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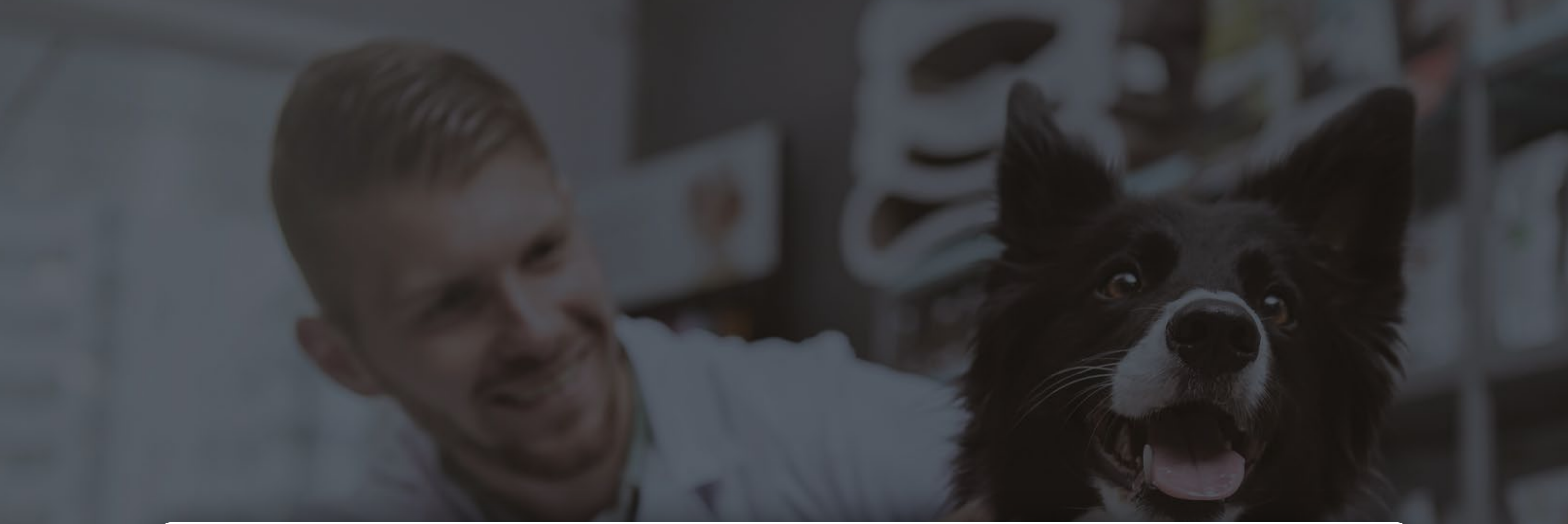

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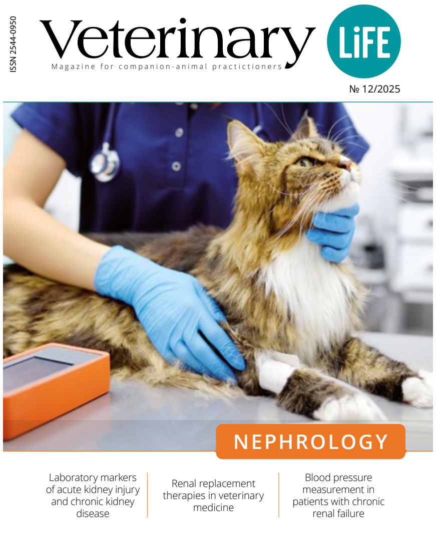
Agnieszka Kurosad
Editor-in-chief

Dear readers,

We are delighted to introduce the newest issue of Veterinary Life Nephrology, a journal devoted to the in-depth study of kidney-related disorders. This subject is particularly pertinent to feline patients, where the incidence of chronic kidney disease (CKD) escalates with advancing age. Epidemiological data indicate that CKD prevalence in cats over 10 years of age ranges from approximately 30% to 50%, with this figure escalating to 70–80% in cats exceeding 15 years. Regrettably, CKD remains an incurable condition. Consequently, early diagnosis, meticulously tailored therapeutic strategies (including nutritional management), and consistent monitoring are paramount. Such interventions are essential to mitigate the risk of disease exacerbations, disruptions in acid-base equilibrium, mineral and bone disorders associated with CKD (CKD-MBD), as well as potential complications such as thromboembolism.

We trust that the articles featured in this issue of Veterinary Life Nephrology, authored by experienced veterinary practitioners and specialists in the field, will serve as a valuable resource, enhancing your clinical approach to managing nephrology patients in your daily practice.

Enjoy reading



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In expert`s opinion:

Cardiovascular-renal disorders

Professor **Agnieszka Noszczyk-Nowak**, DVM, PhD
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Abstract: The cardiorenal syndrome or – more accurately – cardiovascular-renal disorders have been discussed in veterinary medicine for several years. In 2015, a consensus was reached regarding the definition, pathophysiology, diagnosis, and treatment of dogs and cats suffering from cardiorenal disorders (CvRD). This article outlines said issues that are considered to be important due to the notable correlation between cardiac and renal function.

Keywords: cardiorenal syndrome (CRS), cardiovascular-renal disorders (CvRD), dog, cat

Introduction

In 2015, a group consisting of nine veterinary cardiologists and seven veterinary nephrologists from Europe and North America published a consensus statement pertaining to the definition, pathophysiology, diagnosis, and treatment of dogs and cats suffering from the so-called "cardiorenal disorders" (CvRD) (5). To achieve such a goal, a formal Delphi methodology was taken advantage of in order to define/develop a consensus and create fitting guidelines. When it comes to human-specific medicine, the term "cardiorenal syndrome (CRS)" is quite frequently used. Said phenomenon is defined as "heart and kidney disorders, in the case of which acute or chronic dysfunction of one organ can cause acute or chronic dysfunction of the other" (5). CRS was sub-divided into five types (Table 1). The aforementioned classification was taken into consideration when developing the CvRD classification pertaining to both canines and felines.

Predominant objectives set by the representatives of the veterinary expert group discussed were to: 1) define CRS in dogs and cats being veterinary patients, 2) develop recommendations for diagnostic testing and evaluation of CRS, 3) provide general guidelines pertaining to the treatment of CRS patients with an emphasis put on the potential interplay between two organ systems, as well as 4) increase awareness of CRS as an important disease in veterinary medicine that should be investigated further. Quite early, the CRS Consensus Group decided to refer to CRS in veterinary patients as to "**cardiorenal disorders (CvRD)**" in order to focus on the correlation between the entire cardiovascular system and kidneys, as well as due to the fact that, basing on experience in cardiovascular and renal diseases, the clinical signs of CvRD in dogs and cats are expected to be variable among individuals and species, excluding the possibility of classifying them as a single clinical syndrome (3, 4, 5). Experts reached a consensus when it comes to the definition of cardiorenal disorders, which were defined as disease-, toxin-, or drug-induced structural and/or functional damage to kidneys and/or cardiovascular system, leading to the disruption of normal interactions between said systems, with permanent detriment to one or both. They also subdivided said disorders into 3 subgroups. CvRD covers the following subgroups: $CvRD_H$ (renal dysfunction resulting from a disease involving the cardiovascular system), $CvRD_K$ (cardiovascular dysfunction secondary to renal disease), and $CvRD_O$ (impairment of both systems due to concurrent primary cardiovascular and renal disease or "other" disease processes, medications taken, toxins, or toxicants affecting both systems). Basing on clinical imaging of the individual patient, said three categories can be further subdivided into stable (S) or unstable (U) ones.

CvRD diagnosing

CvRD diagnosing requires the synergy of data taken from multiple sources, including additional tests. Blood and urine tests, noninvasive blood pressure measurement, as well as radiographic and ultrasonographic imaging are routinely available diagnostic tools to be utilized to diagnose both renal and circulatory system diseases. Biomarkers play an important role when it comes to the diagnosis of CvRD. With regard to veterinary medicine, biomarkers usually refer to substances that can be measured in blood or urine and reflect the pathological process severity. Biomarkers can also be taken advantage of in order to assess adverse event risk, predict outcomes, and specify treatment (Table 3).

Some of the specified biomarkers are readily available and have been used for

Table 1. Types of cardiorenal syndrome (CRS) in humans

Type	Name	Pathological mechanism	Clinical image
I	acute CRS	sudden deterioration of heart function causing acute renal failure	cardiogenic shock, decompensated heart failure
II	chronic CRS	chronic HF leading to progression of chronic renal failure	chronic heart failure + chronic renal failure
III	acute cardiorenal syndrome	acute renal failure leading to acute cardiac dysfunction	acute renal ischemia, glomerulonephritis
IV	chronic cardiorenal syndrome	chronic kidney failure leading to heart failure	chronic glomerulonephritis / interstitial nephritis
V	secondary cardiorenal syndrome	systemic disease leading to damage to the heart and kidneys	diabetes, sepsis, lupus, sarcoidosis, amyloidosis

Table 2. Classification of cardiorenal disorders in dogs and cats (5)

CvRD class	Etiology
CvRD$_H$	• Systemic hypertension leading to glomerular disease • Cardiogenic shock, low cardiac output and systemic hypotension, leading to decreased renal perfusion, azotemia, and acute kidney injury • Arterial thromboembolism leading to renal infarction • Dirofilariosis leading to glomerulonephritis or acute renal failure (AKI), respectively • Passive renal congestion during heart failure
CvRD$_K$	• Renal-dependent systemic hypertension leading to increased afterload, left ventricular hypertrophy, worsening heart failure, arrhythmia, vasculopathy, or retinopathy • Volume overload leading to systemic congestion or hypertension • Hypokalemia or hyperkalemia leading to cardiac arrhythmias • Reduced renal clearance of medications administered (such as digoxin), leading to their toxicity • Hypodipsia, anorexia or vomiting in the course of uremia, leading to decreased blood volume and reduced cardiac output and perfusion • Uremic pericarditis • Activation of the renin-angiotensin-aldosterone axis, leading to sodium and water retention, cardiac and vascular remodeling, or heart failure • Anemia secondary to chronic kidney disease, leading to volume overload and reduced oxygenation of cardiac tissues
CvRD$_O$	• Septic or neoplastic emboli leading to renal and cardiac infarction • Gastric dilatation and volvulus leading to cardiac arrhythmia and azotemia • Infectious diseases (such as *Trypanosoma cruzi*) • Storage disease leading to glycogen accumulation in the kidneys and heart. • Amyloidosis leading to the deposition of amyloid in the tissues of the kidneys and heart

Table 3. Biomarkers utilized in the course of renal function assessment (5)

Marker type	Material	Parameter
Glomerular filtration rates	**Urine, blood**	• Serum creatinine concentration • Plasma clearance techniques • Symmetrical dimethylarginine (SDMA)
Indicators of selective glomerular permeability	**Urine, blood**	• Serum albumin concentration • Urine protein-to-creatinine ratio • Microalbuminuria occurrence • Presence of immunoglobulin G in urine
Indicators of tubule damage or dysfunction	**Urine, blood**	• Serum electrolyte concentration • Serum bicarbonate concentration • Glucose concentration in urine • Uric acid concentration • Urine protein-to-creatinine ratio • Urine specific gravity • Urine N-acetyl-BD-glucosaminidase (NAG) concentration • Urinary retinol binding protein (RBP) concentration • Gamma-glutamyl transpeptidase (GGT) concentration in urine • Cystatin-C concentration in urine • Kidney injury molecule-1 (KIM-1) concentration in urine • Urinary neutrophil gelatinase-associated lipocalin (NGAL) concentration • Urine clusterin concentration

years in veterinary medicine. Some others are considered to be relatively new and available for testing in selected laboratories. Among the second group, the determination of NGAL concentration seems to be highly promising. Serum NGAL concentration ≥ 16.0 ng/ml has the sensitivity of 90.9% and specificity of 90.0% when it comes predicting CvRD development in dogs with heart disease (2). Podocyturia (presence of podocytes in urine) and podocin-to-creatinine ratio in urine are also interesting markers (8). Nevertheless, studies on their routine utilization in patients require further examinations.

CvRD-specific therapy

The treatment of CvRD has been proven to be rather difficult, predominantly due to the fact that the treatment of renal disease often involves fluid therapy and careful monitoring of both the amount and quality of protein and phosphorus intake (6). In contrast, animals suffering from symptomatic congestive heart failure are typically treated with diuretic medications (loop diuretics, potassium-sparing diuretics), as well as by means of administering protein-based supplementation (1). CvRD treating involves the recognition and frequent assessment of subtle changes in renal or cardiac function. It is also connected with the necessity of understanding how the pathophysiology of one disease may interact with and affect the other. A key factor when it comes to the treatment of CvRD is addressing the underlying cause of clinical signs while attempting to minimize clinically significant deterioration in the other organ. While taking CvRD$_H$ into account, the therapeutic margin is relatively miniscule, as the utilization of diuretics and ACE-I can adversely affect renal function. Nevertheless, it has to be mentioned that their absence quite frequently leads to the exacerbation of heart failure symptoms and even – to the death of the animal being treated. Strategies aiming at the minimization of the risk of azotemia development during treatment of symptomatic congestive heart failure, especially in its acute phase, include reducing the total daily dose (dosage and/or frequency) of parenteral diuretics, using intravenous or arterial vasodilators in order to notably reduce preload and afterload, opting for pimobendan or dobutamine (intravenously) in order to increase cardiac output and renal perfusion, as well as not taking advantage or limiting the utilization of ACE-Is. In the case of patients suffering from CvRD$_K$, careful and gradual fluid replacement is vital, with attention being put on selecting a fluid characterized by relatively low sodium content. It is also highly recommended to carefully monitor body weight, respiratory rate and respiratory effort, blood pressure, as well as the development of jugular venous distension or ascites in the treated patient. A resting (non-gasping) respiratory rate of >40 breaths per minute has been shown to be a valid indicator of early pulmonary congestion (edema) (7). The utilization of renal replacement therapies (such as hemodialysis and ultrafiltration) allowing for the precise control of intravascular volume in $CvRD_K$ may be an alternative to classical fluid therapy, especially in the foreseeable future. When it comes to animals suffering from any form of CvRD, gradual change in diuretics or fluids must be carried out carefully and with simultaneous monitoring of hydration, renal function, as well as resting respiratory rate. Any type of fluid can cause symptoms of congestive heart failure or hypertension if administered too rapidly or in excessive volumes. When it comes to severe CvRD, in the case of which it is problematic to achieve treatment balance, hospital-oriented treatment should be opted for.

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Importance of testing and correctly interpreting general urine test results

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Abstract: Urinalysis and quantitative urine biochemistry are laboratory tests performed on a daily basis. Test selection and the correct interpretation of results are vital when it comes to patient diagnosis, as well as accurate treatment. Numerous causes of false results or factors influencing lab-oriented examinations are reasons for over interpretation and doubts regarding, for example, the possibility of mixing samples in the lab.

Key words: urine, urinalysis, lab result falsification, lab results interpretation

Indications for the test, collection methods, general course of the test

When it comes to everyday medical practice, a general urine test is carried out in numerous scenarios. The most common indications are lower urinary tract-specific symptoms (including frequent urination or visible change in urine color), suspicion of kidney disease or monitoring of its treatment. Urine tests are also taken advantage of as a diagnostic tool while treating internal disorders (such as poisoning or autoimmune hemolytic anemia suspicion), as well as monitoring hypertension (marking proteins and albumin in urine). The proper material acquisition for testing may have a notable impact on the results (Table 1). For example, in the material collected from natural micturition, a different epithelial composition should be expected than in the case of urine collected by means of cystocentesis (5).

A routine urine test incorporates several key steps:

1. Physical evaluation: determination of color, transparency, scent, and specific gravity by means of opting for a urinometer or a refractometer.
2. Chemical evaluation performed by means of using ready-made reaction strips and

Table 1. Methods of urine collection with indications (2, 4)

Collection method	Comments
Collection from micturition into a container	Routine, preventive examination. The material obtained is most often contaminated.
Manual emptying (squeezing)	Not recommended; the method is painful and poses a risk of damaging the bladder, as well as increasing the number of red blood cells and protein concentration (4).
Catheterization	High quality sample; it is the method of choice in suspected bladder cancer (2, 4).
Cystocentesis	Sample of the highest microbiological quality; method of choice for bacteriological testing (4).

opting for the so-called dry chemistry method, as well as by evaluating the field color against the standard on the packaging. Most ready-made test strips available on the market currently contain two unreliable reactions in animal urine testing: specific gravity (chemical reaction is based on the evaluation of ion concentration, while the high specific gravity of urine in animals results from the high concentration of dissolved non-ionic compounds, such as urea) and leukocytes (determination of leukocyte esterase activity gives false positive results in animals, especially in felines, predominantly due to the higher activity of esterases that are not associated with leukocytes) (2,4).

3. Microscopic evaluation of a preparation made from urine sediment done at 400x magnification. The sediment is obtained by means of centrifuging urine as a whole by setting the centrifuge parameter to correspond to a relative centrifugal force (RCF) of 400-500 g for 5-10 minutes (4). The sediment is considered to be material concentrated tenfold. The obtained supernatant is taken advantage of predominantly for the purpose of further quantitative chemical and immunological examinations (including the determination of protein, albumin, and cortisol) (4).

Most frequent falsifications and resulting interpretation issues...

...at the collection stage

The proper and recommended time for urine collection depends on the type of test carried out. The most common method is to collect the first morning urine (after the minimum of 6-8 hours of overnight break) from the midstream (4, 5). Said material is recommended for all routine screening tests, as well as for cortisol determinations (1, 4). Nevertheless, for microbiological tests and examinations alike, urine that has been in the bladder for a shorter period of time will be better (2). When it comes to the impact on the results, in the case of so-called incidental collections, postprandial collection (pH may increase) around the time of heat or mating in female animals or after exercise in very active animals and those used for sports (small hematuria or positive test results for ketones may be observed) may be sensible (4).

The method of collection and transport container utilized are also of great importance. Very often, animal owners collect urine into random containers (Fig. 1, 2, 3). Collection method is vital as well. While no one will be surprised by the presence of the increased number of erythrocytes in the urine sediment collected by cystocentesis, the assessment and

Table 2. Possible false results caused by the contamination of urine by means of cleaning and disinfecting agents (2,4,5)

False results caused by the presence of disinfectants and cleaning agents:
• False positive result for protein (especially quaternary ammonium compounds, chlorhexidine) • False positive result for glucose (especially oxidizing agents, such as hydrogen peroxide, and hypochlorite) • False positive result for blood/hemoglobin

Table 3. Observed interactions between substances taken by the animal and urine test results (4, 5)

Served/consumed substances/food	Possible impact on the examination
B vitamins	Intense yellow urine color may result in a false weak positive reaction to glucose (own observation)
Furazidine (for example: Furagin)	Intense dark yellow urine color may result in a false weak positive reaction to glucose (own observation)
Diuretics (for example: Furosemide)	Reduction in urine pH (4)
Plant-based diet; sodium lactate (for example: Ringer's lactate)	Increased urine pH (4, 5)
Glucocorticosteroids, aminoglycosides, ketamine, xylazine, some nonsteroidal anti-inflammatory medications, poisoning (for example: ethylene glycol)	Positive glucose test result (due to hyperglycemia or nephrotoxic effect) (4, 5)
Cephalexin	Likelihood of a false positive glucose reaction has been identified (5)
Medications having a sulfhydryl group (for example: captopril)	Falsely low blood/hemoglobin test result (4, 5)
N-acetylcysteine, captopril, valproic acid, methionine	Falsely elevated ketone body reaction result (5)
Ascorbic acid	Only during supplemental supply; endogenous synthesis levels should not have a significant effect: False low blood/ haemoglobin; decreased urine pH; false low bilirubin; false positive nitrite (4)
Sulfonamides	False increase in the result of the reaction determining the urobilinogen concentration, possible crystallization (4)
Diuretics or fluid therapy during anuria treatment	Presence of casts in the urine sediment: from glassy, through granular, up to waxy, as a result of the sudden resumption of renal perfusion (4)
Antibiotics (most often ciprofloxacin, sulfonamides)	Crystalluria; most often impossible to identify visually or chemically, especially if the examiner is unaware of the therapy being performed (4)
Ethylene glycol	Presence of calcium oxalate crystals in the monohydrate form (Fig. 10) (5)
Cytostatic medications	Presence of uric acid crystals (increased breakdown of cell nuclei and release of large amounts of purines into the bloodstream) (Fig. 11) (4)

interpretation of epithelia in urine collected by catheterization can turn out to be rather problematic. During catheterization with a rigid catheter, it is relatively straightforward to cause damage to the urethra and mucosa of the urinary bladder (4, 5) (Fig. 4a, 4b).

Urine collected by the animal owner during micturition is most often heavily contaminated with hair, feces, soil, and bacteria (2, 5). In the lab, it is not uncommon to find containers with visible soil, insects, grass, litter or powder from the gloves utilized (Fig. 5-8). They may all affect the obtained results, both when it comes to microscopic and physicochemical examination.

One of the most common and complicating contaminations is a rather small admixture of disinfectants in urine (5). Such contamination may occur both as a pre-laboratory and laboratory error. Pre-laboratory contamination occurs most often as a result of washing the urogenital area before collection (it may be caused by poorly rinsed fur, along which urine flows), when cleaning the litter box (popular toilet cleaning agents contain strongly oxidizing hypochlorite), or when collecting urine from the table during a visit (washing the table between patients). Disinfectant contamination may also occur during the examination. The mere act of wiping the measuring table of the strip reader with alcohol or another disinfectant between tests together with its failure to evaporate may significantly distort the results (6).

The table presented showcases falsifications that may result from the contamination of urine or disinfectant examination (Table 2).

...during storage

Time between collection and testing, as well as conditions in which samples are stored, may affect results obtained as well. It is commonly advised that urine should be tested as soon as possible after collection (especially in terms of assessing crystalluria presence) or stored in a refrigerator until the test. In such a scenario, the sample should be brought to room temperature before testing (2). The prolonged period of time between collection and testing may cause a whole range of changes, regardless of material storage conditions. One such example in the case of hematuria and erythrocyte incontinence is the gradual release of hemoglobin from erythrocytes, manifested by the presence of leached erythrocytes in the microscopic image and by a rapid increase in protein concentration in the biochemical test. Leached erythrocytes also appear as a result of the rupture of erythrocytes in urine with a low specific gravity (<1.008) (4, 5). In the literature of the subject, the presence of leached erythrocytes is mainly described as a symptom of erythrocyte loss in the kidneys. It should therefore be remembered that only a sufficiently high percentage of leached erythrocytes and the absence of other factors that could change their morphology should be interpreted as bleeding being of renal origin (Fig. 9).

Table 4. Exceptions and predispositions pertaining to species and race with regard to urine testing (2, 4, 5)

Species and race-specific exceptions and predispositions with regard to urine testing

- Herbivorous species (including rabbits and horses) have physiologically alkaline urine with the precipitation of calcium carbonate crystals (4).
- Some dog breeds (such as Basenji and Cocker Spaniel) may suffer from primary glycosuria due to a hereditary defect (4, 5).
- A weakly positive (1+) result of bilirubin occurrence in dogs with a high specific gravity of urine is physiological (a species-specific low renal threshold for bilirubin) (4, 5).
- In contrast, cats have a species-specific high renal threshold for bilirubin; the "trace" result will be very significant in this species (2, 4).
- In the case of horses, it is physiological to have a large amount of mucus in urine.
- In the case of some dog breeds (such as English Bulldog or American Staffordshire Terrier) hereditary cystinuria may occur with cystine crystallization in urine (4, 5).

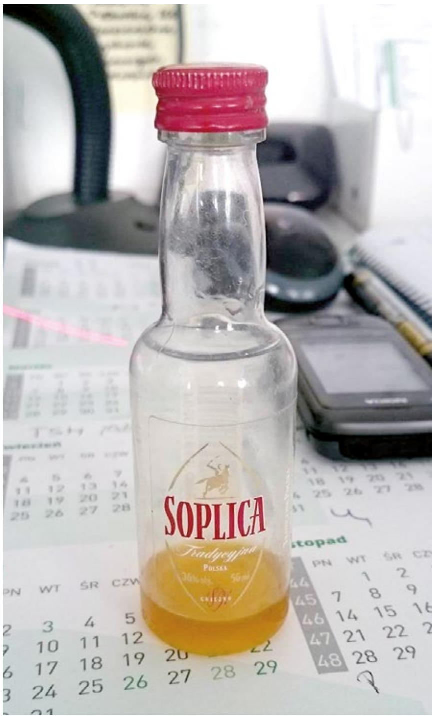

Fig. 1. Collecting urine into a vodka bottle

Fig. 2. Collecting urine into a mineral water bottle

Fig. 3. Collecting urine into a face serum container

Fig.1-3: Collecting the material into the incorrect container may result in the disruption of test results, mainly due to: changes in ionic composition (affecting specific gravity), impact on the urine reaction, false chemical methods (strip methods), or crystallising salt presence.

Fig. 4a, 4b:
Possible epithelial differentiation resulting from the collection technique or the ongoing pathological process

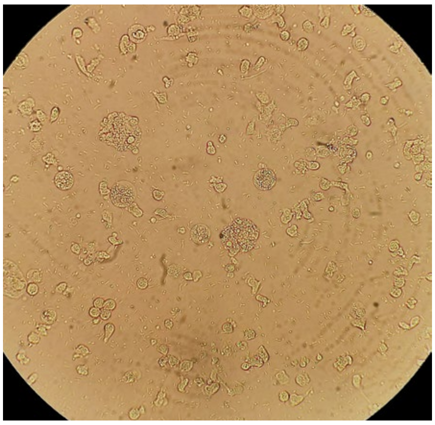

Fig. 4a. Visible squamous epithelial cells (polygonal), as well as transitional urinary tract epithelium (round and caudate cells), leukocytes, bacteria

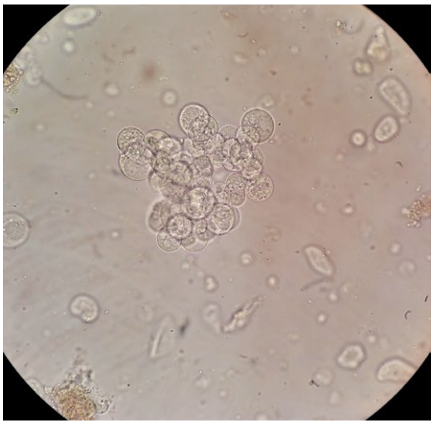

Fig. 4b. Visible epithelial sheet consisting of small round or cubic cells. The image may be difficult to interpret when classifying visible cells as renal tubular or neoplastic ones

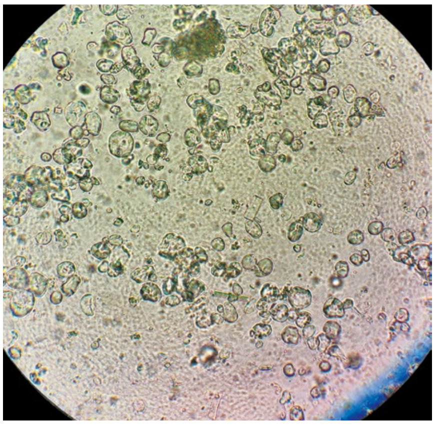

Fig. 5. Talc or glove powder – visible starch grains

Fig. 6. Mite of environmental origin

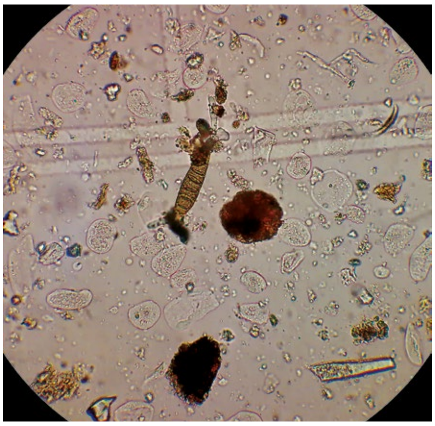

Fig. 7. Sediment of urine macroscopically visibly contaminated with soil

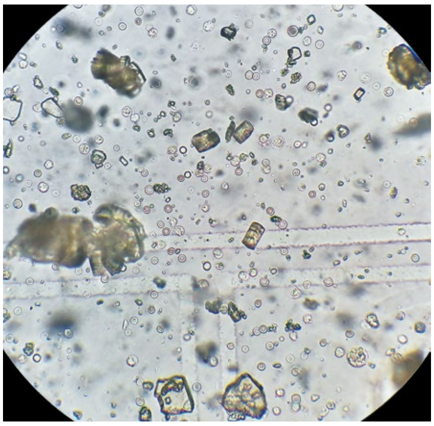

Fig. 8. Urine sediment from a poorly prepared cuvette or contamination with crystallizing salts

Fig. 4-8: Artifacts in urine sediment resulting from contaminated sample collection

Low temperature may cause the precipitation of salts into crystals, which is of crucial importance when assessing struvite crystals (ammonium magnesium phosphate salts) and calcium oxalate presence (2). In exceptional cases, some authors recommend warming urine to 37°C (2) to assess crystalluria. Testing urine without bringing it to at least room temperature may result in the overestimation of specific gravity and inhibition of enzymatic reactions in the strip test (in particular, reduced glucose detectability) (3, 4, 5). On the other hand, keeping urine at room temperature for an excessive period of time may promote the growth of bacterial flora, pH increase (and consequently - the precipitation of phosphate crystals), rarer pH decrease (in the case of the multiplication of bacteria producing acidic metabolites, such as *E. coli*), as well as faster degradation of cells and casts (2, 4). The influence of light (especially the UV one; one should note that many modern refrigerators contain a source of UV light) on urine testing should not be neglected or marginalized. Photosensitive substances dissolved in urine include bilirubin, which is transformed and decomposed into biliverdin under ultraviolet light (urine may take on a greenish color and the reaction for bilirubin may be falsely negative), as well as urobilinogen, which is transformed into urobilin under the light (4, 5). Nevertheless, the determination of urobilinogen concentration is of negligible use in veterinary practice and can be omitted, as positive results that are not caused by the falsification by dark urine color are extremely rare (4).

...resulting from substances or medications taken

One should keep in mind that everything that enters the body and is ultimately filtered by the kidneys can affect urine test results in a myriad of ways. Improper results can occur through changes in urine color (caused by the consumption of beets or dyes /colorful sweets!/, but also – B vitamins or furazidine /Furagina/, which change the color of urine to intensely yellow or dark yellow) or by influencing the enzymatic reaction on the strip. Table 3 showcases the discussed interactions, as well as the author's own observations.

...when urine properties and racial predispositions influence each other

Above all else, while interpreting test results, one must remember about species and breed-specific exceptions, whether physiological or resulting from hereditary disorders that are specific for a given breed. Examples are presented in the table (Table 4). Some properties of urine also affect other reactions in the strip test, either in combination or by falsifying them. The most frequently observed falsification of said type is the strip reaction indicating the presence of protein, which is clearly overstated when

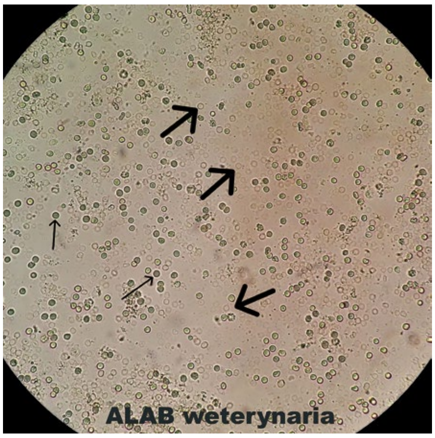

Fig. 9. Fresh (thin arrow) and leached (thick arrow) erythrocytes in urine sediment

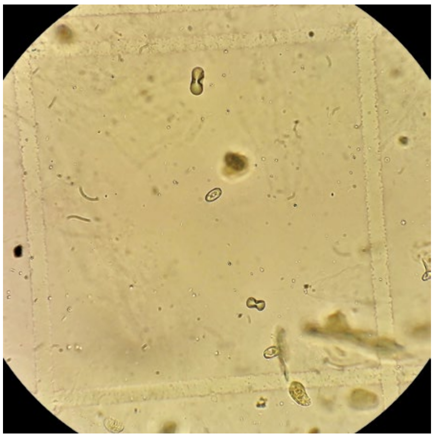

Fig. 10. Calcium oxalate monohydrate crystals in the course of ethylene glycol poisoning with the morphology of dumbbells and millet grains

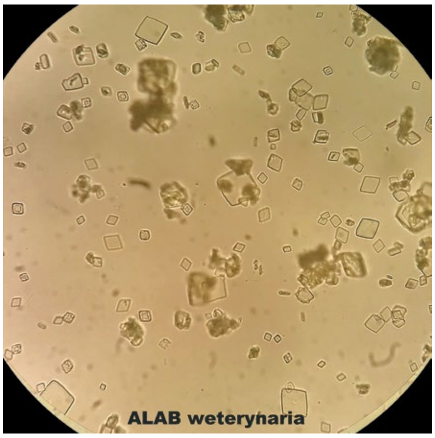

Fig. 11. Uric acid crystals

the tested urine has a high pH (8-8.5), or understated in the case of an exceptionally acidic pH (<6) (2, 4). Therefore, it is crucial to confirm a positive result by means of opting for yet another method (such as quantitative determination or, in the case of a clinic, conducting a turbidity test based on the utilization of sulfosalicylic acid). Standard urine test strips indicate the presence of ketone bodies in a reaction that does not detect beta-hydroxybutyric acid, but rather acetone and acetoacetic acid exclusively (6). Acetone is a compound that evaporates quickly (time of the testing is crucial), while acetoacetic acid can be metabolized by bacterial flora (4). High specific gravity of urine can falsify (lower) the result of the reaction for blood/hemoglobin, while the presence of some bacteria (producing peroxidase) may result in a false positive result of the test oriented towards the presence of hemoglobin in urine (4, 5).

Closing remarks

To sum up, even though urine testing is one of the simplest and most commonplace examinations, it turns out to be quite complicated to interpret, mainly due to a myriad of various dependencies. It has to be pointed out that the process of proper testing begins at the stage of ordering the client to collect urine from his or her pet at the right time and in the right way. Therefore, educating pet owners on how to reduce the pre-laboratory error is an important aspect of said test method. While we do not have a notable impact on reducing laboratory errors resulting from the properties of urine tested, in the post-laboratory process, the ability to interpret various dependencies is important, similarly to the cooperation with the laboratory to which the test was entrusted, predominantly in the case of any and all doubts.

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Laboratory markers of acute kidney injury and chronic kidney disease detected in dogs and cats

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Abstract: Kidney diseases are considered to be a major clinical problem in both canines and felines, predominantly due to significantly deteriorating life quality and shortening life expectancy. Acute kidney injury (AKI) is typically defined as a sudden deterioration of the kidneys' filtration function, developing for various reasons and characterized by its sudden course. Chronic kidney disease (CKD) is a progressive, irreversible loss of nephron function caused by pre-existing nephritis, kidney stones, or systemic diseases damaging the kidneys, such as hypertension, diabetes, or infectious diseases (including leptospirosis, babesiosis, and leishmaniasis).

The early diagnosis of AKI and/or CKD makes it possible to implement proportional therapy, which – in some cases – protects animals from death and/or irreversible complications. The current determination of serum creatinine and SDMA concentration is not fully satisfactory. Therefore, there has been a constant search for new laboratory indicators characterized by high sensitivity and specificity that would enable for early and reliable diagnosis of AKI or the stage of CKD advancement. This article is oriented towards discussing the diagnostic significance of newly recognized and promising proteins, namely: cystatin B, KIM-1, and NGAL. They are highly promising as biomarkers. This paper additionally lists numerous new compounds which are still under research in order to assess their diagnostic and prognostic capabilities in the diagnosis of early stages of kidney diseases in both canines and felines.

Keywords: biomarkers, AKI, CKD, creatinine, SDMA, cystatin B, KIM-1, NGAL

Introduction

In clinical practice, the diagnosis of acute kidney injury (AKI) and chronic kidney disease (CKD) is performed by means of summing up data from the following laboratory tests: in blood serum – urea, creatinine and SDMA concentration, full urinalysis, X-ray (if needed), and ultrasound – thanks to the designated imaging parameters. Nevertheless, changes in laboratory test results are of significant importance, as they can reflect both temporary and permanent conditions. However, the typically used indicators are not sufficiently sensitive and specific. Most often, they are expressed only after several days/weeks/months from the action of a kidney damaging factor, which may cause delayed medical intervention. Therefore, impaired kidney function, mainly in terms of filtration, can be revealed during routine laboratory tests, but said changes are identified relatively late, accompanying already intensifying, unfavorable clinical symptoms. That is why the early, initial phase of kidney diseases remains most often laboratory latent. As a result of that, there is an ongoing search for new biomarkers of AKI and CKD that would allow to indicate kidney damage much earlier, without clinical symptoms present (28, 64, 65). It applies to both CKD and AKI.

CKD is the most frequently diagnosed form of kidney disease in felines and canines. It is always progressive and irreversible (53). Its incidence is estimated at the level of 0.5–3.7% in dogs (41, 49, 52, 59). In younger cats, it is 2–4%. In older felines (> 10 years), it is the main cause of morbidity and mortality, with the incidence reaching up to 30–40% (29, 40, 43, 48). According to the definition, CKD is permanent structural kidney damage, characterized by a gradual, quantitative elimination of active nephrons (43, 55). CKD is a major risk factor with regard to worsening renal function and may lead to the exacerbation of renal dysfunction with the possibility of provoking acute kidney injury (due to renal causes) in the course of using nephrotoxic medications or after major surgical procedures (68).

AKI is defined as a sudden decrease in the kidney filtration function, accompanied by azotemia (hypercreatinemia) and decreased urine output (26, 34). Causes of AKI include prerenal factors, such as hypotension, hypovolemia, and renal factors – including nonsteroidal anti-inflammatory medications taken, poisoning, infectious diseases (leptospirosis), urinary tract infections, neurotoxins, as well as extrarenal factors, such as urinary tract obstruction. Death risk in the case of AKI in cats and dogs remains high. The literature of the subject points out that it may affect up to 53.1% of felines and 45% of canines treated (34).

Quite recently, many studies have been published indicating that both diseases are closely related and connected by common risk factors. AKI can progress to CKD and CKD can cause the development of AKI. Said knowledge brings new data pertaining to both diagnosis and monitoring of kidney diseases, emphasizing the need to create a set of sensitive indicators, defining both functional and structural damage to the organ. They are crucial for medical treatment and forecasts (68).

Biomarker

The "biomarker" term is defined as a compound that is objectively measurable and can be used as an indicator correlating with a physiological response, pathological process, response to a pharmacological agent, or another therapeutic intervention. It can have diagnostic and/or therapeutic applications (64). The path that a biomarker must follow from the lab to the clinic is long. In the last decade, attention has been drawn to numerous new biomarkers measured in blood serum and/or urine and allowing for the diagnosis of AKI and CKD, but few of them have been practically utilized. There are several requirements and strict criteria that are imposed on biomarkers. Their fulfillment is a condition for their acceptance into clinical practice (38, 68). An ideal marker for diagnosing kidney damage should therefore be: reproducibly measurable with standardized, commonly available methods, easy to interpret, non-invasive for the patient, have adequate sensitivity, established threshold value for assessing progression and regression of damage, demonstrate high organ specificity, be associated with a specific etiological factor causing kidney dysfunction, correlate with the histopathological image of kidney biopsies, detect changes in the early phase of damage, as well as identify pathological changes in different tubule segments (38, 63).

Chosen kidney damage markers

Creatinine

Serum creatinine measurement is the most commonly utilized parameter that is taken advantage of to estimate kidney glomerular filtration. Its metabolism, measurement methods, and diagnostic significance in canines have been discussed earlier (6). As a result, renal dysfunction may remain unnoticed in emaciated animals with low muscle mass, while in heavily muscled animals, glomerular filtration may be erroneously overestimated, resulting in a false diagnosis. What is more, analytical methods, age, body weight, diet, and meal times may significantly affect serum creatinine concentration. Due to said fact, obtained results should be interpreted with caution, especially when values approach the lower upper limit of reference intervals (6, 14). Despite all the significant limitations mentioned, serum creatinine concentration assessment still remains a routine method of assessing renal function in both humans and animals. It is caused by the fact that finding and adapting new markers offering higher sensitivity and specificity has turned out to be extremely difficult (68). Therefore, the international IRIS (International Renal Interest Society) group still uses serum creatinine concentration as the basis for classifying the degree of renal damage in AKI and CKD (https://www.iris-kidney.com/iris-guidelines-1. Accessed: March 14th, 2025).

Symmetrical dimethylarginine (SDMA)

SDMA is a stable molecule originating from intranuclear cellular proteins, resulting from the methylation of arginine residues (24). The small size of the molecule (its molecular weight is 202 g/mol) and positive electrical charge both allow for its free filtration (19). Its plasma concentration correlates with changes in kidney glomerular filtration rate (GFR). An increase in SDMA above the reference interval occurs with an average reduction of GFR in both canines and felines by 40%, and by 24% in felines, so it may facilitate the earlier detection of impaired renal excretory function in cats and dogs, especially in comparison to creatinine alone (24, 39, 54). Studies have shown that SDMA concentration measured in serum can serve as a marker of early kidney disease in cats and dogs. What is more, its concentration is also increased in individuals suffering from AKI (13, 16, 23, 24, 39). Additionally, unlike creatinine, SDMA is not dependent on muscle mass. Therefore, it is a more sensitive indicator of kidney function in emaciated or elderly patients. As a result, IRIS has added the aforementioned indicator to its guidelines for diagnosing and managing both AKI and CKD (54). Due to the discussed strengths of SDMA, it has been included in standard diagnostics. It has to be mentioned, however that its effectiveness is still the subject of discussion. When determining its concentration, authors of studies indicate some daily variability and dependence on age, especially when it comes to young dogs (31, 32, 46). Further studies are vital, including those determining the impact of breed on SDMA concentrations. Liffman found that greyhounds have higher mean SDMA concentrations in serum compared to canines of other breeds (36). Furthermore, some dogs with lymphoma without renal azotemia had increased SDMA concentrations and the return to normal values was identified after chemotherapy and clinical remission (2).

Cystatin B

Said protein characterized by the molecular mass of 11 kD is a part of the family of cysteine protease inhibitors. It is commonly found in various types of cells. Additionally, it is an intracellular protein, which is why only trace levels of it are detected in the serum of healthy individuals (1, 33). Cystatin B is released into the urine as a result of epithelial cells of the renal tubules being damaged (68). Said observation has been confirmed by studies conducted in humans suffering from diabetic nephropathy, in the case of whom a higher concentration of cystatin B in urine has been found. Furthermore, the discussed indicator preceded the increase in other measured functional markers (45). Yerramilli was one of the first experts in the field to assess the usefulness of cystatin B in urine and serum as a biomarker of gentamicin-induced AKI in Beagle dogs. The indicator turned out to be promising (68). Similar conclusions were drawn by other authors, who determined the concentration of cystatin B in urine of dogs poisoned with European viper venom, in dogs with ehrlichiosis, in canines undergoing cardiac surgery based on the use of extracorporeal circulation (Starybrat 2022), as well as in dogs and cats undergoing general anesthesia (20, 22, 25, 35, 60). In 2023, Segev showcased that the concentration of cystatin B in urine allowed to differentiate stable CKD from progressive one in stage I according to the IRIS classification. The earliest possible identification of dogs with progressive CKD may provide an opportunity for early intervention, at the same time slowing down the pace of disease progression (57). Basing on the discussed studies, cystatin B appears to be a promising biomarker for detecting active kidney damage in both serum and urine. It has to be mentioned at this point that it is beginning to become available in everyday practice. Nevertheless, it still requires further detailed studies in order to make its assessment more complete and available on a wider scale.

Kidney injury molecule-1 (KIM-1)

Kidney injury molecule–1 (KIM–1; T-cell immunoglobulin, mucin-containing molecule) is a type 1 transmembrane protein. It is a cell membrane protein that passes through its entire layer, reaching both the outer surface of the membrane and the cytoplasm. It has the molecular mass of 104 kDa and is located in the epithelial cell membrane of nephron proximal tubules, in its apical part, directed towards the tubule lumen. It is not found in the glomeruli or interstitial layer of renal medulla (21, 42). In healthy conditions, so in the course of normal kidney function, KIM-1 is a protein absent and undetectable in both urine and serum. Therefore, its presence in blood serum and in urine is considered to be a quantitative marker of kidney damage. It appears rapidly in response to proximal tubule damage and persists until the kidney regenerates (8, 17, 42). Numerous authors being experts in the field believe that the KIM-1 protein allows for epithelial cells to recognize and phagocytize dead cells. By clearing tubules of cellular debris, it limits the immune response. It also protects the body against the increase in hydrostatic pressure and maintains effective glomerular filtration pressure by means of reducing protein-cell conglomerate formation in the lumen of the tubules. Therefore, the physiological role of KIM-1 is probably based on the local control of phagocytosis and regulation of regenerative processes (17, 42). There are also observations indicating that KIM-1 participates in the renal interstitial fibrosis process (61). The role of KIM-1 as a biomarker in pathological kidney conditions is still being studied. As of currently, numerous studies have shown that said protein is a sensitive and specific marker of proximal tubule damage. Its usefulness in humans has been studied with sensible results, contributing to the early diagnosis of both AKI and CKD (4, 8, 17, 58, 61, 67).

The significance of KIM-1 as a diagnostic marker of CKD has also been confirmed in studies conducted on laboratory animals. In mice and rats, it has been shown to be the marker showing change dynamics in the course of CKD. What is more, its concentration was significantly higher in animals with experimentally induced CKD (17). In canines and felines, its usefulness as an early indicator of AKI, both measured in serum and urine, has also been demonstrated (9, 37, 69). Prospects for its broader application with regard to the diagnosis of CKD seem promising. Examinations demonstrating its further usefulness are still being conducted..

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL, or neutrophil gelatinase-associated lipocalin, is a 25 kD molecular protein. It is a part of the lipocalin family, a group of over 20 low-molecular-weight proteins, mainly serving transport-specific functions. Said protein is synthesized in many body areas, including kidneys, lungs, and intestines. What is more, due to the fact that it is an acute-phase protein, it is released from neutrophils and macrophages in inflammatory conditions and in the case of endothelial damage (17, 18, 44). In the kidneys, NGAL undergoes free glomerular filtration and reabsorption in the proximal tubules. Therefore, an increase in NGAL concentration in urine may be a consequence of proximal tubule damage, decrease in glomerular filtration, or damage done to the distal part of the nephron, namely – the distal tubules. The increase in urinary NGAL is therefore mainly considered to be the result of increased renal synthesis of said protein. It is important to note, however that said changes do not affect its plasma concentration (5, 10, 11, 12, 65). Studies conducted in humans with CKD coexisting with other diseases have shown that the concentration of NGAL in blood and urine is correlated with GFR and said values are higher than the concentration of cystatin C (3, 7, 15, 47). Advantages of opting for NGAL in the course of examination of dogs suffering from kidney diseases have been showcased for a decade (27). It has also been found that the NGAL-to-creatinine ratio in urine (UN/CR) is an early indicator of AKI, CKD, as well as urinary tract infection (56). Furthermore, it has been found that the concentration of NGAL in serum and urine is a useful prognostic marker in dogs with CKD. Canines with a higher concentration of the marker have shown a shorter survival time (27). Recent studies have provided valuable pieces of information on the usefulness of serum NGAL determination in a group of canines suffering from heart diseases (especially dilated cardiomyopathy) in the asymptomatic stage, as well as in dogs diagnosed with heart failure in the context of cardiovascular-renal axis disorders (30, 66). It has to be mentioned at this point that the utilization of said protein as a marker of kidney damage in cats has not yet been widely tested (62). NGAL, one of the most promising biomarkers when it comes to determining the early stage of kidney damage in dogs, both during AKI and CKD, is beginning to be used in clinical practice. A test based on the immunochromatographic (IC) method based on lateral flow is being developed for semi-quantitative determination of the concentration of lipocalin associated with neutrophil gelatinase in urine.

Markers of the foreseeable future

When it comes to veterinary medicine, new markers are still being found, allowing for the early diagnosis of AKI and CKD. Several of them may be used in the future to identify kidney damage. Ongoing studies indicate that some compounds are specific indicators of glomerular damage, including immunoglobulins (IgA, IgG, IgM), C-reactive protein, thromboxane B2, as well as transferrin. Studies are also being conducted on numerous renal tubular damage markers, such as RBP (retinol-binding protein), THP (Tamm-Horsfall protein), NAG (N-acetyl-ß-D-glucosaminidase), clusterin, and F2-isoprostanes. Markers of renal parenchyma fibrosis, TGF-ß1 (transforming growth factor ß1) and PIIINP (procollagen III aminoterminal peptide) are also examined, together with altered renal metabolism, FGF-23 (fibroblast growth factor 23). In 2024, papers were published assessing the usefulness of MCPIP-1 protein, also referred to as regnase-1, as a marker of inflammation and kidney damage. Podocin and nephrin, proteins used to detect podocyturia, were used to serve as markers reflecting the degree of glomerular damage (50, 51). Nevertheless, the introduction and determination of the true usefulness of the discussed biomarkers requires time and further studies. Maybe they will become widely used in clinical diagnostics for the purpose of early assessment of kidney damage.

Closing remarks

Considerable progress has been made when it comes to the evaluation of the usefulness of various new biomarkers in diagnosing kidney diseases in both canines and felines. Nevertheless, the usage of traditional markers, especially creatinine and SDMA, for the diagnosis of AKI and CKD in compliance with the IRIS guidelines, still dominates. The number of new tests allowing for the assessment of kidney function and damage degree is still limited. That is why there is the need for further research. This article highlights several new, most promising biomarkers (especially: Cystatin B, KIM-1, and NGAL), which may help detect kidney diseases earlier in both canines and felines. New compounds/markers that are being researched have also been addressed. Nevertheless, it seems unlikely that in the future, a single biomarker will provide a complete picture of kidney function or damage. It is more likely that sets/panels of markers will have to be developed in order to ensure a better chance of assessing, monitoring, and predicting stages of kidney diseases in canines and felines.

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Diagnosis of metabolic acidosis in felines suffering from chronic kidney disease

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Abstract: Chronic kidney disease is a commonly diagnosed condition when it comes to domestic cats. It is also the leading cause of their death. The high mortality rate is believed to result from the inability to stop histopathological changes in the kidney parenchyma and the occurrence of complications, such as metabolic acidosis. This article showcases various methods of diagnosing metabolic acidosis in felines suffering from CKD.

Keywords: chronic kidney disease, cat, metabolic acidosis

Chronic kidney disease (CKD) is a common disease affecting both domestic cats and other felines (3, 4, 5, 29). Studies carried out in Great Britain have shown that CKD is diagnosed in about 40% of domestic cats at the age of over 10 (34). What is more, it is the most common cause of their death (5, 30). It is believed that such high mortality is predominantly caused by the inability to stop the histopathological changes in the renal parenchyma (10, 11, 38), as well as by complications in the form of metabolic acidosis (30), which occurs in most patients with CKD and is usually moderate in nature (10, 26). It has to be mentioned at this point that untreated metabolic acidosis always leads to death, because all biochemical reactions occurring in the body require the circulating blood pH to be within the range of 7.40-7.45. In the case of pH change, the body begins to "switch off" individual biochemical changes, typically starting with the least important ones (1, 10, 13, 24). Clinically, life processes slowly cease to occur. Every veterinarian has certainly treated a feline patient with CKD slowly "fading away".

From the clinical point of view, the key question is as follows: WHEN DOES ACIDOSIS APPEAR? The authors of this paper are going to attempt to answer said question by taking advantage of both their own research and observations of other doctors. Table 1 showcases the international classification of CKD in cats, ranging from mild (I) to severe (IV) one.

Metabolic acidosis occurrence is caused by a constant and progressive decrease in the number of active nephrons (32), which causes filtration decrease. GFR (glomerular filtration rate) in the kidneys fall below 25 ml/min. The dependence of metabolic acidosis on the progressive loss of nephrons results from the fact that in the kidney proximal tubule, there is almost complete (approximately 90%) reabsorption of HCO3-, regeneration of HCO3- in the process of ammonogenesis, as well as the production of said compound from citric acid. In the kidneys, the process of titratable acidity formation also takes place, basing on the use of phosphate buffers (11). Progressive renal failure makes said processes highly problematic to occur and eventually – impossible to take place (18, 26, 31, 32, 33). The resulting metabolic acidosis causes further kidney damage by increasing the amount of ammonia in the remaining nephrons, developing an inflammatory reaction and stimulating the renin-angiotensin-aldosterone system (18, 23). It is believed that the concentration of HCO3- in the blood is a quite accurate indicator of kidney function. Its decrease in the blood below the level of 22 mmol/l is considered to be a risk factor indicating the progression of kidney disease (32). It is assumed that the GFR value in healthy cats should range from 1.30 to 1.40 ml/min/kg (17). It leads to a simple conclusion: GFR being below the specified value indicates the beginning of metabolic acidosis. Nevertheless, the issue is that in clinical practice, GFR is very rarely assessed, which means that such a direct and reliable diagnostic method is practically unavailable in a given veterinary clinic. Metabolic acidosis is therefore diagnosed indirectly, basing on the determination of certain parameter concentration in the blood, the increase or decrease of which may point to disorder occurrence.

Typically, metabolic acidosis is diagnosed basing on the analysis of the concentration of components of the carbonic acid-hydrogen carbonate buffer system in an arterial blood sample. Those are: partial pressure of carbon dioxide (pCO2) and HCO3-, where HCO3- acts as a base and accepts the emerging H+ ions. pCO2, being carbonic acid anhydride, is H+ ion donor. In such a scenario, it acts as an acid. In line with the classical model interpretation principles, metabolic acidosis is characterized by a primary decrease in

Table 1. Stages of CKD in felines based on serum creatinine, urea, and SDMA concentrations (according to IRIS)

CKD				
Criterion	**I**	**II**	**III**	**IV**
Creatinine concentration µmol/L	< 140	140-250	251-440	> 440
SDMA µg/dL	< 14	> 25	> 45	above marking capabilities
Urea mmol/L	4.8-10.1	13.1-19.9	20.3-45.5	45.7-54.0

Table 2. Reference values of carbonic acid-bicarbonate buffer components in felines

pH	7.41 - 7.46
pCO_2 mmHg	26.2 – 34.8
HCO_3- mmol/L	18.0 - 21.6

the concentration of HCO3- in the blood and a compensatory decrease in pCO_2 being the result of increased respiratory action normalizing pH (22, 33). From the practical point of view, it means that the arterial blood sample will show a lower concentration of HCO3- (due to the fact that the kidneys have stopped producing bases) and a lower concentration of pCO2. Blood pH usually remains normal due to the compensation phenomenon described above. Table 2 showcases reference values of said three parameters. The discussed method of diagnosing metabolic acidosis has its advantages, as it is precise and straightforward to interpret. From the practical point of view, however, it has two significant disadvantages that cannot be overlooked:

1. In numerous cases, the concentration of HCO3- remains within the norm for a long time, resulting from the release of carbonates into the blood from the so-called buffer reserve of the body, located in the bone tissue (2, 7). Authors' own experiences show that changes in the concentration of HCO3- in the blood appear so late that oral supplementation of bicarbonates and taurine, which to some extent inhibit pathological processes taking place in the kidneys, is no longer vital (1, 10, 13, 20, 24).

2. Own observations made by the authors also show that collecting arterial blood from a cat is technically difficult. The fact that pCO2 acts as an acid makes the analysis of a venous blood sample unreliable, as pCO2 volume is much higher in it. Table 3 showcases the change in values of carbonic acid-bicarbonate buffer components in arterial blood of cats basing on the CKD stage, obtained in the course of own studies of the authors.

Metabolic acidosis may also be diagnosed basing on the concentration of ions in the blood serum, mainly by determining the anion gap value (AG), and chlorine-to-sodium concentration ratio (Cl-/Na+). In order to maintain the electroneutrality of body fluids, the concentrations of cations and anions has to be equal. Nevertheless, it has to be mentioned that in the case of comparing concentrations of main cations in the blood serum: Na+ and K+ with main anions: Cl- and HCO3-, there will be the apparent lack of anions. There will be the so-called gap, consisting of negatively charged proteins, phosphates, and blood sulphates (9, 12, 25, 28). The AG value is calculated basing to the following formula:

AG = (Na+ + K+) – (Cl- - HCO3-)

In the course of metabolic acidosis, the AG value usually increases, which is associated with the decrease in the concentration, or "consumption" of the HCO3- buffer, which binds the emerging H+ protons (25, 26). Unfortunately, the disadvantage of the discussed method is the fact that the decrease in the HCO3- concentration in the blood is often accompanied by the increase in the Cl- concentration, so the mathematical value of AG does not change (21). From the practical point of view, it means that if one wants to take advantage of AG while diagnosing metabolic acidosis, one should check the Cl- concentration. If the concentration of said ion increases above the reference values, AG loses its diagnostic value (15, 21), which has to be kept in mind.

Acid-base imbalances in the body are also described by the so-called Stewart model (Strong Ion Approach), which assumes that the most important and inexhaustible source of hydrogen ions is body water. H+ ions are formed in the continuous process of its dissociation. Therefore, changes in plasma pH result exclusively from changes in the degree of water dissociation, which is influenced by the difference in the concentration of completely dissociated ions: Na+ and Cl- (9, 35, 36). Said assumption is taken advantage of during the rapid diagnosis of acid-base imbalances based on the assessment of the chloride/sodium ratio (Cl-/Na+). Said indicator is calculated according to the following formula:

Cl-/Na+ = (Cl-) : (Na+)

It is assumed that Cl-/Na+ values being above 0.80 point to acidosis (16, 19, 37). Some authors believe that Cl-/Na+ is the most optimal indicator of metabolic acidosis occurrence (14, 19). Table 4 showcases change in AG and (Cl/Na) values in felines, depending on the CKD stages.

Own research carried out by the authors has shown that AG in felines suffering from CKD is not a precise diagnostic indicator, mainly due to the compensatory increase in Cl concentration. Nevertheless, in a veterinary office, the Cl-/Na+ value is precise enough to specify the metabolic acidosis occurrence in cats with CKD. It can be performed in any conditions.

Table 3. Changes in values of the carbonic acid-bicarbonate buffer components in the arterial blood of cats depending on the CKD stage. K refers to control examination (healthy cats) (38)

	K	I	II	III	IV
pH	7.42±0.04	7.42±0.01	7.42±0.09	7.41±0.02	7.41±0.08
pCO2 mmHg	31.26±1.84	30.78±2.44	29.27±2.07	26.85±1.49	24.90±1.01
HCO3- mmol/L	22.47±2.02	20.02±0.43	19.54±0.42	19.33±0.68	17.71±0.67
n =	20	20	20	20	20

Table 4. Change in AG and (Cl/Na) values in cats depending on the CKD stage. K refers to control examination (healthy cats) (38)

	K	I	II	III	IV
AG	24.93±2.92	24.03±3.85	15.91*±1.43	15,47 *±1,65	17.19*±1.27
Cl/Na	0.71±0.04	0.71±0.02	0.77*±0.08	0.78*±0.01	0.78*±0.01
n =	20	20	20	20	20

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Blood pressure measurement as an important indicator in terms of monitoring patients with chronic renal failure

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Abstract: Systemic hypertension (SH) is a condition in the case of which systolic blood pressure (SBP) exceeds referential values, causing the risk of target organ damage (TOD). Hypertension in felines and canines is identified when SBP is above 160 mmHg. Nevertheless, it is already known that said value may differ due to factors such as breed or temperament. Key organs exposed to negative effects of hypertension (TOD) are kidneys, heart, eyes, as well as central nervous system. In the case of dogs and cats, hypertension often co-occurs with kidney diseases, which points to mutual dependence. Chronic kidney disease (CKD) may lead to hypertension, which causes the progression of kidney failure by means of increasing proteinuria and glomerular damage.

Keywords: hypertension, kidney failure, proteinuria

Introduction

Hypertension is defined as a condition characterized by persistently high systolic pressure. Three types of hypertension can be identified: situational, idiopathic, and secondary one.

Situational hypertension is predominantly caused by changes in the autonomic nervous system related to stress or arousal (1). It is possible to eliminate it by means of reducing medication-related factors in the animal's environment. It is the so-called "white coat syndrome". A short-term increase in blood pressure does not pose a risk to the animal's health condition, but it may often be the cause of an incorrect diagnosis. It is not always easy to distinguish a temporary increase in blood pressure from chronic hypertension. Not all animals react to stress identically. Moreover, it is problematic to specify by how much blood pressure can increase solely as a result of stress.

Secondary hypertension is defined as elevated systolic blood pressure occurring together with a particular comorbidity. It most often results from such diseases as: chronic or acute kidney disease, hyperadrenocorticism, diabetes, hyperaldosteronism, pheochromocytoma, obesity, and hypothyroidism in canines, as well as hyperthyroidism in felines. It may also be the result of administration of medication causing an increase in blood pressure, such as: glucocorticosteroids, erythropoietin, phenylpropanolamine, or pseudoephedrine.

Idiopathic hypertension is defined by experts as high blood pressure occurring in patients not having clinical symptoms of the disease (1). Coexisting diseases that may lead to hypertension should be excluded during laboratory and imaging-oriented tests.

Mechanisms of hypertension development in the case of kidney disease

When it comes to the pathogenesis of hypertension in animals suffering from kidney disease, the activation of the renin-angiotensin-aldosterone system (RAAS) has been identified to be of significant importance. Progressive kidney damage leads to sodium and water retention, at the same time increasing intravascular volume and blood pressure. Structural kidney-specific changes, such as renal vascular fibrosis, additionally reduce the autoregulatory capacity of the kidneys, in turn leading to the further systemic pressure increase. Moreover, hypertension affects increased glomerular filtration in the remaining functioning nephrons, which may paradoxically initially mask the decrease in glomerular filtration rate (GFR). Nevertheless, in the long term, it contributes to the accelerated impairment of key kidney functions. In the case of felines suffering from chronic kidney disease (CKD), increased blood pressure is frequently observed in early disease stages, whereas in canines, it may appear in more advanced stages (1,2).

In some scenarios, it may be problematic to distinguish between idiopathic hypertension causing secondary kidney problems and secondary one, leading to kidney failure. High blood pressure may cause polyuria, which is also called pressure diuresis. It is predominantly connected with low urine specific gravity (<1.030). When it comes to such patients, it is possible to erroneously exclude kidney problems. Therefore, it is highly advised not to limit examinations to morphological, biochemical, and urinalysis tests, but also – to perform ultrasound kidney examination, determine SDMA (Symmetric Dimethylarginine), as well as specify glomerular filtration rate (GFR).

Blood pressure measurement methods and monitoring-related recommendations

Accurate blood pressure measurement is crucial when it comes to both diagnosis and monitoring of hypertension in the case of felines and canines. The gold standard is the invasive method of direct measurement by means of arterial catheterization and utilizing a pressure transducer. Nevertheless, due to the need for sedation or anesthesia, said method is not typically used in everyday clinical practice. In clinical conditions, non-invasive indirect methods are taken advantage of, especially Doppler and oscillometric ones (3).

- Doppler method makes it possible to accurately measure systolic blood pressure (SBP). It is considered more reliable, especially when it comes to feline patients, in the case of which oscillometry often overestimates blood pressure values.
- Oscillometric method is easier to use and allows for the automatic measurement of systolic, mean, and diastolic blood pressure. However, its accuracy may be lower in small animals and in cases of excessive patient excitability (3).

Blood pressure should be measured in a calm, quiet environment, especially away from other animals and people. It should be measured at the beginning of the visit, when no other examination has been done to the patient. One should always grant the patient 5-10 minutes to acclimatize to the environment before starting the measurement. It is recommended for the owner to be with the animal during the measurement, as it also reduces stress and limits the situational increase in blood pressure. The experience of the person taking the measurement and a properly selected cuff (1) are of great importance when it comes to ensuring a remarkable reliability of the test. Most common spots for measuring blood pressure are the thoracic limb and the tail. It is crucial to always take measurements in the same location, using a cuff that is 30-40% of the circumference of the limb at the point of application (3). Taking advantage of a cuff that is too large may give an underestimated measurement, while using the one that is too small may result in a falsely high measurement. It is recommended to take about 7 measurements in a row. The first one should be rejected and the average of the remaining ones should be established (1). All measurements should be similar to each other. In the case individual measurements taken a moment after each other differ significantly, one should make sure that the cuff is properly placed and adheres to the limb with its entire circumference. In some scenarios, it may be sensible to change the measurement spot. It may also happen that the initial measurements are high and the following ones are lower. In such a situation, one should wait for the moment when the measurements stabilize at one level and only then start to include the results in the average cancelations. Some animals, especially felines, are very stressed at first. Nevertheless, after a few cuff inflations, they calm down and their pressure starts to decrease.

Normal values of systolic blood pressure in dogs and cats should not exceed 160 mmHg (1). Nevertheless, it is not a constant value, as there is a large percentage of animals, especially felines, in the case of which, despite compliance with all the above-described guidelines pertaining to measuring, blood pressure measured in a veterinary office is higher, but said animals do not have chronic hypertension. Therefore, the diagnosis of hypertension should be based not only on the measurement of systolic blood pressure itself, but also on taking into account the patient's clinical condition, as well as results of additional tests.

The patient's age may have a significant impact on blood pressure. It is estimated that it increases by about 1-3 mmHg/year. There is no observed effect of gender on blood pressure (1). It seems that breed has the greatest influence on blood pressure, especially when it comes to canines. Studies have shown that blood pressure in healthy dogs, such as greyhounds or hounds, is higher while compared to other breeds. Said fact is most likely caused by the temperament of a given breed.

Chronic arterial hypertension leads to tissue damage. The treatment of hypertension is mainly based on preventing tissue damage, not on achieving normal blood pressure. Organs exposed to the negative effects of hypertension (TOD, Target Organ Damage) are typically kidneys, heart, CNS and eyes (1). Said fact should be taken into account not only while treating patients with hypertension, but also during diagnosis. Changes in TOD organs are often major symptoms suggesting the need for a blood pressure test. Arterial hypertension leads to proteinuria, which is associated with faster progression of kidney disease and increased mortality. The most typical issue in animals is microalbuminuria. Arterial hypertension may occur at any stage of chronic kidney disease. Serum creatinine concentration is not directly related to increased blood pressure. In numerous cases, both canines and felines with hypertension have slight azotemia. Sometimes, it is not observed at all. Nevertheless, increase in SDMA concentration and decrease in GFR are quite commonplace (1.4). Chronic hypertension leads to inward hypertrophy of left ventricular walls (1). Such an echocardiographic image indicates phenotypic hypertrophic cardiomyopathy. Most often, hypertension does not lead to heart failure, but can cause changes in the auscultatory examination, such as: audible gallop (presence of additional heart sounds), arrhythmias, and heart murmurs. In the central nervous system, it is possible to observe hypertensive encephalopathy, in the course of which white matter edema and vascular CNS changes may occur. Symptoms such as lethargy, convulsions, disorientation, and balance disorders may be diagnosed in the discussed scenario. Neurological changes are more often observed in felines than in canines (1).

Most characteristic and noticeable changes resulting from hypertension are usually identified in the eyes. Hypertensive retinopathy may occur. In its course, retinal detachment, retinal edema, and hemorrhages into the vitreous body may be spotted by the expert performing examinations. In said case, vessels on the retina become tortuous and perivascular edema may develop. Swelling of the optic disc is then also visible. Vision loss is a rather common occurrence in the discussed scenario (1). Some of the aforementioned symptoms are easy for the owner to notice. Therefore, patients with changes in the eye area are most often referred for blood pressure measurement.

Indications for regular blood pressure measurement:

- Diagnosing and monitoring chronic kidney disease (CKD)
- Presence of proteinuria without obvious cause
- Diseases predisposing to hypertension, such as hyperthyroidism in felines and

hyperadrenocorticism in canines

- Suspected target organ damage (TOD), such as hypertensive retinopathy, hypertensive encephalopathy (1).

Hypertension diagnosis is typically based on:

- Blood pressure measurement – result above 160 mmHg. Most often, a single blood pressure measurement is not enough to make a diagnosis. It is only useful to rule out a problem if there is a measurement below 160 mmHg. If the blood pressure is above normal values, the diagnostics should be extended before starting treatment.
- Presence of changes in TOD organs
- Detection of diseases that may cause hypertension (1)

If a single blood pressure measurement is above normal, it should be checked whether the patient has any changes in the TOD organs or coexisting diseases that may lead to hypertension. Only after diagnostic-related undertakings being performed is it possible to consider a proper treatment. If it is determined that the patient does not have any organ changes pointing to hypertension, the expert should take further blood pressure measurements. Obtaining 3 consecutive measurements above the minimum of 180 mmHg within the next 2 weeks entitles the professional to consider treating hypertension (1). It should be remembered that each measurement is associated with stress and may cause situational hypertension. Nevertheless, if a disease that causes hypertension is diagnosed in a given patient, one should treat both the primary disease and the hypertension. In most cases, treating the primary disease alone is not enough to lower the blood pressure. It is crucial to explain to the owner the purpose of treatment and the importance of regular use of medications. First-choice medications to lower blood pressure in patients with chronic kidney disease are RAAS inhibitors and calcium channel blockers. Among RAAS inhibitors, the most commonly used ones are angiotensin-converting enzyme inhibitors (benazepril, enalapril) and angiotensin receptor blockers (telmisartan). When it comes to patients with renal failure, calcium channel blockers are avoided when it comes to monotherapy, because they cause dilation of the afferent arteriole, leading to the increased risk of glomerular damage by increasing hydrostatic pressure in the glomerular vessels. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers cause dilation of the efferent arteriole of the glomerulus. Nevertheless, it should be taken into account that RAAS inhibitors should be used with caution in dehydrated animals. It should be kept in mind, because they can lead to a rapid decrease in GFR (5,6). In felines, the drug of choice for hypertension, also associated with proteinuria, is a calcium channel blocker called amlodipine. When using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, it should be remembered that they may cause increased azotemia in felines. Moreover, they should be avoided in dehydrated patients (1). Treatment should always be selected basing on the patient's general condition and the primary disease causing hypertension. In felines, it is possible to opt for monotherapy, while in canines, it is achievable to take advantage of several medications from different groups.

According to recommendations issued by ACVIM (American College of Veterinary Internal Medicine), when it comes to animals being at risk, blood pressure measurements should be performed regularly, at least once every 6–12 months, while in patients with diagnosed hypertension, monitoring should take place every 1–3 months, depending on therapy effectiveness.

Closing remarks

Hypertension is quite a common issue, especially when it comes to older animals. It is vital to remember to monitor blood pressure in patients suffering from chronic renal failure. Owners are not always capable of noticing hypertension symptoms and changes caused by it. Undiagnosed and untreated hypertension in patients with renal failure is likely to worsen proteinuria, which is an unfavorable prognosis for patients suffering from kidney disease.

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Suspected congenital unilateral ureteral atresia and hydronephrosis in a dog – case report

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Abstract: Ureteral atresia is a congenital absence of the ureteral orifice, manifesting itself as a blind ending of the ureter, the opening of which should anatomically be located in the urinary bladder, near the bladder triangle. The consequence of said defect is the development of kidney hydronephrosis on the side of the abnormal ureteral orifice, as well as the risk of secondary changes occurring in the kidney on the opposite side.

The discussed anomaly is rare in dogs, usually unilateral, and typically diagnosed in young animals. It is often accompanied by other ureteral defects, such ectopia ureteri. Secondary changes may include ureter dilatation leading to the development of a megaureter, renal pelvis dilatation causing the development of hydronephrosis, as well as the subsequent development of chronic renal failure.

Keywords: ureteral atresia, ureter, hydroureter, hydronephrosis, kidney failure

INTRODUCTORY REMARKS

Congenital ureter malformations in dogs occur as a result of abnormalities during fetal development. The discussed defects are most often diagnosed in certain predisposed breeds, such as Siberian Husky, Labrador, Golden Retriever, Poodle, and Bulldog. However, they may also be identified in some mixed-breed dogs.

Most common congenital ureter anomalies are as follows:

1. Ureter ectopia, being the abnormal ureters opening into the urinary bladder. It is a defect in the case of which the opening of one or both ureters is in a non-physiological spot, understood as a spot other than the bladder triangle. Ureter displacement can be further subdivided into intramural and extramural one. The former occurs when the ureter openings enter the bladder wall in the area of the bladder triangle, but do not open directly in the anatomical location. The latter is identified when the ureter opening is located outside the bladder triangle, in such areas as the bladder neck, urethra, uterus, or vagina.
2. Ureter hypoplasia or atresia, being the underdevelopment or complete absence of the ureteral opening.
3. Ureterocele, which is a cystic dilatation of the terminal segment of the ureter within the urinary bladder wall.
4. Duplication of the ureter, being the presence of two ureters arising from the same kidney (partial or complete duplication can be identified).

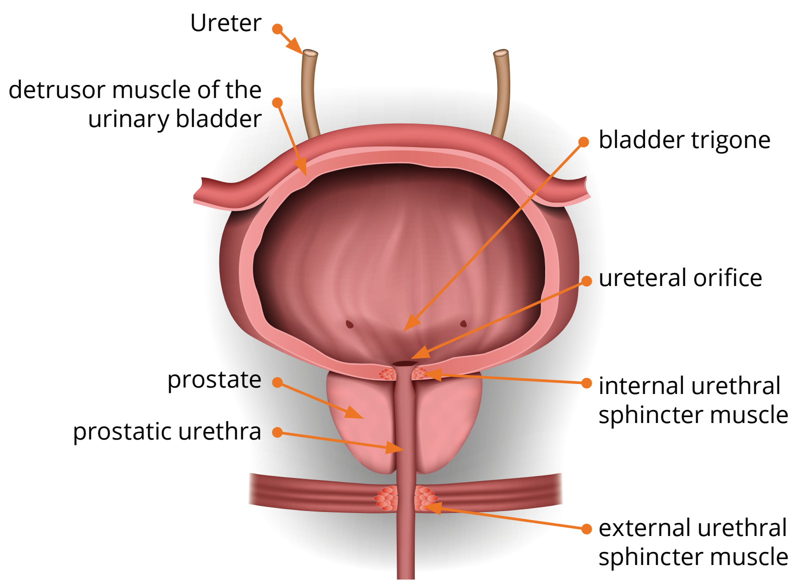


Fig. 1. Anatomy of the canine urinary tract. The ureters open into the bladder trigone

The differentiation of ureteral atresia and ectopia from other urinary tract diseases should be based on additional tests being done. They may, inter alia, include: blood tests (morphology, biochemical parameters), urine tests (general urine test with sediment, bacteriology), as well as imaging-oriented diagnostics (ultrasound, X-ray with contrast, cystoscopy, and computed tomography).

URINATION DISORDER-ORIENTED DIFFERENTIAL DIAGNOSIS

Owners typically visit a veterinarian due to pet's difficulty urinating or urinary incontinence, which tends to have more severe symptoms during walking, playing, and sleeping. In the course of a clinical examination, such a patient often does not have any abnormalities or deviations, aside from the external genitalia area, where skin inflammations are commonplace.

Blood tests may point to elevated renal parameters (creatinine and urea), being the consequence of underlying disorders (renal failure development). Ultrasonography is performed as the initial examination, predominantly due to its low invasiveness. It is helpful when it comes to determining ureteral dilatation, ureter displacement within the urinary bladder, as well as secondary kidney changes (renal pelvis dilatation, hydronephrosis).

Tests that are considered most useful when it comes to making a proper diagnosis include cystoscopy and computed tomography based on the utilization of a contrast agent.

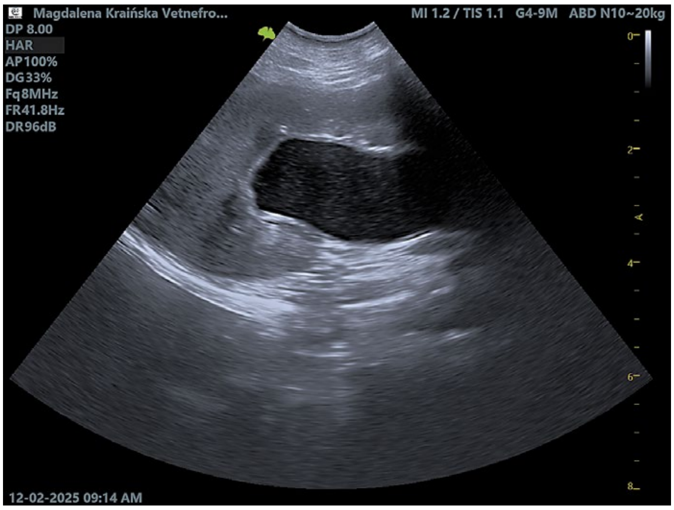


Fig. 2. Image of kidney alterations with features of hydronephrosis and a dilated ureter

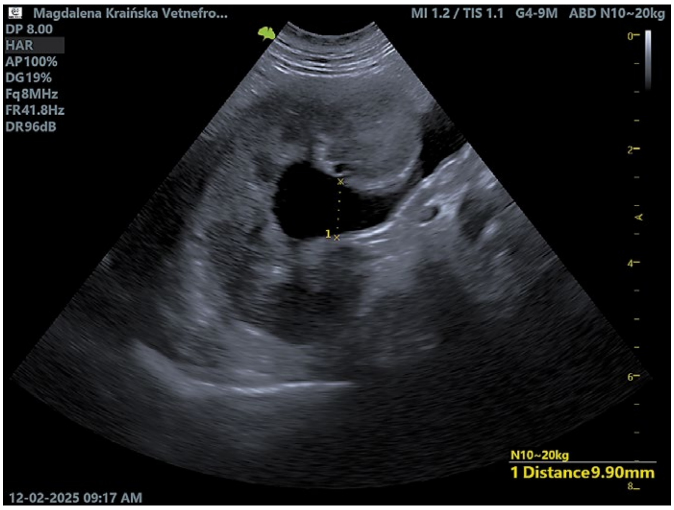


Fig. 3. Image of kidney alterations with features of hydronephrosis and a dilated ureter

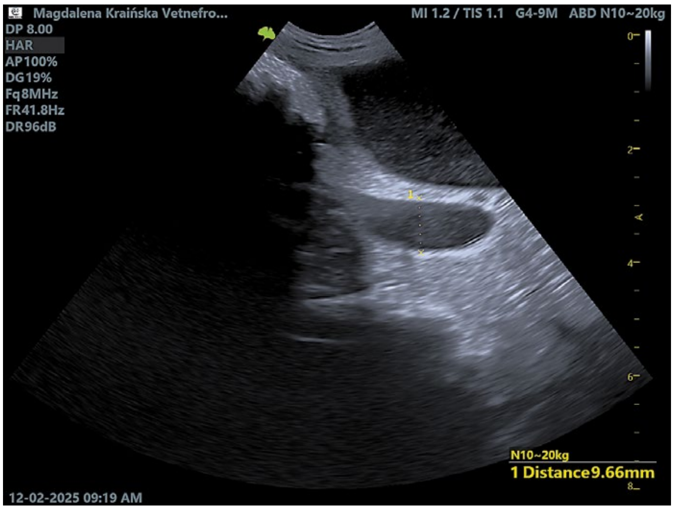


Fig. 4. Dilated ureter at the level of the urinary bladder

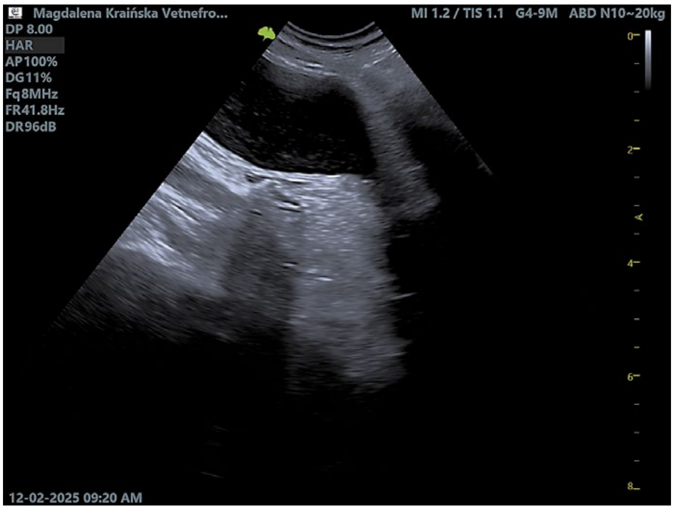


Fig. 5. No opening from the ureter into the urinary bladder identified

Case examination

A 20-week-old mixed-breed female dog was referred for a uro-nephrology consultation due to frequent urination, stranguria, as well as the lack of response to pharmacological antibiotic treatment (amoxicillin with clavulanic acid at the dose of 20 mg/kg bw twice per day for 14 days).

In the course of physical examination, the dog had a tender abdominal cavity and a palpable intra-abdominal mass. Urination resulted in either a weak, intermittent stream or infrequent urination. Hematological and biochemical studies revealed several significant renal abnormalities (creatinine, 1.90 mg/dL; reference range, 0.70-1.30 mg/dL; BUN, 70 mg/dL; reference range, 20 to 50 mg/dL). Bacteriology-oriented urine examination was negative for bacterial growth, presumably due to recent antibiotic administration.

Abdominal ultrasonography revealed right kidney hydronephrosis and severe left renal pelvis dilatation (referential range for the renal pelvis, < 4.0 mm) [1], right ureter (referential range for the ureter, < 1.8 mm) [2], as well as left ureter. No ureter entering the bladder was identified. Dilateral hydronephrosis and bilateral ureteral dilatation (more significant on the right side) were identified. Nevertheless, no cause of said issues was specified. Contrast-enhanced computed tomography and cystoscopy were recommended.

Initially, a computed tomography (CT) scan with contrast was performed at the Computed Tomography Laboratory being a part of the Auxilium Veterinary Clinic in Milanówek.

CT scan confirmed findings in the kidneys and ureters identified by means of opting for the ultrasound method. Nevertheless, an abrupt, blind-ending opening of the right ureter without connection to the urinary bladder was additionally identified.

The next examination opted for was cystoscopy. It revealed a left intramural ectopic ureter and absent right ureteral orifice. Said findings were consistent with right distal ureteral atresia and hydronephrosis, resulting in the extramural compression of the contralateral (left) ureter and bladder. The aforementioned congenital ureteral abnormality resulted in bilateral hydronephrosis and lower urinary tract symptoms.

After the discussed examinations being concluded, the dog in question was discharged pending right ureteronephrectomy and left ureteroplasty (neoureterostomy).

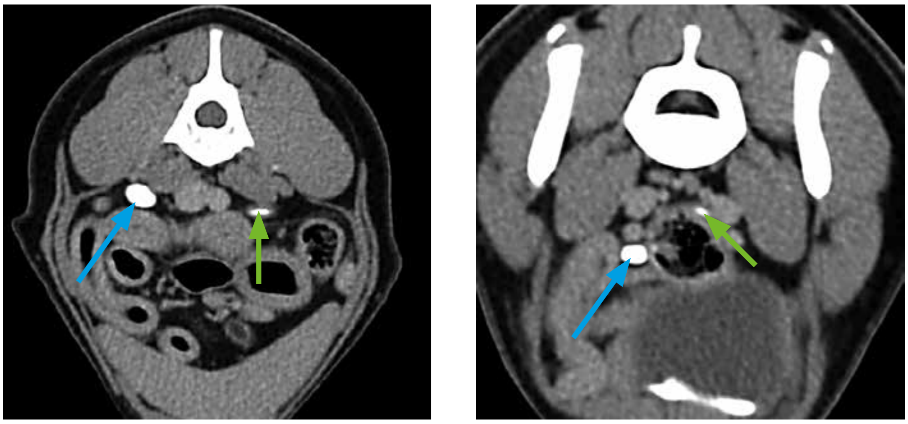
DISCUSSION AND CONCLUSIONS DRAWN

Ureteral atresia is a congenital ureteral orifice absence, which results in the obstruction of urine flow from the kidney, hydronephrosis development, as well as secondary megaureter. Ureteral atresia is rare in dogs. Typically, it is unilateral, occurs in the distal ureter, is associated with a dysplastic or nonfunctioning kidney, as well as is diagnosed at a young age. [3, 4, 5, 6, 7, 8]

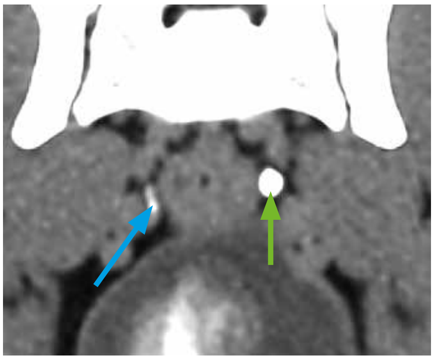
Even though the exact cause of the issue in question is unclear, ureteral atresia is believed to result from developing ureter ischemic injury or genetic tissue differentiation failure. During embryological development, the ureter arises from the ureteral bud, which in turn develops from the mesonephric duct [11]. In the course of ureteral growth, canalization is critical when it comes to establishing ureteral patency [11]. Atresia develops when ureteral patency fails, probably as a result of one of the aforementioned hypotheses. Even though the etiology of ureteral atresia in dogs is also unknown, numerous similarities between the discussed case and the one identified in humans point to a common cause being likely.

Congenital anatomical anomalies of the ureter causing obstructive hydronephrosis and megaureter are rare in veterinary patients. Reported anatomical ureter anomalies include duplication, atresia, stenosis, ureterocele, as well as ectopic ureter. Classic lower urinary tract clinical signs of hematuria, pollakiuria, and stranguria, if present at all, were caused by lower urinary tract bacterial infection.

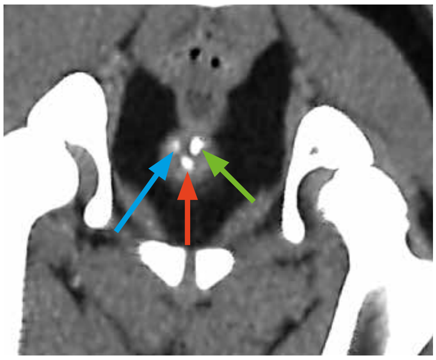
On the other hand, lower urinary tract symptom etiology in the presented case was quite unique and resulted from the external compression of the bladder by a significantly dilated atretic ureter. The questionable diagnosis of urinary tract infection (UTI), lack of clinical symptom improvement after antibiotic therapy, as well as results of both preoperative ultrasonography and computed tomography, point strongly to bladder compression being the cause of the reported stranguria and pollakiuria. Finally, clinical lower urinary tract symptoms seem to be rare manifestations of any of the congenital anatomical anomalies of the urinary tract in small animals.



The abdominal cavity in cross-sectional views, following the administration of a contrast agent. The ureters filled with the contrast agent are visible – the right ureter (blue arrows) and the left ureter (at the sites of narrowing – green arrows). The ureters, with both ureteral openings into the urethra at the level of its internal orifice, are observed. The presence of the contrast agent in the lumen of the urinary bladder suggests partial reflux of urine into the bladder lumen



The ureters in cross-sectional view, following the administration of a contrast agent. The right ureter (at the site of narrowing – blue arrow) and the left ureter (green arrow)



The ureteral orifices in cross-sectional view, following the administration of a contrast agent. The right ureter (blue arrow), the left ureter (green arrow), and the urethra filled with the contrast agent (red arrow)

Fig. 6. Computed tomography. Ureter bilateral ectopia is visible, with both ureters opening into the urethra at the level of its internal opening. The presence of contrast agent in the lumen of the urinary bladder points to partial urine regurgitation into the urinary bladder lumen.

CLOSING REMARKS

Clinical significance

The clinical case discussed above is intended to present veterinarians with the option of taking advantage of differential diagnosis of ureter anatomical defects. Ureteral atresia should be considered as a differential diagnosis for lower urinary tract symptoms and/or bilateral hydronephrosis in young canines. Case description expands expert knowledge pertaining to congenital diseases of the lower urinary tract and symptom etiology in dogs. The surgical removal of the congenital ureteral anomaly may improve renal tissue functioning and prolong the life of patients affected by it.

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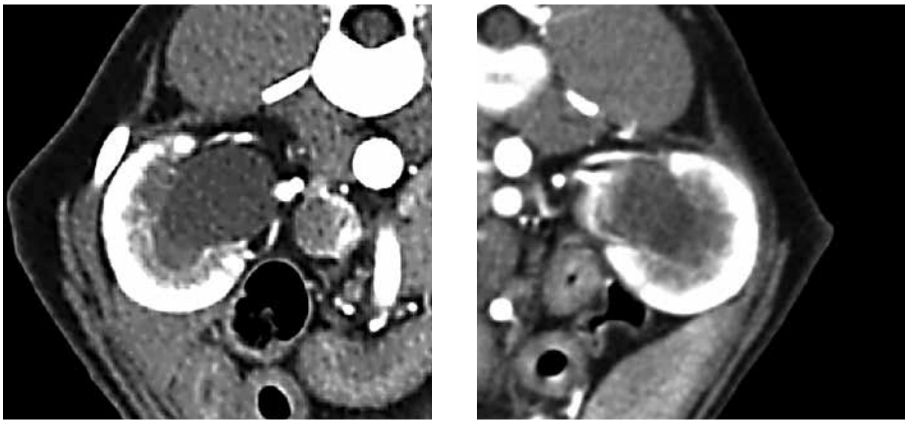
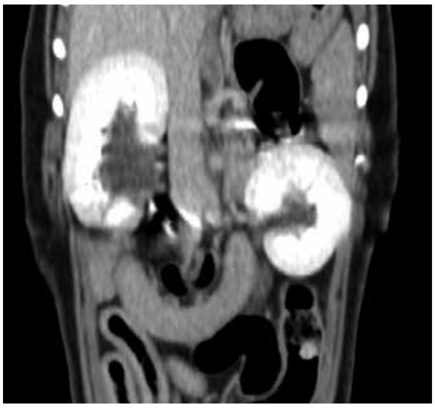
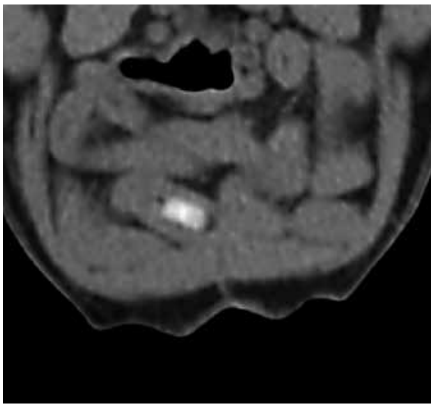


Dilated renal pelvises in cross-sectional views, soft tissue window, post-contrast examination – arterial phase



Kidneys in coronal section. Soft tissue window, post-contrast examination – arterial phase



Foreign body in the intestine. Soft tissue window, native examination, cross-sectional view

Fig. 7. The examination carried out revealed renal asymmetry, with bilateral renal pelvis dilatation and bilateral, uneven dilatation of the ureters with a slightly tortuous course and local narrowing. Hydronephrosis and megaureter, secondary to stenoses or caused by congenital developmental defects, were identified. Ureteral stenoses may result from congenital anatomical anomalies, ureteral orifice hypoplasia or atresia, post-infection fibrosis, or external compression.

Fig. 8. Ureters in MIP (left) and 3D (right) reconstruction

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Renal replacement therapies in veterinary medicine

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Abstract: The continuously developing veterinary nephrology allows for the introduction of new diagnostic and therapeutic methods. Many of them are adapted from human medicine after ensuring their proper modifications. Key indications for renal replacement therapy in animals include acute kidney injury and exacerbations of chronic kidney disease. Nevertheless, extracorporeal blood purification techniques are also taken advantage in the course of treating non-nephrological patients in intensive care units. This article provides a detailed overview of various renal replacement therapy-oriented techniques, including hemodialysis and peritoneal dialysis.

Keywords: hemodialysis, peritoneal dialysis, acute kidney injury, continuous renal replacement therapy

Introduction

Veterinary nephrology is constantly evolving. New diagnostic and therapeutic methods are utilized more commonly than ever. Many of them have been taken from human medicine, but they have required significant modifications to be valid, predominantly due to sizes, temperament, and physiological differences of canines and felines, as well as due to the specificity of the organization of veterinary care and ethical issues. Renal replacement therapies (RRT) in human medicine are primarily associated with the treatment of chronic patients awaiting transplantation. When it comes to veterinary medicine, main indications for renal replacement therapy are acute kidney injury and exacerbation of chronic kidney disease. Nevertheless, it has to be mentioned that numerous extracorporeal blood purification techniques are also taken advantage of in the treatment of non-nephrological patients staying in intensive care units. Severe acute kidney injury is characterized by high mortality, often despite intensive treatment. Said situation is caused by the fact that even if the damage is potentially reversible, kidney regeneration takes time. In the meantime, the patient's clinical condition deteriorates as a result to uremia. In such scenarios, thanks to opting for renal replacement therapy, patients have a recovery chance, as renal replacement therapy cleanses the body of uremic toxins, restores water and electrolyte balance, as well as ensures the acid-base balance of the body, keeping the patient alive until the kidney function returns to normal.

Renal replacement therapy types and other advanced techniques taking advantage of extracorporeal circulation

Renal replacement therapy may opt for extracorporeal circulation and artificial semipermeable membranes in order to purify the blood or a natural semipermeable membrane, such as the peritoneum. Extracorporeal blood purification is based to a varying extent on diffusion, convection and filtration, depending on the therapeutic method selected. When it comes to classical intermittent hemodialysis (IHD), the leading physical process responsible for the transfer of uremic toxins from the blood to the dialysis fluid is diffusion. In the discussed scenario, the driving force for exchange is the difference in concentrations of the substance on both sides of the dialysis membrane. The aforementioned difference is maintained by the countercurrent, rapid flow of the dialysate on the other side of the semipermeable membrane. While taking into account continuous renal replacement therapies, most important mechanisms are usually filtration and accompanying convection. In practice, part of the plasma water and substances dissolved in it are filtered through a semipermeable membrane and

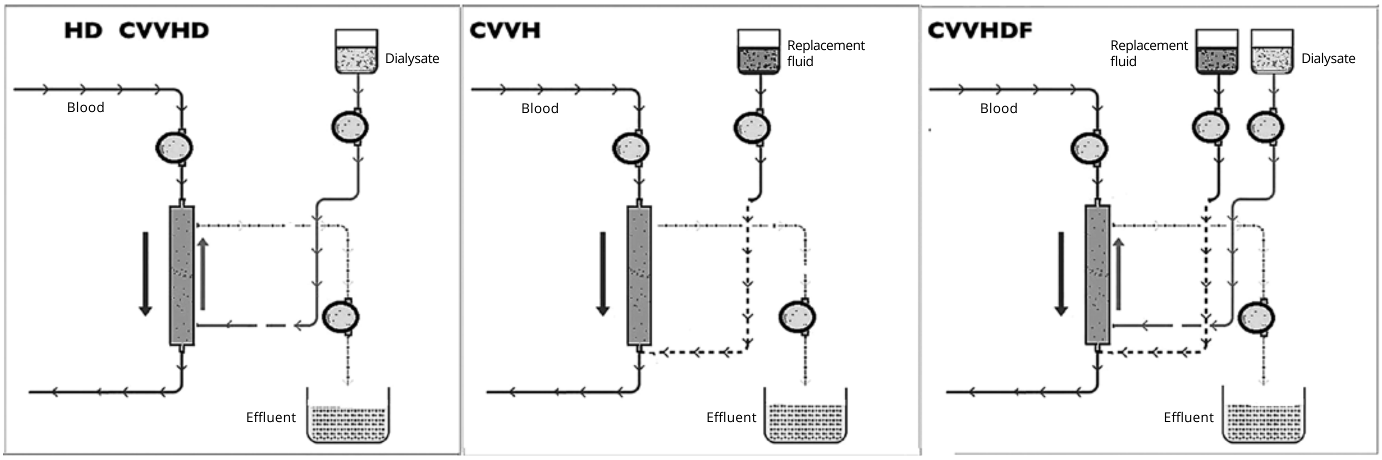

Fig. 1. Schematic representation of the extracorporeal blood circuit with indication of blood flow direction, dialysate flow, and/or connection of replacement fluid in hemodialysis and continuous veno-venous hemodialysis (HD and CVVHD), continuous veno-venous hemofiltration (CVVH), and continuous veno-venous hemodiafiltration (CVVHDF)

Fig. 2. Dog with acute kidney injury of unknown origin during the first hemodialysis procedure

Fig. 3. Cat with acute kidney injury due to lily poisoning during the second hemodialysis procedure

then supplemented with a sterile balanced replacement fluid, typically after the filter (continuous venovenous hemofiltration; CVVH). Continuous techniques may also take advantage of the diffusion process with an additional low-level flow of dialysis fluid (continuous venovenous hemodialysis; continuous venovenous hemodialiftration, CVVHD, CVVHDF) (Fig. 1). All of the discussed types of extracorporeal therapies require the placement of a large double-lumen central catheter in order to ensure blood circulation in an extracorporeal loop containing a dialyzer or a semipermeable membrane filter. The utilization of anticoagulation is also vital.

The RRT method that uses patient's own semipermeable membrane is called peritoneal dialysis. The peritoneum has a surface area comparable to the patient's total body surface area and contains pores of various sizes that allow small molecules and water to pass through, making it a valid semipermeable membrane making it possible to ensure the exchange of substances between patient's body fluids and the fluid in the peritoneal cavity. Said renal replacement method is strongly dependent, in terms of efficiency, on the appropriate placement of a single-lumen, perforated peritoneal catheter, which ensures the desired outflow of the used dialysis fluid, which is also sometimes referred to as effluent from the abdominal cavity.

Extracorporeal blood circulation is also taken advantage of in the case of intensive care patients after poisoning, suffering from sepsis, SIRS, as well as rapid or severe autoimmune diseases, such as autoimmune hemolytic anemia, myasthenia gravis, and pemphigus vulgaris. Nevertheless, in the discussed scenario, hemoperfusion (HP) is opted for, based on the use of a cartridge containing adsorbing material, such as toxins, proinflammatory cytokines, bilirubin, or therapeutic plasma exchange (TPE) that removes toxins bound to plasma proteins and immunoglobulins.

Indications for renal replacement therapy with regard to canines and felines

Renal replacement therapy is indicated in the case of patients suffering from severe renal damage (grade IV and V IRIS), especially if it is progressive and/or may cause secondary damage to other organs. An increasing creatinine concentration above 5 mg/dL (442 μmol/L) in a well-hydrated patient is the basis for opting for renal replacement therapy, especially if the patient has anuria or oliguria (< 0.3 mL/kg/h) lasting > 6 hours despite the use of diuretics. In the case of overhydration of the patient due to anuria, restoration of diuresis without dehydration during dialysis is very unlikely. Therefore, the discussed scenario is yet another indication for RRT, regardless of creatinine concentration. What is more, the presence of severe electrolyte disturbances (especially potassium) and acid-base balance that cannot be controlled with medications administered should be considered the basis for recommending renal replacement therapy. It has to be pointed out that RRT mainly helps prevent impairment of many organ functions in the course of uremia, but if severe complications of uremia have already occurred, renal replacement therapy alone may not grant the expected results having the form of significant clinical improvement and life protection until recovery. As a result, forecasts for patients undergoing dialysis therapy depend, inter alia, on the time of treatment initiation and current complications (anuria duration, overhydration, number of organs damaged by uremic toxins). It is also a commonly known fact that earlier interventions give better outcomes. Other factors that may affect forecasts are the cause of kidney damage, concomitant diseases not caused by the CNS (such as chronic heart failure), advanced age, and (for technical reasons) patient size. Causes of kidney damage that are connected with best forecasts when it comes to dialysis patients include infections (leptospirosis, pyelonephritis) and CNS as MODS element in the course of inflammatory diseases (babesiosis, sepsis), followed by ischemic and post-obstructive damage (for example: after hypovolemic shock, AKI after long-term ureteral or urethra obstruction). On the other hand, worst forecasts are strongly connected with severe toxic kidney damage (especially with large doses of medications, ethylene glycol, and lilies). When it comes to felines, renal replacement therapy may be indicated exceptionally in ureteral obstructions that do not respond to pharmacological treatment, when the patient's biochemical parameters or severe clinical condition/ fluid overload preclude safe, long anesthesia for the procedure, or when the patient has anuria persisting after the procedure. To sum up, survival and improvement in renal function is expected in approximately 50% of patients undergoing treatment, with more than 85% for leptospirosis and babesiosis patients and less than 50% for ethylene glycol and lily (Fig. 2).

Additional indications for hemodialysis or CRRT are some kinds of poisoning. Nevertheless, it should be remembered that pores of dialyzers/filters are small and only allow substances with a fairly low molecular weight (< 500 Da) to pass through. Furthermore, these substances cannot be excessively bound to plasma proteins (< 80%) and have too large a volume of distribution in the body (< 1-2 L/kg). It has to be added that there is no point in conducting detoxification renal replacement therapy if the toxin is subject to very rapid natural elimination and does not impair elimination pathways or if there is an effective antidote. Examples of substances that can be removed by means of using hemodialysis are as follows: ethylene glycol, ethanol, methanol, caffeine, barbiturates, baclofen, and metaldehyde. Hemoperfusion and therapeutic plasma exchange techniques are intended for the removal of larger molecules or those that are more closely bound to proteins. .

Hemodialysis and continuous therapies

Patient selection

Hemodialysis and continuous therapies are opted for in the case of patients weighing more than 3-4 kg, depending on the available equipment and staff experience. It is caused by the need to withdraw a specific volume of blood from the patient and achieve the desired accuracy of body cleansing and dehydration rate. Smallest available extracorporeal loops (blood lines and dialyzer/filter) are characterized by the

Fig. 4. Diagram of establishing dialysis access in a dog with acute kidney injury. From the left: positioning the patient on the left side with the neck elevated, the insertion site shaved and disinfected; insertion of a guidewire through a needle into the external jugular vein; dilation of the insertion path with a dilator threaded over the guidewire; insertion of a double-lumen catheter into the external jugular vein over the guidewire; verification of catheter patency; closure of the catheter ports after filling its lumen with heparin solution

volume of 60-74 mL, whereas the volume of the patient's blood that can be withdrawn without causing symptoms of hypotension and hypovolemic shock is 20%. Blood volume in cats is about 60-70 mL/kg, and in dogs - about 80 mL/kg. When it comes to a feline weighing 3 kg, the total blood volume is 180-210 mL, so 36-42 mL of blood can be safely withdrawn from the body, which is approximately half the volume of the smallest extracorporeal loop. In such scenarios, it is vital to take advantage of donor blood to fill the extracorporeal loop and ensure the patient's hemodynamic stability.

Vascular access

In order to connect the patient to the extracorporeal loop, it is vital to ensure vascular access by using a double-lumen dialysis catheter inserted through the external jugular vein to the border of the right atrium. While treating relatively small patients, the following catheters are suitable: 6-8 Fr 10-15 cm, in medium-sized patients: 8-11.5 Fr 10-20 cm, and in large patients: 11.5-13.5 Fr 15-25 cm. They should be inserted in sterile conditions, most often percutaneously, by means of using the Seldinger method over a guidewire, less often after the dissection of the vessel with the patient lying on his left side. Ultrasound imaging can be taken advantage of to localize the puncture. Most often, patients require only local anesthesia and butorphanol premedication for the insertion of a central line. In some cases, a short infusion anesthesia is necessary. Ideally, the position of the catheter should be checked by opting for an X-ray image. Immediately after catheter insertion, the patient can undergo (the first) procedure. The dialysis catheter should only be used for procedures and otherwise remain closed, filled with an anticoagulant solution (most often heparin), as well as secured with a dressing.

Fig. 5. Lateral X-ray image of vascular access in a dog for renal replacement therapy using extracorporeal circulation

Most common complications in patients with central access are catheter obstruction and catheter-related infections. Access obstruction may result from the presence of a clot, fibrin coating or the tip resting against the vessel wall. Less frequently, it may be caused by polyurethane catheters from catheter kinking and bending at this point. Catheter-related infections result from the contamination of puncture site, infection of the tissue around the catheter, or the introduction of bacteria into the lumen of the catheter. Contraindications to catheter insertion include a current skin infection at the planned puncture spot or disease of the vessel itself. In other scenarios, saving the patient's life outweighs the risk of catheterization (Fig. 3).

To perform the procedure, it is vital to select the appropriate set of drains and dialyser/filter. When it comes to felines and canines, the major criterion for the initial procedures is the size of the patient and the volume of the set. During the further treatment, the efficiency of the dialyser/filter is also taken into account in order to achieve the desired treatment intensity. Typical IHD procedures last between 4.5-5.5 hours. CRRT lasts, depending on the team's capabilities and the viability of the extracorporeal loop, from 8 to 72 hours. During the initial IHD procedures, blood purification is carried out carefully, therefore reducing the intensity of blood purification to 5-10% urea reduction per hour for IHD (in the case of continuous therapies, purification is slower, reaching 20-45 mL/kg/h of effluent) to prevent dialysis decompensation syndrome. During subsequent procedures, treatment intensity is increased to 50-80% for II IHD and to approximately 90% for III IHD and subsequent days of IHD treatment. In order to specify the required urea clearance, the single-compartment Kt/V formula of can be opted for:

$Kt/V = -\ln(1-URR)$; (URR = (UREA poHD – UREA preHD)/UREA preHD

where K – is the urea clearance (equal to blood or dialysate flow), t – treatment time, and V – volume of toxin distribution in the patient, so 60% of body weight, URR – degree of urea reduction, UREA – serum urea concentration.

Fig. 6. Sagittal X-ray image of a dialysis drain in the peritoneal cavity of a cat

By taking advantage of the formula, it can be calculated that assuming a 50% reduction of urea, Kt/V is 0.7. Therefore, for a procedure lasting 5 hours (300 min) in a 5-kilogram patient (V = 3000 mL), the required clearance is 2100 mL for the entire procedure, meaning 7 mL/min of blood flowing through the dialyzer or 420 mL/h of effluent for 5 hours of treatment. Said formula is not intended for peritoneal dialysis, but it can be utilized to estimate the dialysis fluid volume to be exchanged.

Further aspects of dialysis dosing, apart from intensity, are ultrafiltration (which is also known as dehydration), composition of the dialysis fluid, as well as the temperature of the dialysate. Patients can usually be safely dehydrated at the rate of about 10 mL/k/h. However, patient's hemodynamic stability, blood pressure and overhydration degree should always be taken into account. Dehydration rate should be then modified accordingly. In the case of continuous techniques, filtration should not exceed 20-30% of the plasma, mainly due to the possibility of excessive blood thickening causing clotting in the filter. Therefore, flow rate should be set for a known hematocrit at the assumed rate of effluent production to reach plasma filtration fraction of about 25%. The ionic composition of the dialysate/replacement fluid should be adjusted to the patient's parameters. In the case of hyperkalemia > 7 mmol/L, one should opt for fluids with low potassium content (1 mmol/L), while in the case of hypokalemia, one should take advantage of fluids with added potassium 4 mmol/L. Experts should attempt not to exceed 30 mmol/L of bicarbonate in the dialysate. The calcium content should depend on anticoagulation type. While dealing with heparinization, the dialysate should contain 1.5 mmol/L of calcium, while calcium-free fluids should be used when citrate is opted for (in which case, the patient simultaneously receives an intravenous infusion of calcium after the extracorporeal loop). The dialysate temperature should be selected by prior taking into account the rate of blood flow, its cooling in the extracorporeal loop, patient's body temperature, and its hemodynamic stability.

In order to prevent the blood from clotting in the extracorporeal loop, an anticoagulant should be taken advantage of. It most often has the form of unfractionated heparin given in a continuous infusion of 20-50 IU/kg/hour, depending on the size and coagulation status of the patient. The patient can also be given an intravenous bolus of heparin 25-50 IU/kg beforehand.

Possible complications

A complication resulting from the procedure itself may be dialysis decompensation syndrome (DDS), based on water osmosis into (nerve) cells caused by a gradient of uremic toxins between the fluid of the vascular space and the intracellular fluid. Patients characterized by low body weight, very high parameters (serum urea concentration > 600 mg/dL), and previous neurological symptoms are most at risk. In their case, mannitol should be considered as a "preventive" treatment after the procedure.

Yet another crucial set of complications are hemostasis disorders. The patient may bleed excessively during the procedure, mainly from the puncture site, previous postoperative wounds, larger punctures, from the lungs in the case of leptospirosis, or from the gastrointestinal tract. On the other hand, clotting in the extracorporeal loop may occur, requiring the interruption of the procedure and loss of a large blood volume. Quite frequently, dialysis patients experience some blood loss associated with the treatment. If the patient's Ht drops to <20%, blood or packed red blood cell transfusion should be performed each time before the procedure.

Intradialytic hypotension may be identified particularly in septic patients, those with pre-existing low blood pressure, small children, as well in patients requiring intensive dehydration. Due to the said fact, blood pressure monitoring is essential during the procedure. Moreover, proper medications and fluids should be available in case of the need to treat hypotension arising.

Other possible complications include hypothermia, hyperthermia (less frequently), itching, muscle pains and cramps, chills and fever (if there is catheter infection or allergic reaction to dialyzer material), as well as neurological complications caused by too rapid correction of sodium or bicarbonate levels. Rarely, cardiac arrhythmias may develop. In some scenarios, the patient may die.

Treatment duration

The duration of renal replacement therapy is strongly dependent on the severity of kidney damage and time needed for regeneration. Typically, the first 2 treatments are performed day after day in order to reduce serum urea concentration to values being as close to normal as possible. Subsequent treatments are repeated every 2-3 (sometimes 4) days, depending on the kinetics of renal parameters in the patient's serum. Basing on the cause and degree of damage, only 2 hemodialysis treatments or many sessions may be needed during treatment lasting more than a month. Nevertheless, patients with promising forecasts usually require 2 to 6 treatments. Each treatment lasts from 1 to 4 weeks. Signs of regeneration, such as developing polyuria after the period of oligo/anuria, slowed down increase in creatinine concentration between treatments, as well as a spontaneous decrease of the patient's creatinine concentration in between treatments are all signals encouraging to conclude dialysis therapy. In such a scenario, the treatment should be discontinued and conservative therapy should be opted for. The discontinuation of therapy may also be dictated by significant intra-procedural complications or the lack of response to treatment after a long period of time. Once RRT is complete, the central line is removed, the skin wound can be closed with a single suture or tissue glue, the vessel should heal on its own, and there should be typically no major bleeding from the puncture site after catheter removal.

Peritoneal dialysis

Peritoneal dialysis in patients suffering from acute kidney injury is a less effective technique, especially while compared to IHD and even CRRT. Nevertheless, it can be an alternative for very small patients, in the case of whom hemodialysis or CRRT are too risky or impossible to perform, mainly due to the lack of appropriate vascular access (Fig. 4). Nevertheless, it should be remembered that peritoneal dialysis in animals in acute conditions differs from chronic peritoneal dialysis in humans. It requires much more frequent exchanges of dialysis fluid, especially during the initial days of treatment. Contraindications to peritoneal dialysis include peritonitis, severe proteinuria with albumin loss, as well as large adhesions in the peritoneal cavity reducing the efficiency of substance exchange. The first stage of peritoneal dialysis treatment is to obtain access to the peritoneal cavity. It can be achieved by means of using a central vascular catheter or a sharp peritoneal catheter and opting for the Seldinger method. As a last resort, a large-sized intravenous catheter or other drain can be taken advantage of. Nevertheless, it should be noted that the discussed approach most often results in poor dialysis fluid recovery, reduced treatment effectiveness, as well as the risk of patient overhydration. Due to the said fact, the author prefers dedicated pediatric Tenckhoff dialysis catheters inserted through a small incision in the abdominal wall, slightly lateral to the umbilicus, with the accompanying partial omentectomy. Catheter implantation, as well as any subsequent manipulations, must be performed by opting for the so-called aseptic technique, as septic peritonitis is one of the most common and dangerous complications connected with peritoneal dialysis. After insertion, the catheter should be connected to the "Y" system, for example - by using a three-way tap. Such an approach allows for the separation of dialysis fluid supply and effluent flow paths, as well as makes it possible to flush the system, which reduces infection risk. The dialysis fluid should be as similar in composition to deproteinized plasma as possible and contain glucose in concentration ranging from 1.5 to 4%, depending on the dialysis goals. It should be also warmed to the patient's physiological body temperature. Due to the instability of bicarbonate in solutions containing calcium, the buffer in dialysis fluids is often lactate. For treatment purposes, ready-made commercial bags of fluid can be used. Alternatively, such a fluid can be prepared independently by adding an appropriate volume of 40% glucose to Ringer's solution with lactates. When it comes to patients characterized by normal hydration, glucose addition should be 1.5%. To induce ultrafiltration in order to dehydrate the patient, concentrations of 2 or sometimes 4% can be used. The first bag should contain heparin, mainly due to the formation of fibrin precipitates on the catheter after intervention in the abdominal cavity. Dialysis fluid exchanges in patients with acute kidney injury should be carried out with high frequency and be based on gradually increasing the volume of fluid administered for each exchange. During the initial 24 hours of treatment, the fluid should be replaced every 1-2 hours. The administered volume should be gradually increased from 10 mL/kg to 40 mL/kg (or even more if the patient tolerates it) to prevent fluid escape into the subcutaneous tissue (which may be connected with patient overhydration and significantly reduce treatment effectiveness). The volume of fluid recovered after the time spent in the peritoneal cavity should be equal to the volume of fluid administered or greater (if ultrafiltration is forced). Excessive fluid administered may cause discomfort, dyspnea, leakage into the pleural cavity, pressure on the vena cava, and reduced venous return. If the fluid cannot be recovered, gentle abdominal massage can be taken advantage of. Alternatively, the patient can be turned to the other side. Attempts to suck the fluid out will likely result in greater catheter obstruction. The intensity of fluid exchanges should be reduced after achieving the reduction in the patient's creatinine concentration to approximately 5 mg/dL and urea to approximately 200 mg/dL. The fluid should be replaced every 3-4 hours. Renal parameters, ionogram, albumin concentration, total protein and glycemia should be monitored at least once a day. If the patient's renal parameters stabilize after reducing the intensity of exchanges or decrease further, time between exchanges should be preferably extended to 6-8 hours. Renal replacement therapy should be discontinued as the next step.

Summary

Renal replacement therapies are becoming increasingly widely used when it comes to the treatment of canines and felines. They increase the survival rate of animals suffering from severe kidney damage, mainly due to the fact that they allow for patient detoxification, normalization of acid-base and water-electrolyte balance, as well as for the stabilization of the clinical condition until the kidney function returns to normal. Conducting RRT requires appropriate equipment to be used and a trained team to be involved. It is associated with a large amount of work, especially in the case of peritoneal dialysis therapy, which makes it a costly treatment. However, in the case of many animals, it is the only hope, especially in cases where it is known that the survival rate of patients is high, such as when it comes to CNS diseases or babesiosis. It should be kept in mind that the decision to initiate RRT should not be delayed.

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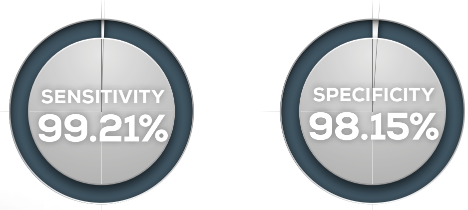
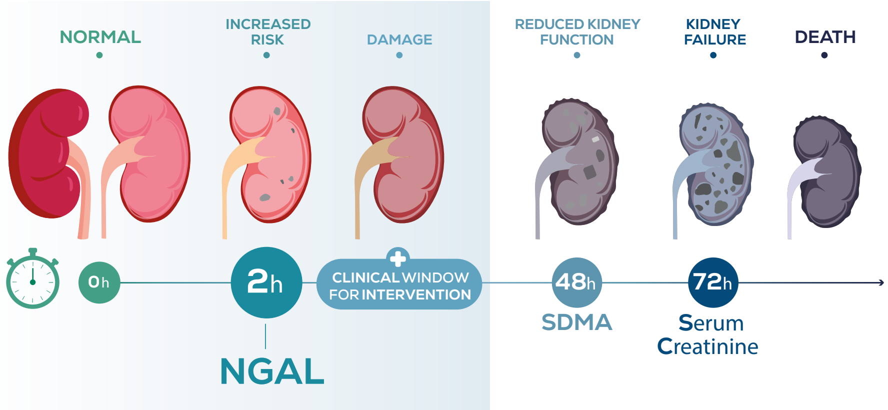
DIAGNOSTICS



CANINE NGAL

– AN INNOVATIVE BIOMARKER FOR KIDNEY INJURY IN DOGS

Early diagnosis of kidney disease in dogs is often a major clinical challenge, and traditional indicators – such as serum creatinine concentration or SDMA – show limited sensitivity in the early stages of nephron damage.



Stages of progressive kidney damage and possible uses of selected diagnostic markers.

The **Vet Expert Rapid Test Canine NGAL** is intended for the semi-quantitative measurement of neutrophil gelatinase-associated lipocalin (NGAL) concentration in canine urine. NGAL is one of the most sensitive markers of early renal dysfunction, with levels detectable as early as 2 hours after the damaging event. Faster than other parameters available on the market, it enables the early detection of acute kidney injury (AKI – Acute Kidney Injury).

WHEN TO PERFORM THE VET EXPERT RAPID TEST CANINE **NGAL?**

- √ in any case of suspected kidney disease in dogs, as part of differential diagnosis
- √ as support for the diagnosis of acute kidney injury (AKI – Acute Kidney Injury) at an early stage
- √ when assessing the risk of progression of chronic kidney disease (CKD – Chronic Kidney Disease)
- √ to evaluate patients with subclinical kidney injury – without a visible increase in serum creatinine concentration
- √ for patients receiving potentially nephrotoxic agents (e.g., chemotherapeutics, cyclosporine, gentamicin)
- √ after procedures performed under general anesthesia, as prophylaxis against complications

DIETS

Complete dietetic feed for adult dogs, that supports renal function in case of chronic renal insufficiency.

RENAL DOG

Composition:
meat and animal derivatives (42% chicken), cereals (5% rice ground), minerals (1%). Source of protein: chicken.

Analytical constituents:
Crude protein (6.3%), crude fat (9%), crude ash (2%), crude fibre (0.3%), moisture (77%), calcium (0.17%), phosphorous (0.07%), sodium (0.07%), potassium (0.2%), Omega-3 and Omega-6 polyunsaturated fatty acids (2.2%). Energy Value: 122 kcal/100 g

Packaging:
400 g

RENAL ELIMINATION

Composition:
Brown rice (31.5%), white rice (20%), duck fat, dried rabbit (10.5%), peas, flaxseed (5%), beet pulp (5%), minerals, dried cranberry (0.01%). Source of protein: rabbit

Analytical constituents:
Crude protein (15.50%), crude fat (19.50%), crude ash (4.00%), crude fiber (3.50%), moisture (8.00%), calcium (0.70%), phosphorus (0.40%), sodium (0.20%), potassium (0.40%), Omega-3 fatty acids (1.20%), Omega-6 fatty acids (3.90%). Energy Value: 403 kcal/100 g

Packaging:
2 kg and 8 kg

Complete dietetic food for adult cats, that supports renal function in case of chronic renal insufficiency.

RENAL CAT

Composition:
Meat and derivatives (chicken 26%, beef 23%), rice (6%), minerals (1%), oils and fats (0.5% salmon oil). Source of protein: chicken, beef.

Analytical constituents:
Crude protein (8.00%), crude fat (7.50%), crude ash (2.00%), crude fiber (0.50%), carbohydrates (6.00%), moisture (76.00%), calcium (0.20%), phosphorus (0.16%), sodium (0.16%), potassium (0.29%), Omega-6 polyunsaturated fatty acids (0.80%), Omega-3 polyunsaturated fatty acids (0.20%). Energy Value: 112.75 kcal/100 g

Packaging:
100 g

RENAL CAT

Composition:
Eggs (26%), yellow peas (26%), hydrolysed salmon protein (10%), hydrolysed chicken protein (8%), chicken fat (8%), buckwheat (7%), dried apple pulp (6%), salmon oil (2%), hydrolysed chicken liver (2%), egg shells (a source of calcium, 1.5%), yeasts (0.8%), potassium citrate (0.8%), pea flour, psyllium husks and seeds (0.6%), dried algae Ascophyllum nodosum (0.4%), shellfish powder (source of chitosan, 0.08%), mannanoligosaccharides (0.025%), yeasts products (β-glucan) (0.022%), fructooligosaccharides (0.02%), Mojave yucca (0.02%), dried sea buckthorn (0.015%), Lactobacillus helveticus HA – 122 inactivated(15x109 cells/kg). Protein source: eggs, yellow peas, hydrolysed salmon protein, hydrolysed chicken protein, hydrolysed chicken liver

Analytical constituents:
Crude protein (22%), crude fat (18%), crude ash (5.1%), crude fibre (2.3%), moisture (10%), calcium (0.8%), phosphorus (0.5%), sodium (0.3%), magnesium (0.09%), potassium (0.5%), Omega-3 fatty acids (0.8%), Omega-6 fatty acids (2.9%), EPA (20:5 n-3) (0.2%), DHA (22:6 n-3) (0.3%), LA (18:2 n-6) (2.0%), taurine (0.22%), arginine (0.63%). Metabolizable energy: 3,940 kcal/kg

Packaging:
400 g, 2 kg and 6 kg

SUPPLEMENTS

RENALVET

The product is recommended for dogs and cats in order to support proper renal function.

Composition:
Refined soybean oil *Glycine max.* (L.) Merr., calcium carbonate, crustacea meal Chionoecetes opilio (chitosan), crude lecithins, beeswax. Nutritional additives (per capsule): vitamin D3 80 IU.

Usage:
Cats and dogs up to 10 kg b.w. – 1 capsule daily. Dogs over 10 kg b.w. – 1 capsule per every 10 kg b.w. daily

Packaging:
45 caps.

RENALVET ULTRA

The product is recommended for adult cats helps to support the proper kidney function. The addition of lanthanum carbonate octahydrate reduces phosphorus absorption.

Composition:
Refined soybean oil *Glycine max.* (L.) Merr., fish oil (source of omega-3 fatty acids), beeswax, lecithins, dried root of *Astragalus membranaceus*, dried horsetail herb *Equisetum arvense* L., freeze-dried melon juice concentrate. Zootechnical additives per kg: lanthanum carbonate octahydrate 202.7 g.

Usage:
Cats: 1 capsule twice a day with meal

Packaging:
45 caps.

BIOPROTECT

The product is recommended for dogs and cats to support proper gastrointestinal microbiome function

Composition:
Yeasts products (MOS), fructo-oligosaccharides (FOS), magnesium stearate. Zootechnical additives (per capsule): 4b1707 *Enterococcus faecium* 25 mg (2.5 x 10^9 CFU), *Lactobacillus acidophilus* 25 mg (2.5 x 10^9 CFU).

Usage:
1-2 capsules per animal, daily

Packaging:
45 caps.

BIOPROTECT ULTRA

The preparation is intended for dogs and cats that helps restore the balance of the intestinal microbiome and the proper functioning of the intestinal barrier in the case of gastrointestinal dysbiosis. Use as a long-term support in cases of abnormal functioning of the digestive tract, in particular pancreas and enteropathies due to various causes

Composition:
Yarrowia lypolitica, galactooligosaccharides, inactivated Limosilactobacillus reuteri, microencapsulated sodium butyrate, magnesium stearate. Zootechnical additives (per capsule): Lactobacillus acidophilus 50 mg (5 x 10^9 CFU), Enterococcus faecium 5 mg (5 x 10^8 CFU). Nutritional additives (per capsule): L-tryptophan 50 mg.

Usage:
1-2 capsules per day, use at least 4-8 weeks

Packaging:
45 caps.

VET EXPERT
BASED ON EVIDENCE

NGAL

AN INNOVATIVE BIOMARKER FOR EARLY KIDNEY INJURY IN DOGS

NOW AVAILABLE AS A RAPID TEST

Vet Expert Rapid Test Canine NGAL is a useful tool for the early detection of kidney disease in dogs.

- quick and easy-to-use test performed on canine urine
- enables semi-quantitative measurement of NGAL (neutrophil gelatinase-associated lipocalin) concentration
- biomarker detectable just 2 hours after kidney injury

SENSITIVITY 99.21%

SPECIFICITY 98.15%

ACT EARLY – KEEP THE KIDNEYS UNDER CONTROL