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Renal disease medical treatment

Bernhard Gerber

Abstract

Medical treatment in chronic renal- or kidney disease is aimed to improve the consequences of the impaired renal function and to reduce progression of kidney disease. Medications may improve the quality of live in patients with kidney disease or may prolong survival; however they can not cure the patient. Different organ systems are affected by kidney disease and specific treatments for these organ systems are used to ameliorate the situation of the patient.

Definition

Renal disease or kidney disease simply describes damage to the kidneys. The damage may be acute or chronic. Acute kidney injury leads to a rapid decline in renal function and to acute uremia, whereas chronic kidney disease is already lasting for a long period of time. The term chronic is used if the damage of the kidneys exists for at least 3 months. A decline in glomerular filtration (GFR) rate is commonly associated with chronic kidney disease. It is assumed that 3/4 of the nephrons must be damaged until azotemia can be detected by routine laboratory methods.
In this text we will focus on the medical management of the patient with chronic kidney disease. Nutritional management of these patients is covered elsewhere. To get an idea of the severity a staging system was established by the IRIS (International Renal Interest Society; www.iris-kidney.com). This staging system is based on the stable patient in which the values were established on at least two occasions.

Stages of chronic kidney disease in cats according to IRIS:		
Stage 1: Non-azotemic:	Creatinine	<140 mcmol/l
Stage 2: Mild renal azotemia:	Creatinine	140-249 mcmol/l
Stage 3: Moderate renal azotemia:	Creatinine	250-440 mcmol/l
Stage 4: Severe renal azotemia:	Creatinine	> 440 mcmol/l

Classification of proteinuria in cats according to IRIS:		
Nonproteinuric (NP):	Urine protein: creatinine ratio (UPC)	<0.2
Borderline proteinuric (BP):	UPC	0.2-0.4
Proteinuric (P):	UPC	>0.4

Classification of blood pressure according to IRIS:		
Substage 0: minimal risk:	systolic blood pressure	< 150 mmHg
Substage 1: low risk:	systolic blood pressure	150-159 mmHg
Substage 2: moderate risk:	systolic blood pressure	160-179 mmHg
Substage 3: high risk:	systolic blood pressure	≥ 180 mmHg

Diagnosis

In chronic kidney disease the damage to the kidney is thought to be irreversible and the compensatory mechanisms of the kidney are exhausted. In contrast, acute kidney injury is potentially reversible. Therefore it is very important to differentiate between acute and chronic kidney disease. In doubt a patient should be treated as a patient with acute kidney injury. The causes of chronic kidney disease are often not known. Historical signs indicating chronic disease

include long lasting polyuria and polydipsia, decreased appetite, weight loss and poor hair coat quality. On palpation the kidneys are typically small with an irregular surface. Enlarged kidneys are also possible in certain kidney diseases. Anemia is common in chronic kidney disease; however dehydration can mimic a normal hematocrit and anemia can be seen in acute kidney injury as well. Differentiation between acute and chronic kidney disease can become even more difficult if an acute kidney injury is added on top of a chronic disease. To differentiate acute from chronic kidney disease, but also to find a specific underlying cause responsible for the chronic disease a full work up is required. Blood and urine must be screened for underlying diseases. Urine culture might detect a possible urinary tract infection. The urine protein: creatinine ratio might indicate the kind of the kidney disease and is also a prognostic factor. With radiographs and/or ultrasound examinations the kidneys can be evaluated, possible renal and extra renal causes of the kidney damage like cystic kidney disease or ureteral obstruction can be detected or ruled out. High systemic blood pressure can further damage the kidneys therefore blood pressure must be measured.

Medical therapy

If the cause of kidney disease or a related factor is identified during the work up this should be treated accordingly. For instance a urinary tract infection is treated with the appropriate antibiotic or obstruction of the ureter is relieved by an adequate intervention like stone removal or a ureteral stent. Because of the reduced kidney function certain medications might not be adequately excreted and a dose adjustment is necessary. However based on the level of the kreatinine it is difficult to determine how much reduction is needed and if a reduction in dose or a reduction in frequency of application is preferable.

Reduction of phosphorus intake

If the GFR decreases, less phosphorus is filtrated and phosphorus accumulates in the body. In early renal disease the decreased filtration is compensated by a decreased reabsorption in the tubules, however at a certain point reabsorption can not be further reduced and the level of phosphorus increases. Phosphorus is involved in the progression of kidney disease and is directly associated with mortality from kidney disease. Furthermore phosphorus is one of the factors promoting renal secondary hyperparathyreoidism. And finally high phosphorus contributes to a high calcium phosphate product, which may lead to metastatic calcifications. Phosphorus should be measured in all patients with chronic kidney disease. The level of serum phosphorus should ideally be below the following values.

IRIS stage 2:	serum phosphorus	< 1.45 mmol/l
IRIS stage 3:	serum phosphorus	< 1.61 mmol/l
IRIS stage 4:	serum phosphorus	< 1.94 mmol/l.

If dietary management does not adequately decrease the serum phosphorus intestinal phosphor binding agents are indicated. Phosphorus binding agents on the basis of aluminum are effective in cats; however it's becoming more difficult to find them because aluminum toxicity is an issue in human medicine. Alternative preparations are calcium-carbonate, –acetate, or -citrate and lanthanum carbonate. One has to be cautious with calcium based phosphorus binding agents as there is a risk of inducing hypercalcemia. These agents should not be given to hypercalcemic patients and calcium should be monitored regularly. Dose recommendations for aluminum-based phosphorus-binders are 30 to 100 mg/kg/d. For calcium acetate 60 to 90 mg/kg/d, for calcium carbonate 90 to 150 mg/kg/d and for lanthanum carbonate about 30 mg/kg/d. The doses might

have to be increased if effect is not sufficient. Phosphorus-binders should be given with the meal. These agents only bind phosphorus in the food. If administered without food no effect is achieved.

Therapy with calcitriol

The production of calcitriol is decreased in chronic kidney disease. This decrease is caused by hyperphospahtemia, reduced renal mass and increased levels of fibroblast growth factor-23 (FGF-23). Calcitriol reduces PTH and enhances intestinal absorption of calcium and phosphorus and its reduction plays an important role in the development of secondary hyperparathyroidism.
In cats calcitriol at a dose of 2.5 ng/kg/d had no effect on the level of PTH. If calcitriol is administered, serum calcium levels should be closely monitored. Calcitriol can lead to hypercalcemia which can lead to further kidney damage.

Correction of anemia

Anemia in chronic kidney disease is caused by decreased erythrocyte live span, possible gastrointestinal bleeding, and reduced production of erythropoietin. Quite often blood sampling for diagnostic purposes is also involved in anemia. Anemia is a negative prognostic factor und should be addressed. Iron deficiency although rarely thoroughly assessed might be a problem in chronic renal disease. Iron supplementation with iron sulfate 50 to 100 mg/day and cat may be started. However gastrointestinal derangements might occur. Iron dextran 50 mg/cat IM every 3 to 4 weeks is an alternative. Together with iron or alone erythrocyte-stimulating agents like the recombinant human erythropoietin darbepoetin are used. Darbepoetin is started at a dose of 1 mcg/kg weekly until the lower end of the reference range of the hematocrit is reached. After that the interval is increased to every two then every three weeks. Besides these agents treatment of possible gastrointestinal bleeding can be tried with for instance a proton pump inhibitor like omeprazole (0.7 mg/kg/d) and sucralfate (0.125-0.5 g/cat/d PO twice or three times a day). If available a fast correction of anemia can be achieved with blood transfusion.

Therapy of hypertension

Hypertension is associated with chronic kidney disease. Hypertension may lead to end-organ damage. Specifically vulnerable organ systems are the eyes the kidneys, the nervous system and the cardiovascular system. In the kidneys high systemic blood pressure might be transmitted directly to the glomeruli and lead to progression of the kidney disease. This may be exacerbated by the fact that in damaged kidneys autoregulation is impaired leaving the glomerular blood vessels unprotected from this high pressure. Hypertension is also associated with proteinuria which leads to further kidney damage. Emergency treatment of hypertension is indicated if the systolic blood pressure is above 200 mmHg or if end organ damage, most often blindness due to retinal hemorrhage and detachment, is confirmed. However one must remember that the so called “white coat effect” might induce a considerable increase in blood pressure and the measured value does not represent the normal blood pressure. Therefore measurements should be repeated at least three times at different days or even weeks. Treatment is started when systolic arterial blood pressure consistently is above 160 mmHg (substage 2). The treatment goal would be to achieve a systolic blood pressure below 150 mmHg. Amlodipine is the most effective drug for the reduction of blood pressure in cats. It also reduces proteinuria in cats likely due to the reduction of the blood pressure. The starting dose usually is ⅛ to ¼ of a 5 mg tablet daily. After institution of the therapy blood pressure is controlled every week until the desired reduction is achieved. Hypotension should be avoided, as this might lead to decreased renal blood flow. Signs of hypotension include weakness, lethargy and somnolence.

ACE-inhibitors

Progression of renal disease, independent of the original insult likely occurs in kidney disease of stage 2 and higher. Reasons for this progression include intraglomerular hypertension in remaining nephrons and proteinuria. Vasodilatation of the glomerular arterioles specifically the afferent in the remaining nephrons leads to higher renal plasma flow and higher single nephron GFR but also to intraglomerular hypertension. This higher pressure and flow leads to an enlarged glomerulus damage of the endothelium, and to hypertrophy of the podocytes. This again promotes several changes including proteinuria and accumulation of macromolecules in the mesangial area. Proteinuria leads to progression of kidney disease by mesangial toxicity, tubular overload and hyperplasia, tubular toxicity and induction of proinflammatory proteins. ACE-inhibitors reduce the intraglomerular pressure, proteinuria and the profibrotic effect of angiotensin II. In cats the ACE-inhibitor benazepril lead to a trend towards longer survival, showed potential to reduce progression and reduced proteinuria in cats with chronic kidney disease.
Benazepril can be started at a dose of 0.5 mg/kg/d. Further studies are needed to evaluate if blockade of the renin-angiotensin-aldosterone system through angiotensin receptor blockade and aldosterone blockade might be of more benefit in reducing progression of kidney disease in cats.

Correction of metabolic acidosis

Diseased kidneys excrete less H+ ions which can lead to metabolic acidosis. Metabolic acidosis can lead to anorexia, vomitus, weakness and lethargy. Therefore it is important to evaluate the acid-base status of cats with chronic kidney disease. A total CO_2 of less than 15 mmol/L warrants intervention. Most kidney diets are designed to reduce metabolic acidosis, however if this is not enough sodium bicarbonate at a dose of 8-12 mg/kg two to three times daily or potassium citrate at a dose of 40 to 60 mg/kg two to three times daily are recommended.

Medical management gastrointestinal complications

Uremia has a strong effect on the gastrointestinal tract. Clinical signs include anorexia, vomiting, gastrointestinal bleeding and diarrhea. Uremia can lead to uremic stomatitis with ulcerations brownish discoloration and necrosis of the tongue and halitosis further contributing to anorexia in cats with chronic kidney disease. Symptomatic treatments for gastrointestinal complications include the reduction of gastric hyperacidity, the reduction of nausea and the reduction of gastrointestinal bleeding. Possible medications are omeprazole (0.7 mg/kg/d) to reduce gastric hyperacidity, sucralfate (0.125-0.5 g/cat/d PO twice or three times a day) to reduce gastrointestinal bleeding, and maropintant (1 mg/kg once daily, up to five days) or metoclopramide (0.2-0.4 mg/kg IM, SC, PO three to four times daily) to reduce nausea.

Correction of hypokalemia

Hypokalemia is common in cats with chronic kidney disease. Hypokalemia may lead to generalized muscle weakness, anorexia and decreased renal function. Furthermore weight loss and poor hair-coat are associated with impaired protein synthesis due to hypokalemia. The main reasons for low potassium are decreased intake and renal loss. Potassium can be supplemented with intravenous fluids or orally as potassium citrate at a dose of 40 to 60 mg/kg/day initially divided in two or three dosages.

Literature

Polzin DJ (2010): Chronic kidney disease. In: Ettinger SJ, Feldman EC, editors. *Textbook of Veterinary Internal Medicine*. Saunders Elsevier, St. Louis: 1990-2021.