Scientific Works. Series C. Veterinary Medicine. Vol. LXVII (1), 2021
ISSN 2065-1295; ISSN 2343-9394 (CD-ROM); ISSN 2067-3663 (Online); ISSN-L 2065-1295

RENAL BIOPSY - CONSIDERATIONS ABOUT ITS USEFULNESS IN DOGS WITH KIDNEY DISEASE

Roxana-Mariana IGNĂTESCU (ȚÎMPĂU)[1], Ana-Maria GOANȚĂ[1], Andreea-Bianca BOFAN[1], Alexandra BRAICA[2], Natalia RĂDULEA[1], Lucian IONIȚĂ[1]

[1]University of Agronomic Sciences and Veterinary Medicine of Bucharest, 59 Marasti Blvd, District 1, Bucharest, Romania
[2] Vasile Goldiș Western University of Arad, 94 Revoluției Blvd, Arad, Romania

Corresponding author email: roxana_mariana_12@yahoo.ro

Abstract

This paper underlines the role of kidney biopsy in the diagnosis of various kidney diseases in dogs. Even though it is an invasive method, kidney biopsy is often required to establish a definitive diagnosis and an accurate prognosis. Its use should always be considered after weighing the indications and potential complications. Several techniques are used to obtain kidney samples, such as percutaneous renal biopsy (blind or palpation technique or using ultrasound guidance, keyhole technique, laparoscopic biopsy) and surgical biopsy. Once the method has been chosen, the renal sample should only be obtained from the renal cortex. This procedure requires a patient that is stable to undergo general anesthesia or deep sedation. Kidney biopsy samples may be evaluated using light microscopy and special stains, transmission electron microscopy and immunofluorescence to obtain a diagnosis of certainty and to guide treatment options.

Key words*: kidney biopsy, indications, contraindications, complications, percutaneous biopsy techniques.*

INTRODUCTION

Renal disease is defined as the presence of renal lesions of any size or degree or clinical pathology abnormalities that pertain to renal function (Lattimer, 2011). Kidney disease encompasses a group of disorders that affect kidney function and structure. Even mild abnormalities in kidney function are associated with an increased risk for developing complications in other organ systems and mortality, all of which occur far more frequently than kidney failure (Levey, 2013).

For some decades, kidney biopsy was rarely used as a diagnostic tool. The main reasons for this limitation were the difficulty and complexity of the technique and fear of complications such as renal hemorrhage. Furthermore, the pathological examination of the sample provided scarcely useful information for the clinical and therapeutical management of the patient.

Today, it is essential to obtain an accurate and definitive diagnosis of renal disease, particularly in acute, congenital, or glomerular forms. It is essential to differentiate between immune-mediated glomerulonephritis and non-immune-mediated glomerulonephritis to prescribe an adequate therapy. Furthermore, various renal diseases in dogs, including acute kidney injury (AKI), chronic kidney disease (CKD), kidney tumors, and glomerulopathies require different diagnostic and therapeutical approaches. Kidney biopsy does not replace the current standard diagnostic methods but completes them in selected kidney pathologies.

The objectives of this study are to provide an overview of renal biopsy and to analyze the utility of this procedure according to current scientific data.

MATERIALS AND METHODS

Comprehensive online databases were used to review the literature describing the procedure of renal biopsy in dogs with kidney disease. The following keywords were used: kidney biopsy, indications, contraindications, complications, percutaneous biopsy techniques. Thirty relevant articles on renal biopsy in dogs were identified. Of these articles, in the last decade, research of Cianciolo et al., Crivellenti et al., focused more on renal biopsy as a means to obtain a specific diagnosis, prognosis, or guidelines for further research and were included in this review.

This article will describe the evolution of the renal biopsy from its introduction as a means of diagnosis in dogs with various kidney diseases to its use today. This study will also systemize its indications and contraindications, describe the most common biopsy techniques, including the required tools and possible complications. It will also emphasize the utility of renal biopsy in dogs as described by retrospective studies conducted in veterinary diagnostic renal pathology centers.

RESULTS AND DISCUSSIONS

The Renal biopsy - the beginning

In human medicine, the first renal biopsy of the native kidney was performed more than one century ago. It happened during a surgical procedure for renal decapsulation performed as a treatment of Bright syndrome (Edebohls, 1905). In 1944, Nils Alwall performed the first percutaneous renal biopsy, but his results were not published until 1952 (Alwall, 1952; Iversen et al., 1951). Since then, other biopsy techniques have been introduced to improve the quality of the samples obtained. Use of a cutting needle (the Vim Silverman needle) on a prone patient was proved to be more successful in providing an adequate tissue sample than the previous percutaneous method (Kark et al., 1954).

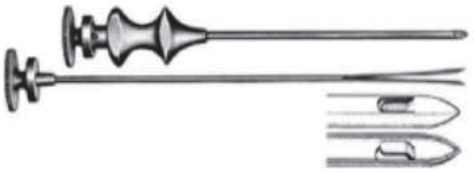

Figure 1. The diagram of a Silverman-needle for percutaneous renal biopsy (Merlini & Pozzi, 2007)

The early 1980s marked by the use of a biopsy 'gun' that employed an automated spring cutting needle and led to more suitable biopsy samples for histopathological evaluation as well as less trauma to the patient (Lindgren, 1982). The initial device evolved into an automatic or semi-automatic spring-loaded biopsy gun, which provides better renal cortex specimens in a safer way (Visconti et al., 2016). Before renal biopsy became common practice, clinicians could only recognize certain clinical syndromes, such as acute nephritis, nephrosis, asymptomatic hematuria, and chronic kidney failure, but they do not ascribe them to distinct pathologic processes. Over the past 50 years, renal pathology has evolved and, by the turn of the last century, the ability to diagnose kidney disease outstripped the knowledge on its pathogenesis.

Figure 2. Automatic disposable biopsy system - Medone® (www.medax.it/soft-tissue-biopsy/automatic-biopsy-system/item/medone?category_id=22)

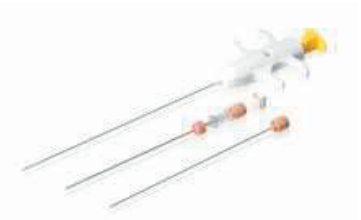

Figure 3. Semi-automated spring-loaded Biopsy system-Medeasy® (www.medax.it/soft-tissue-biopsy/item/medeasy)

In dogs, renal biopsy was reported for the first time in 1967 (Osborne et al., 1967) and it has improved tremendously ever since. Kidney biopsy is now the gold standard technique to determine the type of renal damage, when mildly increased UPC cannot differentiate tubular from glomerular lesions (Vaden et al., 2005; Lees et al., 2011; Salama et al., 2011). Ultrasonography has been proven to have a low diagnostic value due to the poor correlation between renal cortical echogenicity and histopathological lesions (Banzato et al., 2017; Zotti et al., 2015).

According to the International Renal Interest Society (IRIS), staging of chronic kidney disease is based on the concentration of serum creatinine and serum symmetric dimethyl-arginine, SDMA (IRIS Staging of CKD, 2019). Although widely available, creatinine does not increase until renal function declines by approximately 75%. Another disadvantage of

creatinine is that it provides little information about ongoing pathology. Therefore, more specific and sensitive biomarkers are needed to determine risk, establish a diagnosis and prognosis, and evaluate the result of therapeutic interventions (Salama et al., 2011; Yerramilli et al., 2016). SDMA is a more sensitive biomarker; it can detect a reduction of renal function by 25%-40% and is less influenced by lean body mass or other conditions (Nabity et al., 2015; Hall et al., 2014).

Frequently, evaluating kidney disease in dogs based on the history, clinical examination, laboratory tests (hematology, biochemistry, and urinalysis), and ultrasound examination does not identify the cause. In these patients, a renal biopsy may be required for a definitive diagnosis (Jankowski et al., 2008). Renal biopsy plays a key role in defining the disease process, and can also help clarify the pathophysiology of disease to improve therapeutic management. The histopathology result helps devise an adequate prognosis and treatment plan for some conditions, including protein-losing glomerulopathy and AKI (Dhaun et al., 2014).

Indications of renal biopsy

This procedure should only be executed by an operator that is well-trained and experienced in the technique that will be employed and knowledgeable about the potential complications (Walker, 2004).

In canine nephrology, renal biopsy is performed when an assessment of the type of kidney damage and its severity is required. Its use should be considered after careful weighing of the benefits against potential complications. For this purpose, a complete evaluation is required before the biopsy. This prebiopsy checkups should include physical examination, blood pressure measurement, and laboratory tests (complete blood count, biochemistry, urinalysis, urine protein to creatinine ratio, and coagulation tests) (Vaden, 2004).

In dogs, the most common indications for kidney biopsy are protein-losing nephropathy (PLN) or other suspected glomerular proteinuria, AKI, familial renal disease, and renal masses. Its purpose is to establish an accurate diagnosis and prognosis and to guide therapy according to its results (Polzin, 2009; Salama et al., 2011; Lees et al., 2011; Cianciolo et al., 2013; Littman et al., 2013; Vaden et al., 2016).

Contraindications for renal biopsy include severe anemia, coagulopathy, solitary kidney, uncontrolled hypertension, hydronephrosis, perirenal abscess, and bilateral reduction in kidney size (Polzin, 2009; Vaden & Brown, 2017). It is necessary to identify risk factors for bleeding (anemia, severe hypertension, prolonged bleeding time) and to correct them; when not possible, it is recommended to postpone the procedure (Visconti et al., 2016).

According to the IRIS Canine Glomerulonephritis study subgroup, this procedure should not be considered in dogs with stage 4 chronic kidney disease or whenever other medical contraindications cannot be improved. Kidney biopsy is also contraindicated when the results would not modify the treatment, diagnosis, or prognosis. (Pressler et al., 2013)

Current biopsy techniques

In dogs, several methods may be employed to collect renal specimens. They consist of percutaneous biopsy techniques such as blind or palpation biopsy, ultrasound-guided biopsy, keyhole biopsy, laparoscopic-guided biopsy, and surgical biopsy (Cianciolo et al., 2013; Vaden & Brown, 2017).

It should be emphasized that the choice of the kidney biopsy technique depends on the species, the size of the animal, operator experience, available equipment, and the clinical condition of the patient referred for biopsy. This procedure requires that a patient be stable to undergo general anesthesia or deep sedation.

Only cortical tissue should be sampled. The first reason for this reasoning is safety. Large vessels are not located in the renal cortex, so the damage (hemorrhage, infarction, or fibrosis) to the parenchyma will be minimal. The second reason is the structure of the kidney (the cortex contains the glomerulus and convoluted tubules). Special care must be taken when sampling to ensure enough glomeruli have been obtained for evaluation (Brown et al., 2013).

For specific classification of glomerular diseases, renal biopsy samples should be evaluated using light microscopy (LM), transmission electron microscopy (TEM) and immunofluorescence (IF) according to the World Small Animal Veterinary Association-Renal Standardization Study Group (WSAVA-RSSG) (Cianciolo et al., 2016). To be declared suitable for evaluation, a kidney biopsy should contain at least 5-10 glomeruli for LM and additional tissue specimens for TEM and whether to make a definitive diagnosis (Lees et al., 2011; Crivellenti et al., 2018). In a 2008 study, Jankowski et al. reported an average number of 14 glomeruli per sample, even if their cut-off value to ensure histopathological validity was the presence of five glomeruli (Jankowski et al., 2008).
The most common methods to estimate the number of glomeruli in the biopsy sample evolved from eye loupe inspection to light microscopy (Lees et al., 2011). A recent study shows that the most effective method to get an estimate glomerular number is to use a light microscope with lowering of the condenser lens (Costa et al., 2019).

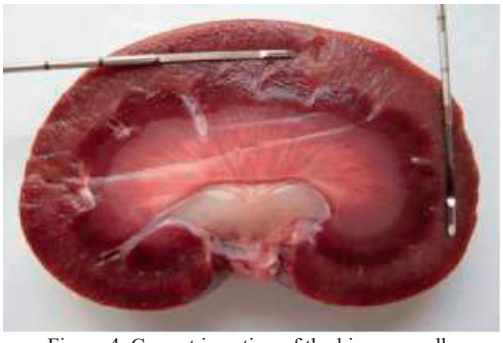

Figure 4. Correct insertion of the biopsy needle (Jankowski et al., 2013)

Whenever possible, the sample should be taken from the caudal or cranial pole of the kidney, as is easier to not accidentally penetrate the medullar tissue. The right kidney is preferred to the left when bilateral pathology is suspected (De Rycke et al., 1999; Brovida, 2003; Nowicki et al., 2005; Vaden, 2004; Rezaie et al., 2008).
The number of core samples required for a valid histopathological examination depends on the type of needle employed and the evaluations that will be performed on the tissue. Using a needle with a short core requires three sampling to ensure an adequate specimen, whereas longer devices (up to several centimeters long) may only need one pass (Yau, 2019). Samples for IF will be frozen or set aside in a special transport solution. The remainder is quickly placed in fixative (formalin or glutaraldehyde) for light LM and TEM and sent to the laboratory. (Vaden, 2004; Walker, 2004).

Required tools and materials vary depending on the technique used. A wide range of dedicated veterinary automated biopsy devices is available. They provide satisfactory renal samples when used properly (Lees et al., 2011). It is recommended to use 14–18 G needles, although no major differences in the quality of the samples were observed between different gauges (Vaden, 2004; Crivellenti et al., 2018).
In human medicine, 14-18 G needles are most commonly employed; 18 G needles are often used in pediatric patients because the internal diameter of the needle is slightly larger than a glomerulus (Tøndel et al., 2012). A recent study from China identified no significant difference in the number of glomeruli obtained or subsequent patient complications between 18 G and 16 G needles (Xie et al., 2020).
The materials, advantages, and disadvantages of each technique will be described below.

The blind or palpation biopsy technique involves sampling after manual localization and immobilization of the kidney through the abdominal wall. In dogs, the right kidney is harder to approach due to its location under the costal arch, but it is more stable puncture is required (Vaden, 2004). The left kidney, even if more mobile can be approached easily due to its anatomical position (Osborne et al., 1971; Vaden, 2004; Jankowski et al., 2013).

The advantage: it is the cheapest biopsy technique because it only requires a biopsy needle.
Disadvantages:
- it is difficult to perform in dogs due to the topography of the internal organs;
- it is challenging to control the biopsy needle in the abdominal cavity, which increases the

risk of complications during the procurement of the specimen (Osborne et al., 1996; Vaden, 2004; Vaden & Brown, 2017).

A keyhole biopsy requires an incision through the abdominal wall, caudal to the right costal arch. Immobilization of the kidney is accomplished with the index finger inserted through the incision. Next, a smaller incision is made in the abdominal wall, through which the biopsy needle is advanced toward the kidney with the help of the operator's fingers (Vaden, 2004; Jankowski et al., 2013).

Advantages of the keyhole biopsy technique:
- it is low-cost as it does not require ultrasound guidance (Stone et al., 1992; Osborne et al., 1996);
- the quality of the tissue samples is good, comparable to that of specimens obtained through laparoscopy (Wise et al., 1989);
- the operator has better control of the biopsy needle compared to a blind biopsy.

Disadvantages:
- this technique can only be used in dogs and only for the right kidney;
- the incision of the abdominal wall is associated with pain (Nowicki & Depta, 2001; Nicpoń et al., 2004; Vaden, 2005).

Ultrasound-guided renal biopsy is currently the least invasive method to obtain cortical tissue specimens in dogs, as well as in humans (Walker, 2004). Ultrasound guidance permits visualization of renal structure and size and enables the correct placement of the biopsy needle (Hager et al., 1985).

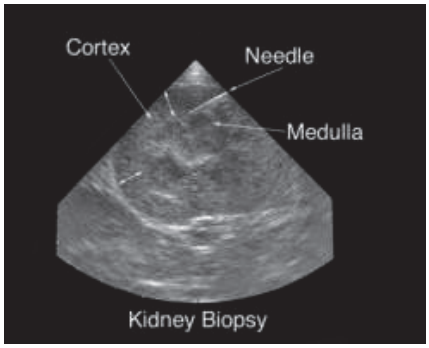

Figure 5. Ultrasound-guided biopsy (Vaden, 2005)

After the kidney is visualized with ultrasonography, the area is clipped and asepticized. A small incision is then made through the skin, through which the needle is advanced toward the renal capsule. The cortical sample is removed using the appropriate technique for each device. It is recommended to apply transabdominal digital pressure to reduce the risk of bleeding (Yamamoto et al., 1991; Bigge et al., 2001; Rawlings et al., 2003; Vaden, 2005; Zatelli et al., 2005).

Advantages:
- it offers high precision in obtaining a suitable specimen with a reduced risk of complications (Lees et al., 2011);
- this technique is relatively economical, rapid and can be performed using most Ultrasound machines (Haaga et al., 1983).

Disadvantage: this method is not recommended in small dogs (adult weight under 5 kg) (Hager et al., 1985).

Laparoscopic biopsy enables the sampling of sterile renal tissue under endoscopic guidance. For better visualization and identification of the organs, it is necessary to introduce a certain amount of gas (usually carbon dioxide) into the abdominal cavity (Grauer et al., 1983; Wise et al., 1989; Nowicki & Lew, 2001; Lew et al., 2003; Vaden, 2005).

Advantages:
- it is a minimally invasive diagnostic technique that provides better visualization of the kidneys and better control of post-biopsy bleeding (Nowicki et al., 2010; Vaden & Brown, 2017);
- it provides excellent tissue samples when 14 gauge double-spring-activated biopsy needles are used (Rawlings et al., 2003). A more recent study showed that the use of biopsy forceps with a 5 mm cup ensures a greater number of glomeruli compared to basic 16-gauge biopsy needles (Park et al., 2017).

Disadvantages:
- it is expensive because it involves special equipment and highly qualified personnel;
- it has additional contraindications: peritonitis, hernia, coagulopathies, obesity, subcutaneous emphysema (Vaden & Brown, 2017; Silvinato et al., 2019).

The open or surgical renal biopsy technique involves performing a laparotomy and

removing a wedge-shaped sample from the renal cortex using a scalpel. In the end, the renal capsule is sutured and digital pressure is applied to control hemorrhage. This method is used only when it is considered that other techniques cannot provide enough cortical tissue (Osborne et al., 1996; Nowicki & Depta, 2001; Vaden et al., 2005; Jankowski et al., 2013).

The advantage: it is the method of choice in dogs under 5 kg, in those with cystic kidney disease or other contraindications (Vaden, 2004).

Disadvantage: being a surgical procedure, it is more invasive than percutaneous techniques; pain associated with the trauma is the most common complication (Vaden & Brown, 2017).

Complications of renal biopsy

From the time of widespread implementation of renal biopsy in dogs until today, the associated complications have been estimated at a rate of 1%-20% (Osborne, 1971; Osborne et al., 1996; Jankowski et al., 2013).

Renal biopsy is a safe procedure and the risk for developing major complications is rare. Minor consequences, nevertheless, are more frequent. They occur due to the chosen technique, patient status, or operator experience and include micro- or macrohematuria, perirenal hematoma, and pain. All these adverse events can be safely managed without further complications for the patient. A study conducted in 2004 in a group of young dogs without renal disease showed that biopsy lesions were minor and the glomerular filtration rate was not affected after biopsy (Groman et al., 2004). Another study proved that ultrasound-guided biopsy had minimal complications in healthy dogs (Rezaie et al., 2008). To minimize the risk of post-biopsy complications, the patient should be hospitalized 24 hours. Isotonic fluids should be given to ensure diuresis and careful monitoring of PCV for possible bleeding should be done (Vaden & Brown, 2017).

However, the reports are radically different when the biopsy is performed on dogs with kidney disease. The most commonly reported complications of renal biopsy are presented in the box below.

Reported complications of renal biopsy (Vaden et al., 2004)
Arteriovenous fistula formation
Biopsy of nonrenal tissue (eg. liver, adrenal gland, fat, muscle, connective tissue, spleen)
Cyst formation
Death
Hemorrhage
Microscopic hematuria
Macroscopic hematuria
Perirenal hematoma
Intrarenal hematoma
Lacerated renal artery or vein
Intra-abdominal hemorrhage caused by laceration of other organs or vessel
Hydronephrosis
Infarction and thrombosis
Infection
Scar formation and fibrosis

Discussion on the utility and limitations of renal biopsy in veterinary medicine

Renal biopsy is indicated in dogs with various kidney diseases when identifying the underlying condition would improve the therapeutic management and patient status or when an accurate prognosis is required. For example, renal interstitial fibrosis is a poor prognostic indicator because it is associated with irreversible renal injury and nephron loss (Lees et al., 2011; Cianciolo et al., 2013; Vaden & Brown, 2017). This procedure is valuable in young dogs who develop chronic kidney disease and in breeds prone to familial (soft-coated Wheaten Terrier, Samoyed) or inherited kidney disease (Samoyed, Bull Terrier, English Cocker Spaniel, Shih-Tzu) (Lees, 1996).

Concerning acute kidney injury, renal biopsies can be evaluated using light microscopy and routine stains to identify tubular causes. This method provides an accurate prognosis based on the appearance of the renal tissue and the integrity of the tubular basement membrane. The most common biopsy findings associated with tubular AKI are acute tubular necrosis and acute tubulointerstitial nephritis. Nonetheless, TEM and IF should be used to identify or rule out a possible glomerular cause of AKI (Vaden, 2004; Vaden & Elliott, 2016; Aresu et al., 2017).

Glomerular disease is clinically suspected when severe and persistent proteinuria is present. In dogs, the most sensitive method to assess glomerular proteinuria is to evaluate the urine protein to creatinine ratio (UPC). A value higher than 2 in a urine sample with inactive sediment is highly suggestive of glomerular disease (Lees et al., 2005; Vaden & Elliott, 2016). The recognition of several forms of glomerular disease was possible by properly performed and analyzed kidney biopsies (Polzin, 2009).

Several clinical trials were conducted in the past years by experienced veterinary nephropathologists (Cianciolo et al., 2013; Schneider et al., 2013; Crivellenti et al., 2018; Vessieres et al., 2019). The results of two extensive retrospective studies will be presented to emphasize the utility of performing renal biopsies in canine nephrology.

One of the most recent studies on this subject was published by Crivellenti et al., in 2018. Their objective was to identify factors affecting the diagnostic quality of renal biopsy samples from dogs with suspected kidney disease. Their team analyzed over 500 renal biopsy specimens from dogs suspected of various kidney diseases that were submitted to the International Veterinary Renal Pathology Service (IVRPS). Out of the 522 samples, 30 were declared non-diagnostic while the remaining 492 were considered histopathologically valid biopsy tissue. They diagnosed immune-mediated glomerulonephritis in 212 dogs, focal segmental to global glomerulosclerosis in 96 dogs, amyloidosis in 64 dogs, tubulointerstitial disease in 43 dogs, non-immune-mediated nephropathy in 38 dogs, glomerulopathy not otherwise specified in 34 dogs, and normal kidney in 5 dogs (Crivellenti et al., 2018). By evaluating these results one can conclude that renal biopsy in dogs is an indispensable tool in the diagnosis of kidney disease and its underlying conditions.

A larger study on the value of the kidney biopsy in dogs was published in 2015 by members of the WSAVA-RSSG. The study identified specific immune complexes or amyloidosis (using LM, IF, and TEM) and to create a guideline for the appropriate evaluation of renal biopsy specimens. The study included 960 canine renal biopsy samples from the IVRPS and Utrecht Veterinary Nephropathology Service. They classified glomerular disease according to biopsy findings into three broad categories based on their significance for prognosis and treatment: amyloidosis, immune complex-mediated glomerulonephritis, and non-immune complex-mediated glomerulonephritis (Cianciolo et al., 2013). The guidelines they provided in this paper optimize the diagnostic workflow in veterinary nephropathology. This study reinforces the utility of kidney biopsy as a key element in the ongoing research on kidney disease in dogs. This finally translates into the necessity of accurate morphological diagnosis to guide the clinical management of dogs with various renal disorders. For example, various diseases and pathophysiological mechanisms can lead to nephrotic syndrome, nephritic syndrome, and AKI, but they can have vastly different prognoses and therapies. These recommendations can guide the decision of renal biopsy in patients with proteinuria as well as the use of immunosuppressive drugs in those patients where renal biopsies were not performed (Cianciolo et al., 2013). Unfortunately, the histopathological findings with light microscopy are not always specific and devising a definitive diagnosis becomes difficult (Dhaun et al., 2014). In these complex cases of kidney disease, complete evaluations (using LM, IF and TEM) by experienced nephropathologists are needed to obtain an accurate diagnosis (Schneider et al., 2013).

CONCLUSIONS

Renal biopsy is an invasive diagnostic technique that is essential for the diagnosis of various kidney disorders in dogs. Accurate identification of the underlying disease can be made through the complete evaluation of the renal tissue; this procedure is a prerequisite for an informed prognosis, decision-making, and specific therapy.

Renal biopsy is a safe procedure and the risk of major complications is low when an appropriate biopsy technique is used. Minor side effects of the procedure occur frequently, but they can be managed and do not usually further harm the patient.

REFERENCES

Adams Aresu, L., Martini, V., Benali, S. L., Brovida, C., Cianciolo, R. E., Dalla Riva, R., Trez, D., Van Der Lugt, J. J., Van Dongen, A., & Zini, E. (2017). European Veterinary Renal Pathology Service: A Survey Over a 7-Year Period (2008-2015). *Journal of veterinary internal medicine*, *31*(5), 1459–1468.

Banzato, T. et al. (2017). Relationship of diagnostic accuracy of renal cortical echogenicity with renal histopathology in dogs and cats, a quantitative study, *BMC Veterinary Research*, 13:24.

Bigge, L. A., Brown, D. J., & Penninck, D. G. (2001). Correlation between coagulation profile findings and bleeding complications after ultrasound-guided biopsies: 434 cases (1993-1996). *Journal of the American Animal Hospital Association,* 37(3), 228–233.

Brovida, C. (2003). Kidney Biopsy: How and When to Perform It? *28th World Congress of the World Small Animal Veterinary Association Bangkok*, Thailand, October 24-27, 2003.

Cianciolo, R. E., Brown, C. A., Mohr, F. C., et al. (2013). Pathologic evaluation of canine renal biopsies: methods for identifying features that differentiate immune-mediated glomerulonephritides from other categories of glomerular diseases. *Journal of Veterinary Internal Medicine,* 27, S10–S18.

Cianciolo, R. E., Mohr, F. C., Aresu, L., Brown, C. A., James, C., Jansen, J. H., Spangler, W. L., van der Lugt, J. J., Kass, P. H., Brovida, C., Cowgill, L. D., Heiene, R., Polzin, D. J., Syme, H., Vaden, S. L., van Dongen, A. M., & Lees, G. E. (2016). World Small Animal Veterinary Association Renal Pathology Initiative: Classification of Glomerular Diseases in Dogs. *Veterinary pathology*, 53(1), 113–135.

Costa, C. A. L., Lima, C. S. de, Uscategui, R. A. R., Silva, G. E. B., & Crivellenti, L. Z. (2019). Methods for glomerular quantification in dogs: a comparative study. *Ciência Rural,* 49(3).

Crivellenti, L. Z., Cianciolo, R., Wittum, T., Lees, G. E., & Adin, C. A. (2018). Associations of patient characteristics, disease stage, and biopsy technique with the diagnostic quality of core needle renal biopsy specimens from dogs with suspected kidney disease. *Journal of the American Veterinary Medical Association*, 252(1), 67–74.

De Rycke, L.M., van Bre,e H.J. and Simoens, P.J. (1999). Ultrasound-guided tissue-cor biopsy of liver, spleen and kidney in normal dogs. *Vet Radiol Ultrasound*, 40: 294-299.

Dhaun, N., Bellamy, C. O., Cattran, D. C., & Kluth, D. C. (2014). Utility of renal biopsy in the clinical management of renal disease. *Kidney international*, 85(5), 1039–1048.

Edebohls G. M. (1905). The surgical treatment of Bright's disease. *Am J Med Sci.* 1905;129:708.

Grauer, G.F., Twedt, D.C., Mero, K.N. (1983). Evaluation of laparoscopy for obtaining renal specimens from dogs and cats. *J Am Vet Med Assoc,* v. 183, n. 6. p. 677-679.

Groman, R. P., Bahr, A., Berridge, B. R., & Lees, G. E. (2004). Effects of serial ultrasound-guided renal biopsies on kidneys of healthy adolescent dogs. Veterinary radiology & ultrasound: T*he Official Journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association*, 45(1), 62–69.

Haaga, J. R., LiPuma, J. P., Bryan, P. J., Balsara, V. J. & Cohen, A. M. (1983). Clinical comparison of small- and large-caliber cutting needles for biopsy. *Radiology*, 146(3), 665–667.

Hager, D.A, Nyland T.G. and Fisher, P. (1985). Ultrasound-guided biopsy of the canine liver, kidney, and prostate. *Vet Radiol*, 26: 82-88.

Hall, J. A, Yerramilli, M., Obare, E., Yerramilli, M., Jewell, D.E. (2014). Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *J Vet Intern Med*. 2014;28(6):1676–1683.

International Renal Interest Society. IRIS staging of CKD - modified 2019. http://www.iris-kidney.com/pdf/IRIS_2019_Staging_of_CKD_09Febr21.pdf.

IRIS Canine GN Study Group Standard Therapy Subgroup, Brown, S., Elliott, J., Francey, T., Polzin, D., & Vaden, S. (2013). Consensus recommendations for standard therapy of glomerular disease in dogs. *Journal of veterinary internal medicine*, 27 Suppl 1, S27–S43.

IRIS Canine GN Study Subgroup on Immunosuppressive Therapy Absent a Pathologic Diagnosis, Pressler, B., Vaden, S., Gerber, B., Langston, C., & Polzin, D. (2013). Consensus guidelines for immunosuppressive treatment of dogs with glomerular disease absent a pathologic diagnosis. *Journal of veterinary internal medicine*, 27 Suppl 1, S55–S59.

Iversen P., Brun C. (1951). Aspiration biopsy of the kidney. *Am J Med*. 1951;11:324–330.

Jankowski, M., Hałoń, A., Kubiak, K., Glińska-Suchocka, K., Grzegory, M. (2013). Kidney biopsy in dogs and cats. *Pak Vet J*, 33(2): 133-138.

Jankowski, M., Hałoń, A., Kubiak, K., Spużak, J., Nicpoń, J. (2008). Usefulness of oligobiopsy and histopathological examination for the diagnosis of glomerulonephritis in dog. *Medycyna Wet*, 64: 1421-1425.

Kark R. M., Muehrcke R. C. (1954) Biopsy of the kidney in prone position. *Lancet* 266:1047–1049.

Lattimer, K. S. (2011). Duncan & Prasse's Veterinary Laboratory Medicine: Clinical Pathology, Fifth Edition, Wiley-Blackwell, John Wiley & Sons, Inc., Ames, Iowa, USA

Lees, G. E. (1996). Congenital Renal Diseases. Veterinary Clinics of North America: *Small Animal Practice*, 26(6), 1379–1399.

Lees, G. E., Brown, S. A., Elliott, J., Grauer, G. E., Vaden, S. L., & American College of Veterinary Internal Medicine (2005). Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal). *Journal of veterinary internal medicine*, 19(3), 377–385.

Lees, G. E., Cianciolo, R., Clubb, F. (2011). Renal Biopsy and Pathologic Evaluation of Glomerular Disease. Topics in Companion Animal Medicine 26(3):143–53.

Levey, A. S., William, B. et al. (2013). Definition and Classification of Kidney Diseases. *Am J Kidney Dis*. 2013;61(5):686–688.

Lindgren, P. G. (1982). Percutaneous needle biopsy: a new technique. *Acta Radiol*. 1982;23:653–656.

Littman, M.P., Daminet, S., Grauer, G., Lees, G. and Dongen, A. (2013). Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease. *Journal of Veterinary Internal Medicine,* 27, 19–26.

Merlini, G. & Pozzi, C. (2007). Mechanisms of Renal Damage in Plasma Cell Dyscrasias: *An Overview. Contributions to nephrology*. 153. 66–86.

Muehrcke R. C., Kark R. M., Pirani C. L. (1955). Biopsy of the kidney in the diagnosis and management of renal disease*. N Engl J Med* 253:537–546.

Nabity, M. B., Lees, G. E., Boggess, M. M., Yerramilli, M., Obare, E., Yerramilli, M., Rakitin, A., Aguiar, J., & Relford, R. (2015). Symmetric Dimethylarginine Assay Validation, Stability, and Evaluation as a Marker for the Early Detection of Chronic Kidney Disease in Dogs. *Journal of veterinary internal medicine*, 29(4), 1036–1044.

Nowicki, M., Rychlik A., Nieradka, R., Kander, M., et al. (2010). Usefulness of laparoscopy guided renal biopsy in dogs. *Polish J Ve*t Sci, 13: 363-371.

Nowicki, M. and Depta, A. (2001). Biopsja nerek u psów i kotów. *Medycyna Wet*, 57: 97–101.

Nowicki, M. and Lew, M. (2001). Laparoskopowa biopsja nerek u psów. *Magazyn Wet*, 10: 13-14.

Nowicki, M., Depta A., Rychlik A., Nieradka R., Kander M. (2005). Badania porównawcze różnych metod biopsji nerek u psów. *Medycyna Wet*, 61: 405–407.

Osborne C.A. (1971). Clinical evaluation of needle biopsy of the kidney and its complications in dog and cat. *J Am Vet Med Assoc*, 158: 1213–1228.

Osborne, C.A., Bartges, J.W., Polzin, D.J, Lulich, J.P., Johnston, G.R., Cox V. (1996). Percutaneous needle biopsy of kidney. Indication, application, technique, and complication. *Vet Clin North Am Small Anim Pract*, 26: 1461–1504.

Osborne, C.A. (2010). Why, when and how to perform percutaneous renal biopsies. DVM 360 Journal. https://www.dvm360.com/view/why-when-and-how-perform-percutaneous-renal-biopsies, "accessed on Feb. 1st, 2021".

Paone, D. B., Meyer, L. (1981). The effect of biopsy on therapy in renal disease. *Arch Intern Med* 141:1039—1041, 1981.

Park, J., Lee, J., Lee, H. B., & Jeong, S. M. (2017). Laparoscopic kidney biopsy in dogs: Comparison of cup forceps and core needle biopsy. *Veterinary surgery: VS*, 46(2), 226–232.

Polzin, D. J. (2009) The Role of Renal Biopsy in Dogs with Proteinuric Kidney Disease--What Are We Learning? *World Small Animal Veterinary Association World Congress Proceedings*, 2009.

Pressler, B., Vaden S. et al. (2013). Consensus Guidelines for Immunosuppressive Treatment of Dogs with Glomerular Disease Absent a Pathologic Diagnosis, *Consensus Statement J Vet Intern Med* 2013;27:S55–S59

Rawlings, C. A., Diamond, H., Howerth, E. W., Neuwirth, L., & Canalis, C. (2003). Diagnostic quality of percutaneous kidney biopsy specimens obtained with laparoscopy versus ultrasound guidance in dogs. *Journal of the American Veterinary Medical Association*, 223(3), 317–321.

Rezaie, A., Mousavi, G., Mohajeri, D., Asadnasab, G. (2008). Complications of the ultrasound-guided needle biopsy of the kidney in dogs. *J Anim Vet Adv,* 7: 1207-1213.

Salama, A. D., Cook, H. T. (2011). The renal biopsy. In: Brenner and Rector's - The Kidney, 9th ed Philadelphia, PA: Elsevier Saunders, 1006–1015.

Schneider, S. M., Cianciolo, R. E., Nabity, M. B., Clubb, F. J., Jr, Brown, C. A., & Lees, G. E. (2013). Prevalence of immune-complex glomerulonephritides in dogs biopsied for suspected glomerular disease: 501 cases (2007-2012). *Journal of veterinary internal medicine*, 27 Suppl 1, S67–S75.

Silvinato, A., Bernardo, W. M., & Branco, A. W. (2019). Laparoscopic renal biopsy. *Revista Da Associação Médica Brasileira*, 65(2), 100–104.

Tøndel, C., Vikse, B. E., Bostad, L., & Svarstad, E. (2012). Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988-2010. *Clinical journal of the American Society of Nephrology: CJASN*, 7(10), 1591–1597.

Vaden S. L., Brown C. (2017). BSAVA Manual of Canine and Feline Nephrology and Urology, Chapter 13, p. 161-171.

Vaden, S. L. (2004). Renal biopsy: methods and interpretation. *Veterinary Clinics of North America: Small Animal Practice*, 34(4), 887–908.

Vaden, S. L. (2005). Glomerular disease. In: Ettinger SJ, Feldman EC, editors. Textbook of Veterinary Internal Medicine. 6th ed. St Louis, Missouri: Saunders (Elsevier), 1786–1800.

Vaden, S. L., & Elliott, J. (2016). Management of Proteinuria in Dogs and Cats with Chronic Kidney Disease. *Veterinary Clinics of North America: Small Animal Practice*, 46(6), 1115–1130.

Vessieres, F., Cianciolo, R. E., Gkoka, Z. G., Kisielewicz, C., Bazelle, J., Seth, M., Adam, F. H., Matiasovic, M., Aresu, L., Jepson, R. E., & Walker, D. J. (2019). Occurrence, management and outcome of immune-complex glomerulonephritis in dogs with suspected glomerulopathy in the UK. *The Journal of small animal practice*, 60(11), 683–690.

Visconti, L., Cernaro, V., Ricciardi, C. A., Lacava, V., Pellicanò, V., Lacquaniti, A., Buemi, M., & Santoro, D. (2016). Renal biopsy: Still a landmark for the nephrologist. *World journal of nephrology*, 5(4), 321–327.

Walker P. D. (2009). The Renal Biopsy. *Arch Pathol Lab Med.* 2009;133:181–188.

Wise, L. A., Allen, T. A., & Cartwright, M. (1989). Comparison of renal biopsy techniques in dogs. *Journal of the American Veterinary Medical Association,* 195(7), 935–939.

Xie, W., Xu, J., Xie, Y. et al. (2020). Adequacy and complication rates of percutaneous renal biopsy with 18- vs. 16-gauge needles in native kidneys in Chinese individuals. *BMC Nephrol* 21, 337.

Yamamoto, K., Ishiyama, N., Yamaga, Y., Hayashi, T., & Kagota, K. (1991). Ultrasound-guided techniques for biopsy of the kidney of the medium-sized dog. *The Journal of Veterinary Medical Science,* 53(2), 345–346.

Yau, T. (2019). Approach to Renal Biopsy. In: Trachtman H., Herlitz L., Lerma E., Hogan J. (eds) Glomerulonephritis. Springer, Cham.

Yerramilli, M., Giosi F. et al. (2016). Kidney Disease and the Nexus of Chronic Kidney Disease and Acute Kidney Injury-The Role of Novel Biomarkers as Early and Accurate Diagnostics. *Vet Clin Small Anim* 46 (2016) 961–993.

Zotti A., Banzato T. et al. (2015). Correlation of renal histopathology with renal echogenicity in dogs and cats: an ex-vivo quantitative study. *BMC Vet Res*. 2015;11:99.