pressure.

Note: Take care not to introduce CCB/RAAS inhibitor treatment to unstable dehydrated cats as glomerular filtration rate may drop precipitously if these drugs are introduced before the patient is adequately hydrated. The benefit of combining drugs to try to reduce blood pressure to below the target should be weighed against the high risk in a stage 4 cat of precipitating an azotemic crisis should be carefully considered.

Monitoring response to antihypertensive treatment:

Hypertensive cats 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 µmol/l or 0.5 mg/dl increase) or SDMA concentration (<2.0 µg/dl), but a marked increase suggests an adverse drug effect. Progressively increasing concentrations indicate progressive kidney damage/disease.

Proteinuria:

Cats in Stage 4 with urine protein to creatinine ratio (UP/C) >0.4 should be investigated for disease processes leading to proteinuria (see 1 and 2 below) and treated with anti-proteinuric measures (see 3 and 4 below).

Those with borderline proteinuria (0.2 to 0.4) require close monitoring (see 1 and 4 below).

1. Look for any concurrent associated disease process that may be treated/corrected.
2. Administer an RAAS inhibitor (ACEI or ARB) and feed a clinical renal diet.
3. Monitor response to treatment / progression of disease:
   - stable blood creatinine concentration and decreasing UP/C = good response.
   - serially increasing 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.

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Note:

a. Use of an RAAS inhibitor 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.

b. Cats with proteinuria and hypoalbuminemia likely share the same thromboembolic risk as dogs, (although evidence is lacking in the published literature), but aspirin is difficult to use in cats to achieve a selective antiplatelet effect. If thromboembolic therapy is deemed necessary, clopidogrel (10 to 18.75 mg/day is the drug of choice. Aspirin (1 mg/kg every 72 h) is an alternative (but see above).

c. Cats with serum phosphate within the IRIS target may be at increased risk of developing hypercalcemia when renal diets are introduced. Monitor serum calcium and if total calcium exceeds 12mg/dl (3mmol/l) switch to a less phosphate restricted diet.

d. If borderline proteinuria is persistent, antiproteinuric treatment could be offered. The rationale for doing so is that there is an association between progression of CKD and proteinuria which extends into the borderline category. However, there is at present no evidence that intervention with anti-proteinuric drugs slows progression.

Reduction of phosphate intake:

Evidence suggests that chronic reduction of phosphate intake to maintain a plasmaphosphate 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 plasma phosphate concentration for cats 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 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. Once serum phosphate is in the target range for stage 4 (<1.9 mmol/l or 6 mg/dl) measurement of serum FGF23 may assist in determining whether further phosphate restriction would be beneficial to the cat. If FGF23 is >700 pg/ml, further phosphate restriction should be applied (e.g. by increasing the dose of phosphate binder) provided there is no evidence of hypercalcaemia, marked anemia or severe inflammatory disease (all of which can increase FGF23 independently of mineral bone disturbance).

Microcytosis and/or generalized muscle weakness and neurological signs suggest aluminum toxicity if using an aluminum containing binder – switch to another form of phosphate binder should this occur. It should be noted, however, unlike the dog, aluminum toxicity has not been reported in the cat and it is possible to measure blood aluminum levels to confirm suspected cases. Hypercalcemia should be avoided – combinations of aluminum and calcium containing phosphate binders may be necessary in some cases.

Additional recommendations for Stage 2, 3 and 4 patients:

1. If the patient is hypokalemic, then potassium gluconate or potassium citrate should be supplemented to effect (typically 1-2 mmol/kg/day).

Additional recommendations for Stage 3 and 4 patients

2. If metabolic acidosis exists (blood bicarbonate or total CO2 <16 mmol/l) once the patient is stabilized on the diet of choice, supplement with oral sodium bicarbonate (or potassium citrate if hypokalemic) to effect to maintain blood bicarbonate / total CO_2 in the range of 16-24 mmol/l.
3. 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.
4. Treat vomiting / decreased appetite / nausea / weight and/or muscle loss with an antiemetic / appetite stimulant / antinausea agent (such as maropitant, ondansetron or 'oral or transdermal mirtazapine or capromorelin). Evidence suggests oral mirtazapine (1.88 mg/cat every 48 h for 3 weeks) reduces vomiting, improves appetite and leads to weight gain in cats showing signs of inappetence and vomiting in this stage. Maropitant (1 mg/kg daily for2 weeks) reduced vomiting but did not lead to weight gain/ improved appetite. Further investigations are needed on the use of these and other drugs to determine whether they are useful for managing gastrointestinal disturbances in cats with CKD and uremia when administered longer term. If pharmacological management of appetite is ineffective and/or supplemental hydration is required long-term, enteral feeding tube should be considered.
5. Give appropriate maintenance fluids parenterally as necessary to maintain hydration (see Footnote).

Additional recommendations for Stage 4 patients

6. Intensify efforts to prevent protein / calorie malnutrition. Consider feeding tube intervention (e.g., percutaneous gastrostomy tube).
7. Intensify efforts to prevent dehydration. Feeding tubes can be used to administer fluids as well as food.
8. Consider omeprazole in cats in the uncommon situation where GI bleeding is suspected (e.g. melena, iron deficiency).
9. Consider dialysis and/or renal transplantation.

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.

Appendix

Reasons for Undertaking Renal Biopsy

1. Renomegaly
2. CKD in a young patient
3. Persistent and severe proteinuria (UP/C>2.0) in a non-azotemic 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 (30-40 mmol/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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