Clinical outcome after diagnosis of hemophilia A in dogs

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Objective—To evaluate the clinical course of dogs with hemophilia A (factor VIII deficiency) and to determine whether factor VIII coagulant activity (FVIII:C) was associated with severity of clinical signs and outcome.

Design—Survey study.

Sample—Respondent information for 39 client-owned dogs with FVIII deficiency.

Procedures—Information was obtained via a survey distributed to the American College of Veterinary Internal Medicine and American College of Veterinary Emergency and Critical Care email list serves and to the Veterinary Information Network community to identify dogs with hemophilia A (FVIII:C ≤ 20%). Severity of FVIII deficiency was classified as mild (FVIII:C, 6% to 20%), moderate (FVIII:C, 2% to 5%), or severe (FVIII:C, < 2%).

Results—Data for 39 dogs (38 males and 1 female) were compiled. Mixed-breed dogs, German Shepherd Dogs, and Labrador Retrievers were most commonly affected. In most (34/39) dogs, disease was diagnosed at < 1 year of age. Bleeding associated with teething, minor trauma, vaccination, and elective surgical procedures most commonly prompted FVIII:C testing. Affected dogs had similar signs of spontaneous hemorrhage regardless of the magnitude of FVIII deficiency. Four dogs were euthanized without treatment at the time of diagnosis. Thirty dogs received ≥ 1 blood transfusion; FVIII:C did not appear to influence transfusion requirements.

Conclusions and Clinical Relevance—Results indicated that dogs with hemophilia A have variations in clinical course of the disease and may have a good long-term prognosis. Residual FVIII:C may not be useful for predicting severity of clinical signs, transfusion needs, or long-term prognosis. (*J Am Vet Med Assoc* 2014;245:677–683)

Hemophilia A is an X-linked recessive bleeding disorder caused by deficiency or dysfunction of FVIII. Although classically inherited in an X-linked familial pattern in both humans and dogs, de novo mutations of the FVIII gene located on the long arm of the X chromosome may also occur, which results in sporadic cases in previously unaffected families.[1,2]

Clinical severity of hemophilia A in humans, as defined by frequency of bleeding events and transfusion needs, is inversely related to residual FVIII:C,[3] but to our knowledge, no such population studies have been reported for dogs. Factor VIII deficiency in humans is classified as mild (FVIII:C, 6% to 20%), moderate (FVIII:C, 2% to 5%), or severe (FVIII:C, < 2%).[2–4] Severely affected humans have frequent episodes of spontaneous hemorrhage that require periodic FVIII replacement therapy, which is most often administered as FVIII concentrates and rarely as transfusions of cryoprecipitate, FFP, or fresh whole blood. Recipients of multiple transfusions may develop anti-FVIII antibodies that bind to transfused FVIII, thereby inhibiting coagulant activity; this has been verified in both humans and dogs.[5–8]

Abbreviations

FFP	Fresh-frozen plasma
FVIII	Factor VIII
FVIII:C	Factor VIII coagulant activity
VIN	Veterinary Information Network

Hemophilia A in dogs is most commonly suspected because of episodes of clinical hemorrhage and is confirmed by identification of a specific deficiency of FVIII:C in the absence of deficiencies of other coagulation factors. Clinical signs in dogs with hemophilia A include subcutaneous hematoma and intermittent bleeding at an injection site, prolonged bleeding at eruption sites of deciduous teeth, hematoma formation or prolonged bleeding after surgery, abnormal bleeding from minor wounds, and lameness attributable to hemarthrosis.[9] Although dogs with hepatic synthetic failure and consumptive and dilutional coagulopathies may have markedly low FVIII:C, these patients typi-

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cally have obvious underlying disease and combined deficiencies of coagulation factors and fibrinogen that differentiate them from dogs with hemophilia A.

The long-term management and survival rate of dogs with hemophilia A maintained in a research colony have been described[6]; however, to the authors' knowledge, no comparable information is available regarding client-owned pet dogs. The objectives of the study reported here were to describe the long-term outcome for a group of dogs with hemophilia A at clinical practices and to determine the relationship between FVIII:C at diagnosis and severity of clinical signs and prognosis.

Materials and Methods

Sample—An Internet survey[a] was created with an online survey tool and distributed via the American College of Veterinary Internal Medicine small animal internal medicine email list serve and the American College of Veterinary Emergency and Critical Care email list serve. Responses were received between January 2012 and December 2013. The survey was replicated, modified by use of a second survey tool through the VIN, and distributed to 127,866 VIN members. Responses by VIN members to the survey were acquired between May and October 2012. The survey obtained information about dogs with hemophilia A at clinical practices, as determined on the basis of FVIII deficiency (defined as FVIII:C ≤ 20%).

Data collected included patient signalment (date of birth, age at diagnosis, breed, sex, and reproductive status), FVIII:C, and the circumstances surrounding diagnosis (specifically, if FVIII deficiency was identified as a result of clinical signs of hemorrhage or on the basis of results of a screening test). Respondents also were asked to describe the therapeutic interventions, if any (specifically, the number and type of blood products transfused). Finally, respondents were asked how they would advise owners if they identified dogs with hemophilia A in the future. Responses were excluded if the FVIII:C was > 20% or was not specified. Additionally, dogs were excluded if there were inconsistencies in the data reported or test results could not be confirmed by review of the medical records by the investigators.

In an attempt to further verify diagnoses, signalment and test results of the dogs were cross-referenced with information in a database of hemophilia A cases maintained at a referral coagulation testing laboratory.[b] The laboratory criteria for the diagnosis of hemophilia A included FVIII:C ≤ 20% in a sample with specific prolongation of the activated partial thromboplastin time, prothrombin time and fibrinogen concentration within respective reference limits, factor IX activity within reference limits or FVIII:C ≤ 20%, and values for other coagulation factors in the intrinsic and contact pathways (factors IX, XI, and XII) within respective reference limits. Because of the sex-linked nature of the familial form of the disease, respondents who reported hemophilia A in a female dog were subsequently contacted to verify the diagnosis and, in an attempt to obtain a current blood sample from these dogs, to repeat FVIII:C analysis.

Data analysis—Severity of FVIII deficiency was classified on the basis of human criteria as mild (FVIII:C, 6% to 20%), moderate (FVIII:C, 2% to 5%), or severe (FVIII:C, < 2%).[3] A χ^2 test was used to compare the proportion of dogs with mild, moderate, and severe FVIII deficiency that had spontaneous bleeding as well as to compare differences in the types of blood products and total number of transfusions among groups. Additionally, the proportion of dogs alive at the time of the survey versus the proportion of dogs that died or were euthanized because of FVIII deficiency was compared among groups. Values of $P < 0.05$ were considered significant.

Results

Responses were received for 59 dogs with FVIII deficiency. Twenty dogs were excluded; 17 were excluded because of missing values for FVIII:C or a FVIII:C > 20%, 1 dog was a duplicate that had already been reported, and 2 female dogs originally considered deficient for FVIII did not have hemophilia A on further review. Those 2 female dogs represented a sexually intact Doberman Pinscher that was excluded because it was evident from coagulation test results that the dog had von Willebrand disease, rather than hemophilia A, and a Labrador Retriever that had 1 report of a low FVIII:C, but subsequent testing at 2 laboratories did not confirm the low FVIII:C. Therefore, data for 39 dogs with FVIII:C ranging from 0% to 20% were included in the final analysis. Hemophilia A was diagnosed in these dogs between 1983 and 2013.

Of the 39 dogs, 30 were sexually intact males, 8 were castrated males, and 1 was a spayed female. The FVIII:C of the spayed female (a Yorkshire Terrier) was verified by medical record review and confirmation by comparison with information in the referral coagulation testing laboratory database; however, this dog was euthanized because of bleeding shortly after the diagnosis and thus was not available for repeated FVIII:C analysis.

Thirty-four dogs were < 1 year old at the time of diagnosis. Of the 5 dogs > 1 year old at the time of diagnosis, median age was 25 months (range, 16 to 56 months). A variety of breeds were represented; German Shepherd Dogs and German Shepherd Dog crossbreds (n = 5) and Labrador Retrievers and Labrador Retriever crossbreds (4) were the most common. Other breeds included American Pit Bull Terriers (n = 2), Beagles (2), Dachshunds and Dachshund crossbreds (3), Parson Russell Terriers and Parson Russell Terrier crossbreds (2), and West Highland White Terriers (3). One mixed-breed dog of unidentified breed origin was included, as were 1 each of Australian Kelpie, Bassett Hound, Boston Terrier, Chihuahua, Chow Chow, English Bulldog, Golden Retriever, Japanese Chin, Miniature Schnauzer, Pug-Beagle crossbred, Redbone Coonhound, Rhodesian Ridgeback, Rough Collie, Saint Bernard, Shih Tzu, Yorkshire Terrier, and Welsh Corgi.

Ten dogs were classified as mildly affected, 13 as moderately affected, and 16 as severely affected. Clinical signs were variable (**Table 1**). Spontaneous bruising or hematoma formation was the most common initial sign and was seen in 15 of 39 dogs. Other commonly observed initial clinical signs included excessive or unanticipated bleeding during an elective surgical proce-

dure, gingival bleeding during loss of deciduous teeth, bleeding after minor trauma, and spontaneous bleeding into a body cavity or organ. Additional initial bleeding events described as resulting from FVIII deficiency that could not be classified in one of the categorical choices included hematochezia, hematemesis, scleral hemorrhage, and epistaxis. Comparison of dogs with mild, moderate, and severe FVIII deficiency revealed no significant ($P = 0.19$) differences in the proportion of dogs with spontaneous bleeding.

The site of bleeding was variable (**Table 2**). Subcutaneous tissues were the most common site of bleeding (n = 26). Other common sites of bleeding included joints (n = 20), surgical sites (10), and gums (14). Other sites of bleeding included the trachea, nasal passages, and penile parenchyma. Severity of FVIII deficiency did not appear to be associated with the site of bleeding, although this was not compared statistically because of the small sample size for each location.

Owners of 35 of 39 (90%) dogs elected to start treatment for their pets after diagnosis of hemophilia A, and 4 opted for euthanasia. Three of 4 dogs euthanized had a FVIII:C < 2%, and the other euthanized dog had a FVIII:C of 2%. One survey respondent reported that euthanasia was based on guidance provided by the internal medicine service of a local referral practice.

Blood products were transfused in 30 of 35 (86%) dogs that were treated. Responses to survey questions about transfusion were summarized (**Table 3**). When considering how often transfusions were required, respondents indicated that most dogs required only a single transfusion (n = 10) or transfusion every few months (12). Fewer dogs received multiple transfusions in a single day (n = 3) or a transfusion monthly (2), weekly (1), yearly (1), or every few years (1). Fresh-frozen plasma was transfused most commonly to dogs with hemophilia A (n = 22 transfusions); fewer transfusions consisted of cryoprecipitate (9), fresh

Table 1—Number of initial bleeding events by site and trigger for dogs with hemophilia A categorized by residual FVIII:C.

Nature of bleeding	Mild deficiency (n = 10)	Moderate deficiency (n = 13)	Severe deficiency (n = 16)	All dogs (n = 39)
Excessive or uncontrolled bleeding associated with a triggering event				
Loss of deciduous teeth	4	5	4	13
Minor trauma	3	5	4	12
Elective surgery with hematoma or bruise	3	2	3	8
Venipuncture or IV catheter site	0	0	2	2
Nail trimming	0	0	1	1
Spontaneous bleeding				
Bruise or hematoma in subcutaneous tissues without known cause	5	2	8	15
Body cavity or organ	3	4	6	13
Other	2	1	6	9
Total*	**20**	**19**	**34**	—

Severity of FVIII deficiency was classified on the basis of human criteria as mild (FVIII:C, 6% to 20%), moderate (FVIII:C, 2% to 5%), or severe (FVIII:C, < 2%).
*Dogs may have had > 1 event. — = Not applicable.

Table 2—Number of bleeding events at various anatomic sites for dogs with hemophilia A categorized by residual FVIII:C.

Site of bleeding	Mild deficiency (n = 10)	Moderate deficiency (n = 13)	Severe deficiency (n = 16)	All dogs (n = 39)
Subcutaneous tissues (bruise or hematoma)	6	10	10	26
Joints (hemarthropathy)	6	5	9	20
Surgical site	2	3	5	10
Gums	3	5	6	14
Wounds	0	2	4	6
Gastrointestinal tract	1	3	2	6
Peritoneal cavity	1	2	2	5
Pleural cavity or mediastinum	0	2	3	5
Brain or spinal cord	0	1	2	3
Nails (after trimming)	0	1	2	3
Lungs	0	0	2	2
Venipuncture or IV catheter site	0	0	2	2
Retroperitoneal cavity	0	1	1	2
Other	1	0	4	5
Total*	**20**	**35**	**54**	—

— = Not applicable.
See Table 1 for remainder of key.

whole blood (5), and packed RBCs (10). There was no significant difference among groups with regard to the type of blood products transfused ($P = 0.97$) or the total number of transfusions required ($P = 0.43$).

Outcomes for the 35 dogs that received treatment (ie, not euthanized at the time of diagnosis) were summarized (**Figure 1**). Treated dogs had a median follow-up time of 11 months (range, 1 month to 10 years). Approximately half (18/35) of the dogs not euthanized at the time of diagnosis were alive and being treated at the time of the survey; median follow-up time for those 18 dogs was 1.5 years (range, 1 month to 9 years). Seven dogs were euthanized because of FVIII deficiency, and 5 dogs died as a result of bleeding consequences from FVIII deficiency. Four dogs were lost to follow-up (2 each from the mild and severe FVIII:C groups). This included 1 dog for which ownership was transferred to a pharmaceutical company. One dog in the moderate FVIII:C group was euthanized after developing myelopathy; it was listed separately because it was unclear whether this was a consequence of hemorrhage from hemophilia A.

To better understand outcomes of the dogs with hemophilia A that were treated, outcome was also analyzed by FVIII:C category. The outcomes of dogs with mild, moderate, and severe FVIII deficiency, relative to the time of the survey, were determined (Figure 1).

Table 3—Transfusion interval, type of blood product administered, and total number of transfusions administered to dogs with hemophilia A categorized by residual FVIII:C.

Variable	Mild deficiency (n = 10)	Moderate deficiency (n = 13)	Severe deficiency (n = 16)	All dogs (n = 39)
Transfusion interval				
Never transfused	3	0	2	5
Only a single transfusion	1	5	4	10
Multiple transfusions per day	2	0	1	3
Weekly	0	1	0	1
Monthly	0	1	1	2
Every few months	4	3	5	12
Yearly	0	1	0	1
Every few years	0	1	0	1
Type of blood product				
Fresh whole blood	1	2	2	5
Packed RBCs	2	5	3	10
FFP	6	9	7	22
Cryoprecipitate	1	5	3	9
Total No. of transfusions required				
0	3	0	2	5
1	1	5	3	9
2–5	3	2	5	10
6–10	1	3	0	4
> 10	2	2	3	7

No significant differences were detected among groups for type of blood product ($P = 0.97$) or number of transfusions ($P = 0.43$).
See Table 1 for remainder of key.

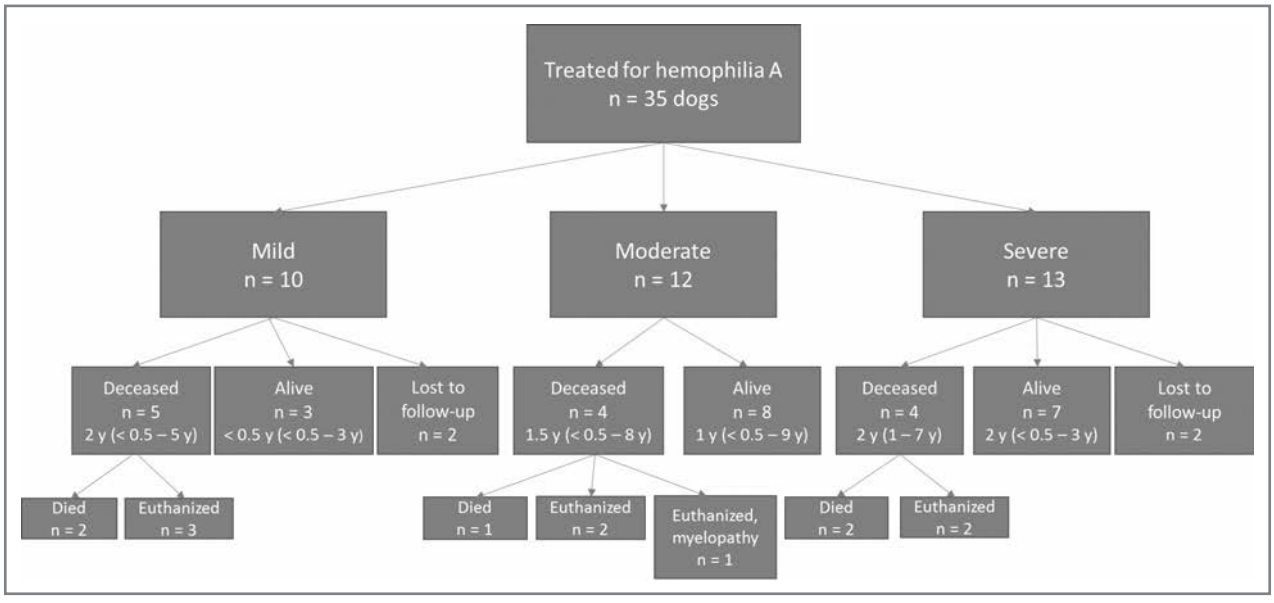

Figure 1—Outcome and duration of treatment for dogs with hemophilia A that received treatment after the initial diagnosis, by category of FVIII:C. Outcomes represent results for dogs at the time of the survey. Severity of FVIII deficiency was classified as mild (FVIII:C, 6% to 20%), moderate (FVIII:C, 2% to 5%), or severe (FVIII:C, < 2%). Duration of treatment is reported as median (range).

Severity of FVIII deficiency was not significantly (P = 0.24) associated with whether dogs were alive at the time of the survey versus died or were euthanized because of FVIII deficiency.

Survey responses for dealing in the future with the decision to treat or euthanize a dog with hemophilia A revealed that 23 of 39 respondents would unconditionally recommend treatment. No respondents recommended euthanasia at the time of diagnosis without also providing additional recommendations and conditions in the comments section. These responses were best classified as recommending treatment for appropriate patient and owner conditions. Concerns cited by respondents included owner finances (n = 6), owner commitment (5), concurrent illness (1), response to treatment (2), level of deficiency (2), and site of bleeding events (3). Of the veterinarians who euthanized the 4 dogs without treatment, 1 would recommend treatment in the future to owners of dogs with hemophilia A, and 3 would recommend euthanasia on the basis of severity of clinical signs and the owners' finances and ability to manage the medical needs of the pet.

Discussion

An Internet survey of veterinary clinicians was used to determine characteristics of a large group of dogs with hemophilia A. Of the 39 dogs with confirmed hemophilia A, 18 were alive and receiving treatment at the time of the survey in the present study. For the 35 dogs that were not euthanized at the time of diagnosis, median follow-up time was 11 months (range, 1 month to 10 years), which suggested an acceptable long-term outcome for hemophilia A. This may have underestimated the expected life span after a diagnosis of hemophilia A given that 18 of the 35 dogs were still alive at the time of the survey. We did not find an association between the FVIII:C at the time of diagnosis and the severity of clinical signs (as assessed by spontaneous bleeding and type and number of transfusions received) or outcome in this population of dogs, which suggested that prognosis should not be made solely on the basis of FVIII:C.

The survey was targeted to 3 large cohorts of clinicians with the goal of obtaining a large sample population of dogs with this rare condition. Furthermore, a large and diverse population of respondents should provide responses about disease management perspectives that best reflect real-world situations. Hemophilia A is the most common hereditary clotting factor deficiency in dogs; however, the incidence in the general population is low, with approximately 60 confirmed cases diagnosed annually at the comparative coagulation laboratory[b] (unpublished data). By use of 2 list serves for board-certified veterinarians as well as the VIN, we were able to collect information on a large number of cases. Additionally, by collecting data from board-certified specialists and general practitioners, we believed that we were better able to describe real-world outcomes for these dogs at clinical practices. To improve the quality of the survey data reported, we excluded dogs for which FVIII:C was not reported or could not be verified.

As expected for an X-linked recessive trait, most dogs with hemophilia A were males. Represented breeds did not appear to differ substantially from the general population of dogs.[10] The large number of breeds, including crossbred dogs, is consistent with the reported occurrence of de novo mutations with sporadic incidence patterns resulting in the hemophilia A phenotype. Particular scrutiny was paid to survey results reporting hemophilia A in female dogs; 3 of 4 female dogs initially identified were subsequently excluded from the data set.

The remaining female dog, a Yorkshire Terrier, was confirmed to have hemophilia A on the basis of review of test results and a medical history and clinical signs consistent with the disease. Possible causes of hemophilia in females include inbreeding (affected male bred to carrier female), chromosomal abnormality (XO) or male pseudohermaphrodism (XY), nonrandom X inactivation in a carrier female, and acquired FVIII inhibitors. On the basis of the history provided by the respondent veterinarian, that female dog's reproductive tract was grossly normal at the time of ovariohysterectomy. The dog's pedigree was evaluated and did not reveal inbreeding; however, parentage and identity of the dog were not independently confirmed. The dog was euthanized 7 months after initial diagnosis because of suspected CNS hemorrhage, so subsequent samples were not available for testing.

Initial clinical signs that led to the diagnosis of hemophilia A were similar to those reported previously.[5,9,11] When the dogs were categorized on the basis of residual FVIII:C, there were similar numbers of each clinical sign among groups. The most common site for a bleeding event in all groups was the subcutaneous tissues, which was consistent with the literature. Hemarthrosis was noticed commonly in both the mildly affected and severely affected groups. The data collected throughout the survey did not identify an obvious difference in the clinical signs or site of bleeding events among the 3 groups. Although it was challenging to interpret data regarding the frequency of transfusions and transfusion interval for the dogs in the present study because of limitations with the survey, most dogs receiving medium to long-term treatment after diagnosis were transfused with a blood product every few months. This suggested that a substantial proportion of dogs with hemophilia A receiving medium to long-term treatment likely had clinically serious spontaneous hemorrhage every few months. This is consistent with results for research dogs with severe hemophilia A that reportedly have 4 to 6 episodes of spontaneous hemorrhage/y.[12,13]

Fresh-frozen plasma was the blood product most commonly used to treat bleeding events in the dogs with hemophilia A in the present study. This likely reflected the greater availability of FFP, compared with the availability of cryoprecipitate, in clinical veterinary practices. Cryoprecipitate has the advantage of supplying FVIII at relatively lower volumes than for FFP, and cryoprecipitate contains fewer plasma proteins capable of inducing a transfusion reaction.[13,14] The use of packed RBCs and fresh whole blood was similar among groups. Packed RBCs were likely given to treat anemia

that developed as a consequence of blood loss. Dogs that received packed RBCs also received FFP to replace FVIII. Fresh whole blood may have been used in practices at which component treatment was not available or to replace FVIII and treat blood loss anemia concurrently. The comparable use of blood products among groups may have indicated similar severity of bleeding events regardless of FVIII:C. Ideally, hemophilia A in dogs would be treated by directly replacing the deficient FVIII, such as in humans with the use of FVIII concentrate. Although not commercially available, a recombinant canine B-domain deleted FVIII has been produced and was found to be safe and efficacious when used to replace FVIII in research dogs with hemophilia A.[15]

Overall, the prognosis for dogs with hemophilia A in the present study was considered fair. The clinical outcomes were similar among groups, and approximately half the dogs were alive and receiving treatment at the time the survey was completed. In a response field at the end of the survey, many clinicians included justification for the recommendations they would give to owners concerning future cases of hemophilia A. Reasons for euthanasia cited by clinicians differed but commonly included an owner's financial and other resource limitations. Clearly, maintaining a dog with hemophilia A requires close communication between the client and clinician. For the present study, clinical outcome could not be predicted on the basis of the FVIII:C at time of hemophilia A diagnosis. We recommend counseling owners about the increased need for veterinary care and potential financial burden associated with treating a dog with hemophilia A, although analysis of our data revealed that with appropriate care, many dogs can be successfully managed for a long period.

The survey format introduced inherent limitations, including selection and recall bias. Given its retrospective nature, completion of the survey relied on the memory of respondents and information contained in medical records of a group of clinicians. Some details, particularly regarding discussions with owners, may not have been recorded, and complete medical records were not submitted to the authors for review. To improve confidence in diagnosis, the authors requested coagulation test results that included FVIII:C for dogs that were part of the final data set. These were reviewed for all dogs in the study and confirmed a diagnosis of hemophilia A. Given the retrospective nature of this study, it was also impossible to confirm that all plasma samples submitted for FVIII:C testing were collected before dogs were transfused with a blood product. Thus, it is possible that FVIII:C may have been falsely increased if samples were obtained after transfusion. Obtaining the complete medical records of all dogs included in the study may have provided more detailed information about each dog.

Another potential source of bias related to the study was that responses were available only from clinicians participating in the American College of Veterinary Internal Medicine or American College of Veterinary Emergency and Critical Care email list serves or the VIN; therefore, the results were biased to board-certified specialists and VIN members. However, given that > 100,000 VIN members received the email request to participate in the survey, we believe that the respondents encompassed a broad spectrum of the veterinary community in clinical practice who would be likely to encounter dogs with hemophilia A.

Another limitation of the study was sample size. Although the survey-based format allowed accrual of cases from a number of veterinary hospitals, the overall number of dogs was still small. A larger sample size potentially would have allowed us to more thoroughly analyze FVIII:C in relation to clinical signs and outcome.

During design of the survey for the present study, the authors deliberately attempted to limit the number of questions and amount of information required, which we believed would allow respondents to complete the survey in a reasonable amount of time and thereby would maximize response rates. In doing so, it was difficult to include detailed questions regarding the frequency of bleeding events and the treatment required for each event. It is possible that hemophiliac dogs with a FVIII:C < 2% had similar inciting causes and sites of bleeding events but that the hemorrhage was more protracted in nature or was refractory to transfusion. In hindsight, the survey questions could have been written more clearly so that they would have better characterized the nature of each bleeding event in each hemophiliac dog and better differentiated clinical signs at the time of initial diagnosis from those of subsequent bleeding events. In addition, we did not ask about the specific volume of blood products administered relative to patient body weight. Therefore, we cannot rule out that, for example, dogs with a FVIII:C < 2% required higher doses of blood products to control bleeding or that dogs listed as requiring multiple transfusions per day actually received an initial subtherapeutic dose of a blood product. The clinical expression of hemophilia A in human patients, albeit related to residual FVIII:C, is also influenced by numerous factors, including function of other hemostatic proteins and platelets, development of inflammatory or degenerative disease, body weight, and physical activity.[4,16,17] It is possible that some of these other factors played a role in the dogs reported here and accounted for the apparent lack of a relationship between FVIII:C and bleeding characteristics. It would have also been valuable to determine the cost of care for the dogs that received long-term treatment, considering that this too may have influenced owner decisions.

In the present study, data were collected for 39 dogs with hemophilia A at clinical practices. We concluded that dogs with hemophilia A have differences in FVIII:C, although FVIII:C did not appear to be associated with differences in clinical signs at initial evaluation, transfusion requirements, or long-term outcome when treatment was pursued.

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