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Topical Review

Inherited Disorders of Hemostasis in Dogs and Cats

James W. Barr, DVM, DACVECC,[a] and Maureen McMichael, DVM, DACVECC[b]

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[a]Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, USA
[b]The University of Illinois College of Veterinary Medicine, Champaign, IL, USA

The authors declare no conflict of interest.

Address reprint requests to: James W. Barr, DVM, DACVECC, 4474 TAMU, Texas A&M University, College Station, TX 77843.

E-mail: jbarr@cvm.tamu.edu.

A B S T R A C T

Inherited disorders of hemostasis encompass abnormalities in primary hemostasis, coagulation, and fibrinolysis resulting from genetic mutations. There is significant variation in the phenotype expressed ranging from life limiting to the absence of overt clinical signs. Von Willebrand disease is the most common primary hemostatic disorder in dogs, and hemophilia A is the most common coagulation factor disorder. The diagnosis of inherited bleeding disorders is made by functional and/or quantitative evaluation. Genetic testing has added to the knowledge base, allowing prevention through targeted breeding. Avoidance of trauma and injury is paramount in the prevention of bleeding in animals diagnosed with inherited hemostatic disorders. Current therapeutic options include platelet transfusions, broad replacement of coagulation factors (e.g., plasma), targeted factor replacement (e.g., cryoprecipitate), antifibrinolytic agents and specific factor replacement, and treatment of the symptoms (i.e., bleeding) with blood transfusions.

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Historical reference to inherited bleeding disorders dates back to the Jewish Talmud in the 2nd century A.D. and in the writings of the Arab physician Albucasis in the 10th century.[1,2] In some cases, they have been instrumental in shaping history. Some historians believe the fall of the Russian imperial family and the birth of the Soviet Union came about in part because of the illness of the heir to the throne. Tsarivich Alexis suffered from hemophilia along with other members of the Romanov royal family in Europe. The relationship of the czar's family to the healer Rasputin, who was enlisted to treat the heir to the throne, contributed to the Bolshevik Revolution in the early 1900s and thus the start of communism in earnest.[3]

Young animals are frequently diagnosed when first challenged with an injury that requires appropriate hemostatic function, commonly when deciduous teeth fall out or when surgical procedures are performed.[4] This review will focus on common hemostatic disorders that have a genetic component in companion animals.

Genetic Basis of Disease and Diagnosis

Most inherited bleeding disorders are caused by a defect or breakdown in a single component of hemostasis. Many of the known disorders in veterinary medicine have been characterized and can be identified genetically.[5]

The mutation of the diacylglycerol guanine nucleotide exchange factor I (CalDAG-GEFI) was described first in canine platelets in 2007.[6] There are distinct breed predilections and documented heredity, but some of these diseases occur because of de novo point mutations in the DNA sequence. Hemophilia is well recognized as a heritable disease, but can be an acquired mutation. The new trait can be inherited when the individual reproduces.[7]

Identification of functional, quantitative, structural, or genetic abnormalities can help elucidate the specific disorder. In veterinary medicine, most clinicians test the functional ability of a specific subset of the hemostatic system. Examples of functional tests are buccal mucosal bleeding time, PFA 100 PFA 100; Siemens HealthCare Diagnostics, Deerfield, IL, USA, or thromboelastography TEG; Haemoscope Corporation, Niles, IL, USA. Quantitative assessment reports specific concentrations of the particular factor, cell, or protein of interest. Structural assessment is performed via electrophoresis to determine molecular size and structure.[5] Assessment of the genome can identify particular mutations to further characterize the disorder.[4]

Genetic mutations are quite varied among individuals and groups of individuals, and expression of disease may have numerous genetic abnormalities accounting for the dysfunction. Genomics and the study of the genome of domestic animals will likely advance the diagnosis and treatment of diseases of hemostasis in the future.[5,8] Among other modalities, newly discovered epigenetic therapies may be able to alter genetic expression so that a patient's phenotype appears normal.

Diseases of Primary Hemostasis

Platelet dysfunction is classically divided into extrinsic and intrinsic causes. Extrinsic disorders present with a deficiency of an extrinsic protein necessary for platelet function. The most common cause of extrinsic disorders is von Willebrand Disease (VWD). Disorders of fibrinogen, either hypofibrinogenemia or dysfibrinogenemia, can also cause extrinsic defects because fibrinogen is necessary for platelet aggregation. Acquired forms of fibrinogen defects are much more common than genetic forms. Intrinsic disorders affect function of the platelet. Defects can arise from abnormalities in membrane receptors, storage granules, or signal transduction.[5,9]

Intrinsic platelet defects that have been described in the veterinary literature include Glanzmann's thrombasthenia (GT), Chediak-Higashi syndrome (CHS), cyclic hematopoiesis, leukocyte adhesion deficiencies, May–Hegglin anomaly, Adenosine Diphosphate (ADP) abnormalities, macrothrombocytopenia, and various thrombopathies.[9]

A defect in platelet function usually manifests itself as bleeding from mucosal surfaces, bruising, or in extreme cases, cavitary bleed-

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ing. When platelets are low in number but normal in function, the animal typically presents with petechiae or ecchymosis due to extravasation of red blood cells. Trophogens, secreted from platelets, are needed to maintain endothelial tight junctions and, when low, can lead to red blood cell leakage.[4,5,10,11] The portion of this review dealing with primary hemostasis will focus on diseases associated with normal platelet numbers but abnormal function.

Von Willebrand Disease

von Willebrand factor (vWF) is thought to be an essential protein in the adhesion of platelets to areas of damaged endothelium. It is synthesized by endothelial cells and megakaryocytes and stored in endothelial cells and, to a lesser degree, platelets.[12] In its active form, vWF circulates as various-sized molecules join together to make multimers that range in size from 500 to 200,000 kDa.[10] The large-molecular-weight multimers are important in hemostasis because they are the most effective at supporting platelet adhesion.

The most common inherited bleeding disorder in humans and dogs is vWD.[4,13,14] It is caused by both structural and quantitative deficiencies of vWF, depending on type, and has been classified into 3 different categories.[4]

Type 1 is the most common form of vWD and is characterized by a low concentration but normal function of all multimers. Most animals with type 1 vWD have mild clinical signs that occur most commonly with trauma, hematuria, or deciduous tooth loss. There can be life-threatening intraoperative or postoperative hemorrhage in some cases.[10]

The degree that an individual patient is affected tends to be correlated with the absolute level of vWF activity. Very low levels are correlated with clinical signs. The Cornell University Comparative Coagulation Laboratory classifies patients as normal if their vWF is 70% to 180% as compared with pooled normal canine plasma, borderline if 50% to 69%, and abnormal if $<$ 50%. Heterozygous carriers of vWD, animals with type 1 usually have less than half the normal concentration of plasma vWF, and homozygous carriers produce virtually no vWF protein.[15]

The activated partial thromboplastin time (aPTT) and activated clotting time (ACT) can be normal or prolonged in patients with vWD. Because vWF serves as a carrier molecule for FVIII, decreased concentrations of vWF are associated with decreased factor VIII levels. Prolongation of the aPTT or ACT usually occurs when the factor levels are below 30% of normal. If the FVIII is below 30%, a prolonged aPTT will be seen in patients with vWD. It does not appear that aPTT provides a specific or sensitive measurement of vWF despite documented cases of lowered FVIII concentrations in dogs with vWD.[15-17] Studies in dogs with vWD report that FVIII concentrations average 46%,[18] 45%,[19] and 38% of normal.[20] Corresponding aPTT values are generally normal to slightly prolonged.[17]

Type 2 vWD is characterized by a low concentration of vWF with a preferential deficiency in the high-molecular-weight multimers. The lack of the high-molecular-weight multimers makes platelet adhesion much less effective. A complete absence of all multimers characterizes type 3 vWD.[4,5,10]

Intrinsic Platelet Disorders

Glanzmann's Thrombasthenia. GT is a disease that results from a deficiency of the glycoprotein receptor IIb-IIIa (GPIIbIIIa), also known as integrin αIIb-β3 or the fibrinogen receptor.[9,10] Described by Glanzmann in 1918, the disease was first identified as the lack of platelets clumping together on a blood smear when the individual platelets otherwise appeared normal.

The IIb-IIIa complex is an integrin receptor made up of 2 subunits that are encoded by 2 separate genes. The GPIb subunit binds to vWF, fibronectin, and vitronectin. The GPIIb subunit binds to fibrinogen, and, in order to function properly, both subunits must be present and functioning normally. Subsequently, patients with GT have platelets that attach to the subendothelial vWF-collagen complex but then suffer a defect of aggregation of additional platelets at the site of injury.[21] GT has been primarily associated with a mutation associated with the gene-encoding GPIIb portion of the receptor, which prevents platelet-fibrinogen binding. Platelet aggregation with ADP, thrombin, epinephrine, or collagen is usually impaired in these patients. The incidence of this disease in veterinary patients is largely unknown, but it has been best characterized in the Great Pyrenees and the Otterhound breeds of dogs and has not been reported in cats.[22-24] Gene therapy, in an attempt to correct the defect, has been used at the Medical College of Wisconsin.[25]

Other Platelet Receptors and Signal Transduction Disorders. ADP, an important agonist of platelets causing activation of neighboring platelets, is released from dense granules. Platelets have 2 ADP receptors, P2Y1 and P2Y12. P2Y12, an ADP receptor, initiates a G protein–mediated signaling that results in irreversible platelet aggregation, granule release, thromboxane generation, and expression of a procoagulant platelet membrane.[26,27]

P2Y12 is also of interest clinically as the target of the antithrombotic drug, clopidogrel, as well as newer generations of P2Y12 inhibitors. Clopidogrel's metabolite couples to the P2Y12 receptor and disables it. It makes this disulfide bridge at specific sites on the extracellular portion of the receptor.[28] Unfortunately, it has been recognized that the metabolism of clopidogrel is necessary for proper functioning of the drug and a significant proportion of humans have been identified as poor metabolizers. If a patient is discovered to be a poor metabolizer via a mutation in the gene encoding the P450 2C19, the enzyme that metabolizes clopidogrel, then a different medication can be chosen.[29]

A deficiency in the P2Y12 receptor has been identified across 5 generations of a family of Greater Swiss Mountain dogs.[26] The first individual was identified after bleeding excessively with routine surgery and required multiple transfusions. The patient's platelets were not responsive to ADP but were otherwise normal. Genetic analysis demonstrated a 3 base-pair deletion that resulted in a dysfunctional P2Y12 receptor. In these patients, spontaneous bleeding was not present.[26]

Signal transduction disorders, newly described in veterinary patients, are characterized by normal receptor interactions without appropriate signal transduction. Some experts suggest that these disorders may be a common cause of inherited platelet disorders in dogs.[9]

Diacylglycerol guanine nucleotide exchange factor I (CalDAG-GEFI) is essential for the receptor GPIIb-IIIa to conform to a high affinity state for fibrinogen binding and subsequent platelet aggregation.[30] A deficiency in CalDAG-GEFI has been demonstrated in Basset Hounds, Spitz, and Landseer dogs.[6] Affected individuals have normal clot retraction through a thrombin-mediated pathway, but clinically they suffer from bleeding.[6,9] A deficiency of another IIb-IIIa receptor activator, Kindlin-3, has been identified in a German Shepherd dog. Kindlin-3 is an important cofactor in the activation of the IIb-IIIa receptor to its high affinity state.[31]

Chediak-Higashi Syndrome and Storage Pool Disorders. CHS is a genetic disorder that is characterized by abnormal skin pigmentation and platelet and immune system dysfunction. A storage pool disease, it results from a deficiency in granule formation and function of melanocytes, platelets, and leukocytes. This disorder limits the ability of the platelet to respond to and generate ADP, serotonin, and divalent cations. The net effect is inadequate platelet aggregates that are not activated in vivo.[10,32]

CHS is autosomal recessive and heterozygous individuals are normal. This disease has been reported in Persian cats and has not been characterized in dogs.[9,33]

Other storage pool disorders that have been reported in dogs are cyclic hematopoiesis in Grey Collies and dense granule defects in American Cocker Spaniels and both are quite rare.[9,33]

Cyclic hematopoiesis is characterized by fluctuations in circulating neutrophils, reticulocytes, and platelets and has been described in Grey Collies.[34,35] Defects in bone marrow stem cells result in neutropenic episodes approximately every 12 days. Most patients with cyclic hematopoiesis die from infections early in life. Platelet numbers are normal to elevated, but the platelets have no dense granules. Clot retraction and platelet adhesiveness are both impaired.[9]

Platelet-dense granule defects have been reported in 3 families of American Cocker Spaniel dogs with patients suffering from moderate to severe bleeding after minor trauma, venipuncture, and surgery.[36] Platelets have a decrease in the ADP content but normal Adenosine Triphosphate (ATP), resulting in an inappropriate ratio of ATP to ADP, whereas the dense granules appear normal.[36]

Disorders of Coagulation

Disorders of coagulation make up a smaller percentage of the inherited hemostatic disorders than do the primary hemostatic disorders.

Hemophilia A

Hemophilia A is a deficiency of factor VIII and the most common inherited deficiency of coagulation.[5] This disorder has a well-characterized X-linked recessive inheritance pattern and is expressed in male individuals almost exclusively. De novo mutations occur sporadically in individuals leading to an acquired form of the disorder.[5]

Clinical bleeding is inversely proportional to the relative factor levels in plasma as FVIII is instrumental in the propagation phase of coagulation. The FVIIIa generated in the amplification phase of coagulation joins with factor IXa to form the intrinsic tenase complex. This is responsible for the bulk of the FXa and thus the thrombin that is formed in vivo.[8] A severe deficiency in FVIII results in the inability to generate enough thrombin for mature clot formation.[7] Hemarthrosis, subcutaneous bleeding, and prolonged bleeding from minor injuries are typical.[5,7,37] The anatomic location of the bleeding tendency in patients with hemophilia is localized to areas with little tissue factor, particularly skeletal muscle and joints.[38]

The diagnosis of hemophilia A is relatively straightforward in affected males. In the bleeding patient, a deficiency in the intrinsic pathway may be evident by a prolongation of the aPTT or ACT with a normal prothrombin time (PT). Factor analysis will demonstrate a moderate or severe deficiency in factor VIII.[5,7]

In non-effected carriers, it is not as easily identified, because there is a large amount of overlap in the normal values of factor VIII. Targeted genetic analysis of the affected patients' relatives may elucidate the genetic mutation in the female carriers.[5]

Hemophilia B

Hemophilia B is a deficiency of FIX and is also called Christmas disease after the Canadian man originally diagnosed with the disease.[1] In 1952, at the age of 5 years, Stephen Christmas had his case history published in the *British Medical Journal*. As an adult Mr. Christmas worked in Canada for the Hospital for Sick Children in Toronto and was an advocate for transfusion safety in Canada. He ultimately died of AIDS, at 46 years of age, likely acquired from the hundreds of plasma transfusions he received over his lifetime.[39]

Hemophilia B is an X-linked recessive trait but occurs much less frequently than hemophilia A. It is estimated to have an incidence of 25% of hemophilia A.[5] It has a clinical presentation that is very similar to hemophilia A and has been found in many different breeds of dogs and in cats.[5] The diagnosis of hemophilia B is similar to that of hemophilia A as factor analysis will demonstrate the deficiency in the affected patients.

PennGen Laboratories
http://research.vet.upenn.edu/PennGen

Vetgen^{tm}
http://www.vetgen.com

Cornell Comparative Coagulation Section
http://ahdc.vet.cornell.edu/sects/Coag/

Fig. 1. Selected commercial laboratories available for testing of inherited coagulation disorders and their web sites.

Other Factor Deficiencies

Additional factor deficiencies identified in veterinary patients are much less common than hemophilia[7] and most are autosomal factor deficiencies.[5,7]

Defects or deficiencies in fibrinogen are reported infrequently in veterinary patients. These disorders can manifest as afibrinogenemia, hypofibrinogenemia, or dysfibrogenemia (abnormal production). Factor II (prothrombin) deficiency has been reported sporadically in veterinary patients and humans.[7]

Another group of deficiencies results in the inability to convert prothrombin to thrombin. A deficiency in either factor V, VII, or X will result in decreased thrombin production and this can result in significant clinical signs.[40] The bleeding tendency associated with a decreased thrombin production tends to be related to the degree of in vitro clotting factor activity.[5]

Deficiencies of the contact factors FXII, Prekallikrein (PK), and High molecular weight kininogen (HMWK) result in markedly prolonged aPTT with a lack of clinical bleeding. Factor XII deficiency is well recognized in veterinary patients, particularly cats.[5,7]

Because of its high prevalence in cats, factor XII deficiency should be considered as a likely diagnosis in cats with a prolonged aPTT, a normal PT, and no clinical signs of bleeding. The confirmation is straightforward as a simple functional assay of FXII. Patients with FXII deficiency need no specific therapy.[7]

Diagnosis of Inherited Coagulopathy

There are several reference laboratories that specialize in disorders of hemostasis (Fig. 1). The phenotypic identification of an inherited genetic disease is centered around assays that determine the functional, quantitative, and structural characteristics of a patient's coagulation proteins (Table 1). Functional testing is frequently used as a screening test to determine if the pet has a coagulopathy. Specific quantitative and structural analytical tests are used to determine the exact nature of the disease.[5]

Functional tests are the most common diagnostic tools used by most veterinarians. Examples of functional tests are the buccal mucosal bleeding time (BMBT), aPTT, ACT, PT, thromboelastography (TEG; Haemoscope Corporation, Niles, IL, USA), thromboelastometry (ROTEM; Pentapharm GmbH, Munich, Germany), Sonoclot (Sienco Inc., Arvada, CO, USA), and platelet function analysis (PFA 100; Siemens HealthCare Diagnostics, Deerfield, IL, USA). The functional tests can guide specific testing.[5,41]

Quantitative testing allows for definitive diagnosis of a deficiency of a factor or protein. The quantitative analyses do not demonstrate normal function. They simply quantify how much of the protein in question is present or how active it is. Examples of quantitative analyses are the von Willebrand assay and all of the factor analyses. These tests do not always demonstrate if a patient is a carrier of the gene

Table 1
Selected Inherited Coagulation Abnormalities

Factor Deficiency	Screening Tests Abnormal	Screening Tests Normal	Definitive Test	Propensity to Bleed?
Fibrinogen	TT, fibrinogen, all tests*	aPTT, PT, ACT	Factor assay	Variable, spontaneous or after trauma
Factor II (prothrombin)	aPTT, PT	TT, fibrinogen,	Factor assay	After trauma
Factor VII (proconvertin)	PT	aPTT, ACT, TT, fibrinogen	Factor assay	Variable, after trauma
Factor VIII (hemophilia A)	aPTT	PT, TT, fibrinogen	Factor assay	Spontaneous or after trauma
Factor IX (hemophilia B)	aPTT	PT, TT, fibrinogen	Factor assay	Spontaneous or after trauma
Factor X (Stuart Prower factor)	aPTT, PT	TT, fibrinogen	Factor assay	Spontaneous or after trauma
Factor XI (PTA deficiency, hemophilia C)	aPTT	PT, TT, fibrinogen	Factor assay	Mild after trauma
Factor XII (Hageman factor)	aPTT	PT, TT, fibrinogen	Factor assay	None
Type 1 vWD	BMBT, PFA100	aPTT†, PT, ACT, fibrinogen	vWF activity, genetic	Variable, spontaneous or after trauma
Type 2 vWD	BMBT, PFA100	aPTT†, PT, ACT, fibrinogen	vWF activity, vWF collagen binding, genetic	Severe, spontaneous or after trauma
Type 3 vWD	BMBT, PFA100	aPTT†, PT, ACT, fibrinogen	vWF activity, genetic	Severe, spontaneous or after trauma
Glanzmann's thrombasthenia (GP IIb-IIIa)	BMBT, PFA100	aPTT, PT, ACT, fibrinogen	Flow cytometry, genetic, platelet mapping	Variable, spontaneous or after trauma
Chediak-Higashi syndrome	BMBT, PFA100	aPTT, PT, ACT, fibrinogen	Genetic, platelet mapping, electron microscopy	Variable, spontaneous or after trauma
Cyclic hematopoiesis	BMBT, PFA100	aPTT, PT, ACT, fibrinogen	Genetic, platelet mapping, electron microscopy	Variable, spontaneous or after trauma
Dense granule defects	BMBT, PFA100	aPTT, PT, ACT, fibrinogen	Genetic, platelet mapping	Variable, spontaneous or after trauma
Signal transduction defects (CalDAG-GEFI)	BMBT, PFA100	aPTT, PT, ACT, fibrinogen	Genetic, platelet mapping	Variable, spontaneous or after trauma

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; BMBT, buccal mucosal bleeding time; CalDAG-GEFI, calcium diacylglycerol guanine nucleotide exchange factor I; PT, prothrombin time; PTA, plasma thromboplastin antecedent; TT, thrombin time; vWD, von Willebrand's disease.
* Severe deficiency.
†In cases of very low vWF concentrations, the aPTT can be prolonged because of its effect on factor VIII.

because there is a lot of overlap between normal and heterozygous patients.[5]

The molecular structure of particular proteins that are involved in coagulation can also be evaluated. Identification of the glycoprotein amino acid structure or electron microscopy to identify the membrane characteristics of a cell are options available for structural analysis. Protein electrophoresis can determine the size of proteins, as is the case in vWD.[5] In type 2 vWD, protein electrophoresis can detect the presence of the high-molecular-weight multimers of vWF. A particularly useful test is the vWF collagen-binding assay, which relies on the presence of high-molecular-weight multimers in the sample to get a normal result.[7]

Genetic testing offers an inviting alternative, identifying specific genes that can be correlated with the phenotype of bleeding. It also allows for the characterization of the phenotypically silent carriers of the disease in question. Because of the lack of clinical signs in many carriers, the genetic defects often go untested, preventing the elimination of carriers from the breeding pool.[5]

Sample preparation and collection are paramount in the accurate diagnosis of the presence or absence of a disease. A thorough discussion of this topic can be found in the Diagnostic Approaches article found in this issue. A clean, atraumatic puncture of the blood vessel is important as well as the appropriate anticoagulant to blood ratio. This is especially true in functional testing because contamination of the sample with tissue factor may erroneously skew the results.[42]

Treatment of Inherited Coagulopathy

The treatment of inherited coagulopathy has made significant progress since the days of Rasputin and the Romanov dynasty. Avoidance of rough play, unnecessary trauma, optimal dental hygiene, and non-essential surgical procedures are important preventative measures.

Preparation in advance by having hemostasis agents and blood products (Table 2) on hand is also important for any practitioner who does routine surgery. Topical hemostatic agents, such as gelfoam, fibrin sealants, and polyethylene glycol polymers, should also be accessible and may be all that are needed for the treatment of superficial wounds. Avoidance of antiplatelet drugs and nonsteroid anti-inflammatory drugs or weaning well before any elective surgeries is an important part of prevention.

Antifibrinolytic agents (e.g., aminocaproic acid, tranexamic acid) can be very helpful for arresting bleeding after minor surgical procedures, epistaxis, or gingival bleeds. They are used in humans as a sole treatment, as an adjunctive treatment (along with other agents such as desmopressin), and topically on bandages.[43] They are also used as an oral rinse for gingival bleeds. Aminocaproic acid, as an oral rinse, is given at 60 to 80 mg/kg every 6 to 8 hours.[44,45] Aminocaproic acid has been reported for use in Greyhound dogs with postoperative bleeding.[46] These drugs represent an attractive option for veterinary practitioners because of their low cost and safety margin.

Table 2
Blood products and their use in selected coagulation disorders

Product	Dose	Disease Indication
Fresh-frozen plasma	10-20 mL/kg	All factor deficiencies, DIC, vWD
Frozen plasma	10-20 mL/kg	Vitamin K antagonist poisoning (replace all factors except V, VIII, and vWF)
Cryoprecipitate	1 unit/10 kg	Hemophilia A, vWD, hypofibrinogenemia
Cryosupernatant	10-20 mL/kg	Hemophilia B, factor II, VII, IX, X, XI deficiency
Recombinant human factor VIIa	35-120 μg/kg	Factor VII deficiency, to augment therapy in DIC, hemophilia A or B

Abbreviations: DIC, disseminated intravascular coagulation; vWF, von Willebrand factor.

Plasma has been the traditional blood product used for the treatment of factor deficiencies such as hemophilia A and B. A dosage of 10 to 15 mL/kg of fresh-frozen plasma supplies the minimal amount of factors that would be needed to stop most bleeding associated with inherited coagulopathy. Whole blood would be useful in the treatment of factor deficiency if there is concurrent anemia associated with blood loss.[10]

Transfusion of fresh platelet concentrates is an expensive and, often, impractical strategy in veterinary medicine. Stored, frozen, or lyophilized platelet concentrates likely have significantly diminished function and a brief half-life. In humans, platelet transfusions are used sparingly because of the risk of alloimmunization against human leukocyte antigen (HLA) antigens and/or platelet glycoproteins.

Exogenous supplementation of vWF is impractical, and the volume of plasma needed to substantially raise the plasma vWF is equivalent to an entire plasma volume. Cryoprecipitate has been used traditionally to replace vWF in a smaller volume than that associated with plasma.[4] Administration of cryoprecipitate is effective and has been shown to increase the plasma vWF concentration.[47]

Cryoprecipitate has been used for the treatment of factor II (fibrinogen) deficiency, hemophilia A, and vWD. Cryoprecipitate will not supply factor IX for treatment of hemophilia B. Treatment for the balance of the factor deficiencies can be accomplished with cryosupernatant, but this is unlikely to be available in places without an active blood bank. Frozen (stored) plasma likely has little use in the treatment of hereditary coagulopathies because it is devoid of FV and FVIII.[10] It is important to note that these transfusion strategies are temporary measures in a crisis and will last only as long as the half-life of the particular factor will allow.

Desmopressin acetate (DDAVP) has been used with some success in patients with vWD. Desmopressin is a vasopressin analog that causes release of preformed, high-molecular-weight multimers of vWF from endothelial cells. Subsequent doses of desmopressin will not result in a substantial increase of vWF because the stores of vWF in the endothelial cells will have become depleted.[10,12] Studies that examined the use of DDAVP in dogs, however, demonstrated no elevation in vWF concentrations or preferential elevations in the high-molecular-weight multimers of vWF as is the case in humans.[48,49] Administration of DDAVP to Dobermans with type 1 vWD resulted in improved hemostatic function despite minimal increase in vWF concentration.[48] To date, the mechanism of action of DDAVP has not been fully characterized.[43] DDAVP has been shown to be effective in humans with inherited platelet disorders. It decreased the bleeding time in delta storage pool disease, disorders of signal transduction, and granule secretion and thromboxane receptor anomalies.[50-52] Improved hemostasis after DDAVP is thought to be due to increases in platelet adhesiveness to the subendothelium, increased platelet aggregation at high shear rates, and increased levels of plasma vWF.[53] However, these mechanisms do not explain improved hemostasis seen in patients lacking the vWF receptor. Recent speculation suggests there may be additional vWF-independent benefits from DDAVP.[43] The dosage recommended for DDAVP in patients with vWD is 1 μg/kg.[48]

Conclusions

Active research is ongoing in novel therapies such as the use of recombinant coagulation factors, engineered longer-acting coagulation proteins, gene therapy, and tissue engineering to supply the factors that are needed.[8]

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