



# Unexpected Bleeding Disorders

*Louis M. Aledort, David Green, and Jerome M. Teitel*

**Patients with known coagulation deficiencies, either congenital or acquired, may bleed spontaneously with trauma or with surgical intervention. In contrast, however, are the unchallenged patients who bleed in a variety of clinical settings that demand rapid diagnosis so that appropriate therapy can be instituted.**

In the first section Dr. Louis M. Aledort demonstrates a series of vignettes of actual cases who presented with unexpected bleeding or a screening laboratory abnormality prior to a needed surgical intervention. Settings include dental, oral surgical, obstetrical, surgical and gynecological. The differ-

**ential diagnoses of these cases are discussed.**

In the second section Dr. David Green also uses vignettes to demonstrate how the laboratory is used to differentiate the various clinical entities. The choice and priority of required tests indicated by the settings, history, site and type of bleeding, and the syllogisms used to define the abnormality are stressed.

In the third section, Dr. Jerome Teitel reviews in detail the therapeutic armamentarium available to the clinician and presents algorithms for the management of these bleeding disorders.

## I. INTRODUCTION AND CASE VIGNETTES REGARDING SETTINGS AND CHALLENGES

*Louis M. Aledort, MD\**

The hematologist is frequently called upon to unravel the problems associated with the bleeding patient. Often the diagnosis and past medical history are simple to discern, and appropriate therapy a consequence. There are, however, many settings in which patients with no prior bleeding history present with either unrelenting bleeding, unusual sites of bleeding, or life-threatening hemorrhage. This review will deal with settings in which unexpected bleeding occurs and where laboratory diagnosis (if possible) is critical. An approach to therapeutic options for these patients will also be presented.

### Case 1: Mild Hemophilia

A 30-year-old African-American male sought dental care for a painful tooth and was referred to an oral surgeon for a dental extraction. A careful history revealed no medical disorders, prior surgery, oral cavity manipula-

tion, or injury requiring sutures. The procedure was uneventful until that evening, when the patient developed oozing that increased to substantial bleeding. By the next morning, the patient, still bleeding, was hypotensive, and his hemoglobin had fallen to 7 grams. His activated partial thromboplastin time (aPTT) and prothrombin time (PT) were normal. Further testing revealed a factor VIII of 18%. Factor IX, factor XI, bleeding time, von Willebrand factor (vWF) and vWF antigen [vWF(ag)] were all normal. On speaking with his family, he learned that his maternal grandfather had been admitted to another hospital years earlier with unexplained gastrointestinal bleeding. Evaluation of his grandfather revealed a similar factor VIII level.

This case demonstrates the importance of the clinical impression, based on personal or family history of a bleeding disorder, in deciding when to go beyond screening laboratory tests to make a specific diagnosis. Hemostasis usually requires coagulation factor activity levels at least 30% of normal. The aPTT may be normal with a factor level as low as 15-18% of normal, demonstrating the potential insensitivity of this assay for the diagnosis of mild but clinically significant congenital disorders.

Substantial hemorrhage following oral cavity manipulation is frequently a sign of an underlying bleeding disorder. This complication is partly related to the fact that saliva contains fibrinolytic activity. The addition of antifibrinolytic therapy to minimize replacement therapy in hemophilia patients requiring dental extraction has

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been a standard approach for years. Amicar ( $\epsilon$ -amino caproic acid) is given post-extraction at 6 grams P.D. q 6 hours for 10 days. Lightheadedness and nausea may be the major adverse reactions. The recognition that platelet adhesion may aid in hemostasis has led to the use of microcrystalline collagen as an adjunctive measure.<sup>1-3</sup> This bovine-derived material, packed into a recently extracted socket, promotes platelet adherence and aids in hemostasis. Mild hemophilia A patients usually respond to both intravenous and nasal spray desmopressin (DDAVP). A trial is warranted to assure achievement of hemostatic levels for either treatment of a future bleeding episode or surgery.

#### **Case 2:**

A 50-year-old white male entered the hospital for prostatic surgery. Following the uneventful surgical procedure, the patient began to have hematuria. His bleeding continued unabated, requiring transfusions and re-exploration. No obvious bleeding site was determined. Preoperative screening had revealed a normal PT and aPTT. He received fresh frozen plasma (FFP), but the bleeding continued. Hematologic consultation was requested. The platelet count was normal, as were the PT, aPTT, fibrinogen and fibrin split products (FSP), making consumption coagulopathy unlikely. As in the prior case, this patient had no prior bleeding history, surgery or injury. A suspicion of a bleeding disorder led to performance of clotting factor levels. Factor VIII was 125%; the factor IX was low at 23%. This level is insufficient for surgical hemostasis and is consistent with the diagnosis of a mild factor IX deficiency (hemophilia B; Christmas disease). The treatment with FFP only partially corrected the deficiency state. Factor IX concentrate gave the patient adequate correction, and bleeding stopped. Post-discharge, the patient was found to have a factor IX of 17%. The initial goal was to achieve a level of 100% for factor IX and not let the trough level fall below 30% for 10-14 days. All future surgery or trauma were adequately handled by prophylactic and post-intervention factor therapy.<sup>4</sup>

Patients with mild or moderate congenital factor VIII and IX deficiency do not suffer from spontaneous bleeding. Patients who have never had trauma or surgery may present relatively late in life, and their screening tests can be normal. Factor IX is a smaller molecule than factor VIII and therefore has greater distribution into the extravascular space. Therefore FFP given to this man did not elevate the plasma factor IX level sufficiently to secure hemostasis. For a severe (< 1%) factor VIII deficient adult, intravenous infusion of 40 u/kg of a factor VIII concentrate will elevate the patient's level to approximately 100%; as much as 80 u/kg may be required to elevate a severe IX deficient patient to 100%.

#### **Case 3: Acquired Hemophilia**

A 42-year-old white woman was diagnosed as having severe systemic lupus erythematosus several years before her current admission and was treated for symptoms with corticosteroids. On admission to another hospital for gastrointestinal bleeding, she was found to have a prolonged aPTT. A factor VIII activity of 1% of normal was found. She was treated with a small dose of cryoprecipitate, but the aPTT did not correct nor did her bleeding stop. She was endoscoped, and no lesion was found. On transfer to the University Hospital, she continued to require 2-4 units of packed red cells (PRBC) daily. Her aPTT was greater than 100 seconds, her PT was normal, and her factor VIII was 1%. Her anti-human factor VIII inhibitor titer was 100 Bethesda Units (B.U.; normal < 0.6), and her porcine B.U. was zero. She was treated with porcine factor VIII. A factor VIII level of 100% was achieved, and her bleeding stopped. She was treated for several more days, and attempts at immune suppression to eliminate her acquired inhibitor were begun.

Acquired inhibitors to coagulation factors occur most commonly against factor VIII. The majority of patients who develop an acquired inhibitor are elderly patients without any underlying disease. Among those with associated diseases, the most common are disorders of the immune system. Lupus, rheumatoid arthritis, myeloma, and lymphoma have all been associated with this phenomenon.

It is important to point out that patients with acquired inhibitors most frequently have bleeding into fascial planes and mucous membranes, rather than into joints as classical hemophiliacs do. The diagnosis is frequently obscure, and FFP and/or cryoprecipitate are often transfused before a diagnosis is made. This reflex approach to bleeding leads to several problems. One is the potential for an anamnestic immune response, and another is exposure to viral infection. Solvent/detergent-treated FFP eliminates hepatitis B, C, and HIV. At present, there is no viral inactivation method for cryoprecipitate.

The therapeutic challenges posed by these inhibitors are monumental as indicated by Case 4. The issue of therapeutic options and adverse reactions will be covered in the third section of this paper.<sup>5,6</sup>

#### **Case 4:**

A 24-year-old female patient, gravida 3 para 3 without a prior history of a bleeding disorder, underwent an uneventful vaginal delivery after a prior cesarean delivery. All coagulation parameters were within normal limits, including fibrinogen, PT, and aPTT. The patient had had an uneventful tooth extraction one week before delivery. Four days after delivery, the patient developed bleeding from the episiotomy site and increased vaginal bleed-

ing was noted. She underwent an episiotomy revision and a dilatation and curettage (D&C) for suspected retained placenta. After the procedure, the patient became tachycardic and hypotensive and underwent an emergency abdominal hysterectomy. Her bleeding was noted to be intermittent and severe. During the surgical intervention, she was resuscitated with crystalloid and given a transfusion of 2 units of PRBC. Her aPTT was 45 seconds (normal: 22.9-33.1 seconds). Over the next several days, the patient was taken back to the operating room four times and had sutures and packing placed at the vaginal cuff. She was transferred to the University Hospital on post-delivery day 19. Before the transfer, the patient received 12 units of PRBC, 10 units of cryoprecipitate and desmopressin (DDAVP).

On arrival, she was hemodynamically unstable and was taken to the operating room for exploratory surgery. The hypogastric arteries were ligated and hemostasis was achieved. Her laboratory values are shown in **Table 1**. Further coagulation testing revealed a factor VIII level of 8%, a factor IX level of 121%, a factor XI level of 73%, and a factor VIII inhibitor titer of 3.5 B.U.<sup>7</sup>

This patient was treated with DDAVP, 51 units PRBC, 53 units of FFP, 53 bags of cryoprecipitate, 44 vials of porcine factor VIII and 21 vials of an activated prothrombin complex concentrate (aPCC). She received immunosuppressive therapy with prednisone and cyclophosphamide. With time, her inhibitor disappeared and she subsequently had normal factor VIII levels. This and the previous case demonstrate that, in patients with inhibitors, even large amounts of cryoprecipitate and/or FFP are of little use in attempting to achieve hemostasis.

This patient had little functional circulating factor VIII in vitro despite the presence of an inhibitor. In this situation, treatment with DDAVP may raise endogenous factor VIII, which is not itself immunogenic. As in the previous case this patient developed an autoantibody, in

contrast to alloantibodies that arise in congenital hemophiliacs in response to treatment. In congenital hemophilic patients, re-exposure to exogenous factor VIII will generally result in an anamnestic immune response.

### Case 5: von Willebrand's Disease

A 28-year-old white female sought care from her gynecologist for increased menstrual bleeding. When she reached menarche at age 13, her menstrual bleeding was heavy enough to keep her out of school for several days each month. She discussed her bleeding pattern, which required the use of extra heavy tampons for the first three days, with her mother and sister. They told her that this was normal for the women in their family, going back at least as far as her maternal grandmother. She eventually had two uneventful pregnancies, and the deliveries were uncomplicated by excess bleeding. She denied hematuria, GI bleeding or epistaxis. A few months before seeking further gynecologic work-up, she found that she again experienced severe menorrhagia associated with dysmenorrhea. She found that aspirin or ibuprofen alleviated the symptoms but not her bleeding, which they exacerbated. Over the ensuing few months her menses became progressively worse. She had flooding despite using extra duty tampons. She began to feel weak and sought care. Her gynecologist noted her Hb to be 8.2 g/dL and her MCV was 79 fL. She had a serum iron of 25 µg/dL and TIBC of 412 µg/dL. Her pelvic examination was normal, and the gynecologist recommended a D&C. She was started on 325 mg FeSO<sub>4</sub> tid and on the advice of a friend she sought a hematologic evaluation. Her evaluation included a bleeding time of 10½ minutes, normal PT, aPTT, fibrinogen and platelet count. Factor VIII was 22%, vWF 24%, and vWF(ag) 30%. She was blood group A; normal levels of vWF for group A individuals are 50 to 200. She was tested with intravenous DDAVP at 0.3 µg/kg. One-half hour later her bleeding time was normal, factor VIII was 102%, vWF 97%, and vWF(ag) 120%. She was subsequently tested with nasal spray DDAVP (Stimate®). One hour after her first dose of this preparation her factor VIII was 87%, vW factor 72%, and vWF(ag) 81%, and the bleeding time normal. She has used nasal spray on the first day of her period for the past three years. All her periods are normal, and her Hb and iron levels are normal.

The prevalence of von Willebrand's disease (vWD) varies with the population studied and has been reported to be as high as 1%. It is the most frequent genetic bleeding disorder. Although there are many subtypes of this disorder, 80% are type 1, in which coagulant factor VIII and vWF are diminished but structurally normal. Menorrhagia is one of the more frequent manifestations of an undiscovered bleeding disorder. Historically, many women in the original kindred described by von

**Table 1. Case 4: Acquired hemophilia.**

	Patient	Normal Range
aPTT (seconds)	45	22.9–33.1
PT (seconds)	Normal	
Fibrinogen (mg/dL)	286	170–400
Bleeding time (minutes)	7.5	2–7.5
Platelet count (/µL)	323,000	150–400,000
Factor VIII	8%	> 50%
Factor IX	121%	> 50%
Factor XI	73%	> 50%
Factor VIII inhibitor titer (B.U.)	3.5	< 0.6

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time; B.U., Bethesda units

Willebrand died of hemorrhage from menorrhagia or childbirth. Before specific therapy, it was recognized that pregnancy elevated vWFs to almost normal near term. This is true for most patients with type 1 disease.

Mucosal bleeding is not uncommon, with menorrhagia being one of the most frequent complaints. Resultant iron deficiency anemia can only be corrected by controlling menstrual flow. vWD is a frequently missed diagnosis, and many women have had D&Cs as well as hysterectomies unnecessarily. Although estrogen therapy and antifibrinolytics were used in the past, the advent of DDAVP has altered therapy substantially. During pregnancy, the coagulant VIII and vWFs increase, so that deliveries, including cesarean sections when required, may be accomplished without excessive bleeding. However, the increased levels rapidly dissipate, and postpartum hemorrhage may occur, requiring therapy.<sup>8-14</sup> Medications that produce a platelet functional defect, such as ASA, frequently cause a previously asymptomatic von Willebrand patient to bleed.

#### **Case 6: Factor XI Deficiency**

A 19-year-old white multiparous female entered the obstetrical suite in labor. She had had no prenatal care. The fetus had a breech presentation, and a cesarean section was entertained. CBC demonstrated a mild anemia, Hb 11 g/dL, Hct 32%, with a normal WBC and platelet count. A PT was normal, but an aPTT was elevated to 72 seconds. A past medical history revealed some bleeding when she had sutures. She had never had a dental extraction or surgery. A factor VIII was 150%, IX 82%, XI 5% with no detectable factor XI inhibitor. She was transfused with two units of solvent-detergent treated FFP. The cesarean section was uneventful. Two days post-partum, she began to bleed again from the suture site and required replacement therapy every two days over a period of ten days. All bleeding stopped and she was discharged without event.<sup>15</sup>

Factor XI deficiency is the most capricious of all the clotting factor deficiency states. The bleeding tendency is often unrelated to the factor level. The phenotype of the patient and his or her family is most important. One frequently encounters patients with factor XI deficiency who require surgery. A past bleeding history requires prophylactic and post-surgical therapy. In a patient who has never undergone surgery, dental extraction, or sustained trauma, the bleeding history of the family may be the only key to whether a patient is or is not a clinical bleeder. Although there is some evidence that factor levels may slightly increase over the course of pregnancy, they also rapidly fall to baseline levels after delivery, so that hemorrhage may occur post-partum. As with vWD, menorrhagia is often a major problem for women with factor XI deficiency.<sup>16</sup>

The next section will deal with the use of the laboratory in making the appropriate diagnosis. Once made, our therapeutic armamentarium for dealing with these bleeding disorders is plentiful.

## **II. LABORATORY EVALUATION OF BLEEDING DISORDERS**

*David Green, MD, PhD\**

The coagulation laboratory is essential for the accurate diagnosis of bleeding disorders. While the clinical examination can lead one to suspect that a patient may have a bleeding problem, the laboratory provides both a qualitative and quantitative description of the condition. In this section, typical case histories of patients with inherited and acquired bleeding disorders will be presented, and in each case the laboratory evaluation will be described. It will become apparent that the clinical assessment of the severity of the disorder often is at odds with the laboratory evaluation; patients thought to have clinically mild disorders may in fact have severe deficits of clotting components, and in other cases the reverse may be true. Therefore, careful laboratory evaluation is warranted for every patient with a clinically suspected hemorrhagic disorder.

#### **Case 7: Inherited Coagulopathy**

This 61-year-old woman was referred because of a prolonged aPTT. Two years earlier she was suspected of having colitis and surgery was proposed but deferred because of abnormal pre-operative screening tests. One year later, she presented with shortness of breath, fatigue, and left lower quadrant pain. The hemoglobin was found to be 7.6 g/dL. Colonoscopy showed narrowing of the descending colon and signs of inflammation. Again, surgery was postponed because of abnormal clotting tests.

The patient had a past medical history of hypertension and peptic ulcer disease, but denied previous bleeding problems. There was no family history of bleeding; one aunt had gastric cancer. The physical examination was unremarkable; specifically, no petechiae or ecchymoses were observed. The initial assessment was that the patient had bleeding from the colon, probably secondary to inflammatory bowel disease, and perhaps exacerbated by a coagulopathy.

The laboratory evaluation is shown in **Table 2**. The patient had blood group A. The bleeding time performed

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**Table 2. Case 7: An inherited bleeding disorder.**

Test	Pre-desmopressin	Post-desmopressin
Bleeding time (minutes)	14	10
aPTT (seconds)	44	29
Ristocetin-platelet aggregation	Absent	Present
von Willebrand Factor antigen (%)	10	27
Ristocetin cofactor activity (%)	< 20	< 20
Factor VIII (%)	6	46

Abbreviations: aPTT, activated partial thromboplastin time

with the template method was increased to 14 minutes. The aPTT was 44 seconds. The platelet count was increased, but platelet aggregation with ristocetin was absent. vWF(ag) was 10%, ristocetin cofactor activity less than 20%, and factor VIII 6%. An inhibitor to factor VIII could not be detected. These values were similar to those recorded by the referring institution one month earlier.

Following the administration of nasal spray DDAVP (Stimate®), the bleeding time was 10 minutes. The level of vWF(ag) rose to 27%, platelet aggregation occurred with ristocetin, but ristocetin cofactor activity was still undetectable, and the factor VIII was 46%. Multimer analysis of the plasma collected at this time showed the presence of all multimers but in decreased concentration. Evaluation of 2 of the patient's 5 children indicated that both had type A blood. While the levels of vWF, ristocetin cofactor, and factor VIII were close to 100% in one daughter, the other daughter had levels of 60% to 70%.

Because the laboratory evaluation suggested that the severity of the disorder was more severe in the propositus than the clinical history indicated, an experienced clinician interviewed the patient. She had her five children without unusual bleeding. However, extensive dental extractions were complicated by large hematomas and a brief episode of post-operative bleeding that spontaneously subsided. Her menses had been heavier than normal, but prior to the current bowel problem she had never been treated for anemia. Her parents were of Italian and Polish extraction; she again denied any family history of bleeding.

The diagnosis of the propositus is probably severe, Type 1 vWD.

#### Discussion

vWD is considered one of the most common inherited bleeding disorders. However, the clinical assessment of bleeding and the laboratory evaluation of disease severity are often discrepant. In one study, only 8 of 30 persons with a significantly reduced level of vWF(ag) had

a personal or family history of bleeding.<sup>1</sup> In the case described, the initial history was unremarkable; it was only when specific questions were asked regarding menstrual history and experience with dental extractions that the extent of bleeding became apparent. The fact that the patient had such a history helped in excluding an acquired bleeding disorder. The absence of bleeding with labor and delivery is not surprising; vWF levels rise during pregnancy in most individuals with this disorder.<sup>2</sup> The absence of a family history of bleeding is somewhat unexpected, but a lack of association between genotypes, bleeding history, and ristocetin cofactor levels occurs in many families.<sup>3</sup>

The laboratory diagnosis of vWD is based on the demonstration of a prolonged bleeding time; decreased levels of vWF(ag), ristocetin cofactor activity, and factor VIII; impaired ristocetin-induced platelet aggregation; and the multimeric analysis of plasma vWF.<sup>4</sup> Newer tests include the closure time with the platelet function analyzer (PFA-100™) and the vWF binding assay. The closure time refers to the time required for a platelet aggregate to occlude the aperture of a collagen-coated membrane. The PFA-100 is sensitive to the ability of the vWF to induce platelet adhesion to collagen under high stress, and may be useful for diagnosis and monitoring treatment.<sup>5,6</sup> The vWF binding assay is used to detect abnormal binding of factor VIII as seen in vWD Normandy.<sup>7</sup>

vWD is classified into three types.<sup>4</sup> Type 1 patients have a partial, quantitative deficiency of the factor, whereas type 2 patients have a qualitatively abnormal protein, and those with type 3 have a total deficiency. Initially, the patient under discussion was thought to have a type 3 defect, based on the absence of ristocetin-induced platelet aggregation, very low vWF(ag), undetectable levels of ristocetin cofactor, and low concentration of factor VIII. However, the mild clinical disease and the modestly prolonged bleeding time would be very atypical for a type 3 disorder, which often is characterized by joint and muscle bleeding as well as mucocutaneous hemorrhage. The study that indicated that the patient had type 1 disease was the DDAVP stimulation test. Patients with type 3 disease fail to increase their levels of von Willebrand related activities in response to DDAVP<sup>8</sup>; in the propositus, clear-cut improvement in all activities were recorded. In addition, it was now possible to detect all multimers in the DDAVP-stimulated plasma, albeit in reduced amounts.

Two of the patient's five children were examined. Neither had a bleeding history, and all studies were well within the normal range in one. However, the other child had a modest decrease in vWF activities, considering that she had Group A blood type. There is a significant linkage between the ABO locus and the vWF(ag),<sup>9</sup> such

that persons with Groups A (106%) and B (117%) have considerably higher levels of the factor than those with Group O (75%). Thus, the values of 60% to 70% found in this daughter are at least one standard deviation below the levels found in other persons with blood Group A, suggesting that she may carry the mutant gene.

### Case 8: Acquired Coagulopathy

A 19-year-old pharmacist's wife presented with a 2-day history of epistaxis and spontaneous bruising. She denied previous bleeding problems; extraction of wisdom teeth had been performed without complications. Her menstrual periods were not characterized by excessive bleeding and she had never been pregnant. Her general health was good, there had been no recent weight loss, and she was not taking any medications. The family history was negative for hemorrhagic disorders. On physical examination, there were many large ecchymoses but no petechiae. There was no lymphadenopathy or hepatosplenomegaly. An examination of the stool did not reveal occult blood.

Laboratory evaluation showed a hemoglobin of 12.5 G/dl, hematocrit of 36%, and platelet count of 269,000 per  $\mu$ L, with normal platelet aggregation in response to a variety of agonists. Coagulation studies are shown in **Table 3**. Mixing equal volumes of patient plasma with

normal plasma showed complete correction of the PT test.

It was concluded that the patient had a deficiency of the vitamin-K related clotting factors. The administration of vitamin K<sub>1</sub>, 10 mg subcutaneously, resulted in a decrease in the PT to normal within 24 hours. One week later, a report was received that the patient's serum contained 9 mg/L of warfarin (warfarin levels with therapy are usually 2-4 mg/L). The patient denied the ingestion of warfarin, signed out of the hospital, and did not return for follow-up.

### Discussion

This patient had surreptitious ingestion of warfarin. As a pharmacist's wife, she may have had access to this medication, or it may have been administered by another person. Examples of "anticoagulant malingerers" were reported over 30 years ago<sup>10</sup> and still occur today. An inherited coagulopathy was excluded by the absence of a prior history of bleeding, the negative family history, and the pattern of the laboratory abnormalities.

In the laboratory evaluation of a patient with clinical evidence of bleeding, the basic examinations are the platelet count, a test of platelet function that may be the bleeding time, platelet aggregation, or PFA-100, the aPTT and the PT. In our patient, platelets were normal but both the aPTT and the PT were prolonged. **Table 4** indicates the clinical conditions associated with prolongation of the aPTT, the PT, or both. In patients with hemophilia, the aPTT is abnormal but the PT is normal. Conversely, in patients with factor VII deficiency, the PT is abnormal and the aPTT is normal. Early during the course of warfarin therapy, the factor VII levels fall, and the PT becomes prolonged. With continued treatment, the concentrations of prothrombin, factor IX and factor X also decline and the aPTT becomes prolonged as well.

When the screening tests of hemostasis are abnormal, it is necessary to exclude the presence of a circulating anticoagulant. Most commonly, this may be heparin that has been introduced inadvertently into the clotting tube from a heparinized venous access device. Adding a heparin absorbing resin or heparin-inactivating enzyme to the plasma sample will usually produce a normal clotting result. Another type of anticoagulant that prolongs the aPTT but may also affect the PT is the lupus anticoagulant. This antibody interferes with the activation of clotting factors by anionic phospholipids, thereby prolonging clotting assays.<sup>11</sup> These antibodies may be neutralized by the addition of phospholipids or platelet

**Table 3. Case 8: Clotting Studies.**

Test	Normal Range	Case 8
Bleeding time (minutes)	4-9	5
aPTT (seconds)	25-35	117
Prothrombin time (seconds)	10-12	53
Thrombin time (seconds)	15-18	18
Factor V (%)	50-150	100
Factor VII (%)	50-150	8
Factor IX (%)	50-150	5
Factor X (%)	50-150	7

**Table 4. Interpretation of prothrombin time (PT) and activated partial thromboplastin time (aPTT).**

PT long; aPTT normal	aPTT long; PT normal	PT & aPTT long
Low Factor VII	Low Factor XII, XI	Low Factor V, X
Vitamin K deficiency	Low Factor VIII, IX	Low fibrinogen, prothrombin
Warfarin	Lupus anticoagulant	High hematocrit
Liver disease	Heparin	Vitamin K deficiency
	Low prekallikrein/high molecular weight kininogen	Warfarin
		Liver disease

Adapted from reference 23.

extracts, thus aiding in their identification. A final type of circulating anticoagulant is an antibody directed against a specific clotting factor (see Case 9). Most often this is factor VIII, but any clotting factor may be attacked. When factor VIII is the target, the aPTT but not the PT is prolonged. Often, the inactivation of the clotting factor is time-dependent, so that one should incubate the mixture of patient and normal plasma for an hour or more before concluding that such an inhibitor is not present.<sup>12</sup> Decreased levels of the affected clotting factor will be observed in one-stage clotting assays; however, other clotting factors may also appear to be decreased simply because assays of those factors depend, in part, on the activity of the altered factor. Antibodies to factor VIII may be quantified by the Bethesda assay, which provides a rough estimate of the strength of the inhibitor.

If the patient is deficient in one or more clotting factors, mixtures of equal volumes of patient plasma with normal plasma should result in clotting times that are within 4 seconds of the normal plasma clotting time. One usually uses whichever test, PT or aPTT, that was most abnormal with the patient's plasma alone. Since both the PT and the aPTT were abnormal in the case presented, deficiencies of factors V, X, prothrombin, and fibrinogen, along with other clotting factors, must be considered. A decrease in fibrinogen is readily detected by a specific assay for this factor; alternatively, the thrombin time, which is very sensitive to fibrinogen levels, may be performed. The thrombin time is also prolonged by the presence of heparin or fibrin degradation products. A less common cause for a prolonged thrombin time is previous exposure to the hemostatic agent, fibrin glue.<sup>13</sup> This material, which is occasionally prepared with bovine thrombin and factor V, may elicit antibodies that crossreact with human thrombin and factor V.<sup>14</sup> The normal thrombin time excludes fibrinogen deficiency and thrombin antibodies in this patient. Measurement of factor V is important in differentiating liver disease from vitamin K deficiency or warfarin effect. While isolated factor VII deficiency may be an early indication of liver disease, prolongation of the aPTT usually indicates more advanced liver failure. At this stage, factor V is invariably decreased; the normal value excludes serious liver disease in this patient.

Prothrombin and factors VII, IX, and X require  $\gamma$ -carboxylation of glutamic acid residues for functional activity;<sup>15</sup> this step requires the reduced (hydroquinone form,  $\text{KH}_2$ ) of vitamin K, which acts as a coenzyme for the carboxylase enzyme.<sup>16</sup> Thus, defects in the vitamin K-dependent clotting factors may be due to a deficiency of the vitamin, a lack of responsiveness to the vitamin because of liver disease, or to agents such as coumarins that impair its transition to the reduced form. The diet is

the major source of vitamin K; vitamin produced by the intestinal flora cannot replace dietary vitamin K.<sup>17</sup> Evidence of lack of the vitamin, as reflected by a prolonged PT, is often observed in persons unable to eat, such as those in intensive care units. In addition, because vitamin K is fat-soluble and mainly absorbed in the proximal bowel, deficiencies may occur in persons with celiac disease or other malabsorption syndromes.

The most common cause of deficiencies in prothrombin and factors VII, IX, and X is warfarin therapy. In the case presented, warfarin ingestion was suspected because other causes of vitamin K deficiency, such as poor nutrition or malabsorption, were not evident. The diagnosis was confirmed by identification of warfarin in the blood. The management of warfarin overdose is dependent on the extent of clotting factor deficiency and whether the patient is experiencing serious bleeding. For patients who are not bleeding and have International Normalized Ratios (INRs) of 4.5 to 9.5, vitamin K may be given orally in doses of 1 mg with the expectation that the INR will be between 2 and 3 sixteen hours after dosing.<sup>18</sup> Patients who have higher INRs or are bleeding require more vitamin K, which may be given subcutaneously in a single dose of 10 mg. Intravenous doses ranging from 0.5 to 10 mg have also been effective but anaphylactic reactions were recorded in 1.9% of those receiving the vitamin by this route.<sup>19</sup> Patients who are experiencing serious bleeding should receive blood products; fresh frozen plasma in a dose of 20 ml/kg will transiently raise clotting factor levels until vitamin K increases endogenous synthesis. However, Makris et al<sup>20</sup> observed that factor IX levels may be low in FFP, and the INR may not be completely corrected. On the other hand, prothrombin complex concentrates were very effective in normalizing the PT. Recently, recombinant factor VIIa (rFVIIa) was also shown to be able to correct oral anticoagulant-induced coagulopathy.<sup>21</sup> The disadvantage of these concentrates is the possibility of thrombosis; therefore, they are reserved for use in patients with intracranial or other life-threatening hemorrhage.

In the patient under discussion, a single dose of vitamin K restored normal hemostasis, and blood component transfusion was not required. However, there have been reports of the surreptitious ingestion of long-acting vitamin K antagonists, usually rodenticides.<sup>22</sup> Very large doses of vitamin K, administered for months, are often required to reverse the coagulopathy in these cases.

### Case 9.

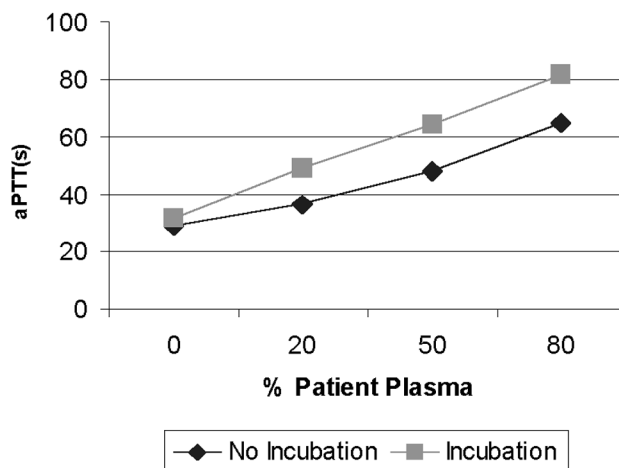
A 62-year-old man with asthma had a radical retropubic prostatectomy complicated by bleeding, but a cause for the bleeding was not determined. Eighteen months later he was involved in a motor vehicle accident and sus-

tained minor trauma to his right flank. Forty-eight hours later, he experienced hematuria. The physical examination was unremarkable. Laboratory studies showed a hemoglobin of 10.1 g/dl, white blood cell count of 9000/mL, and platelets of 326/mL. Platelet aggregation was normal with adenosine diphosphate, collagen, epinephrine, and ristocetin. Additional coagulation studies are shown in **Table 5**. A mixing study was performed (**Figure 1**). This showed that mixing one part of patient plasma with 4 parts of normal plasma prolonged the aPTT from 28 seconds to 36 seconds, suggesting the presence of an anticoagulant. The prolongation of the aPTT was especially apparent after incubation; the clotting time rose from 31 seconds to 49 seconds. This prolongation with incubation is very typical of factor VIII inhibitors. The Bethesda assay indicated that the titer of the inhibitor against human factor VIII was 40 B.U.

**Table 5. Case 9: Clotting studies.**

Test	Patient
aPTT (seconds)	107
PT (seconds)	12
von Willebrand factor (%)	256
Factor VIII (%)	1
Factor VIII inhibitor (B.U., human)	40
Factor VIII inhibitor (B.U., porcine)	< 0.6

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time; B.U., Bethesda Units



**Figure 1. Patient plasma was mixed with normal plasma in the proportions indicated, and activated partial thromboplastin time (aPTT) tests were performed on the mixtures immediately and after 30 min of incubation at 37°C. Slope: non-incubated, 0.4; incubated: 0.6.**

### Discussion

The aPTT was prolonged and the PT was normal, indicating a problem with the intrinsic pathway of coagulation. The specific clotting factors that might be altered are factor XII, prekallikrein, high molecular weight kininogen, and factors XI, IX, and VIII. Deficiencies of the first three are not associated with bleeding. Of the remaining three, factor VIII is the most commonly affected and in this patient was severely decreased. The differential diagnosis of factor VIII deficiency includes classical hemophilia, vWD, and a spontaneous (autoantibody) inhibitor of factor VIII. vWD was excluded by the high level of vWF(ag) and the normal platelet aggregation in response to ristocetin. The patient did not have a lifelong history of bleeding as would be characteristic of severe classical hemophilia, and therefore an inhibitor of factor VIII was most likely. The Bethesda assay indicated an inhibitor titer of 40 B.U. A value of 5 or less is considered low and titers greater than 5 predict that therapeutic doses of human factor VIII would be unlikely to secure hemostasis. No inhibitory activity was detected against porcine factor VIII, suggesting that this material should be clinically effective.

The patient was treated with porcine factor VIII (Hyate-C®) and the hematuria ceased. He was discharged but returned two days later with recurrent hematuria. Cystoscopy showed only diffuse oozing from the bladder wall. Continuous bladder irrigation with ε-aminocaproic acid was begun. Re-treatment with porcine factor VIII decreased the extent of bleeding, but after two weeks of therapy inhibitory activity against this factor was detected (1.3 B.U.) and it was discontinued. He was subsequently treated with recombinant human FVIIa and aPCC, and bleeding stopped. He was discharged on an oral regimen of prednisone and cyclophosphamide.

### III. TREATMENT APPROACHES TO SELECTED BLEEDING DISORDERS

*Jerome M. Teitel, MD\**

#### Mild Hemophilia

The severity of hemophilia may be defined by either clinical criteria or by levels of the deficient clotting factor, and the two usually correlate well. The Scientific Subcommittee on Factor VIII and IX of the International Society on Thrombosis and Haemostasis has suggested that hemophilia be classified as mild when factor levels are between 5% and 40% of normal (0.05-0.40 IU/ml).<sup>1</sup> Most of these patients bleed only with trauma, and are at little risk of the deforming arthropathy, muscle

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contractures, and life-threatening hemorrhage which characterize severely affected hemophiliacs. The conventional management approach for patients with mild hemophilia is on-demand coagulation factor replacement. This is given therapeutically to treat established bleeding or prophylactically when imminent hemorrhage can be anticipated, following trauma or at the time of surgery. Treatment options for such patients include desmopressin for mild factor VIII deficiency, or high purity concentrates of factor VIII or IX.

Desmopressin recruits factor VIII from as yet unidentified storage sites, and the resulting "auto-infusion" may raise baseline factor VIII levels by two- to five-fold in both normal individuals and patients with mild hemophilia A.<sup>2</sup> Although this factor VIII increment is relatively modest, it is often sufficient to arrest or prevent minor bleeding. Any hemostatic response to desmopressin in patients with hemophilia B would be minimal at best, and the drug should not be used in this disorder. Specific details on the clinical use of desmopressin are given below, in the section on von Willebrand's disease.

Exogenous replacement therapy for mild hemophilia may be given as either plasma-derived or recombinant factor VIII or IX concentrate. All the commercially available concentrates are effective and safe, so the choice may be based on considerations such as availability and affordability. The historically devastating complications of life-threatening blood-borne virus transmission, specifically HIV, hepatitis B and hepatitis C, have been virtually eliminated by the introduction of recombinant concentrates, and by the application to plasma derivatives of complementary steps of donor screening (by serological, antigenic, and nucleic acid amplification testing), viral exclusion by chromatographic and immunoaffinity purification techniques, filtration (currently applied only to factor IX concentrates), and viral inactivation by thermal or chemical means.<sup>3</sup> In fact, there have been no instances of transmission of HIV, hepatitis B, or hepatitis C by any of the recombinant or plasma-derived factor concentrates currently used in North America. These processes are less efficient at inactivating small non-enveloped thermostable viruses such as hepatitis A and parvovirus B19, both of which have been transmitted by viral-inactivated factor concentrates. This experience underscores the danger of complacency about viral safety, and highlights the theoretical risk to the blood supply of other unrecognized or novel human pathogens, either conventional viruses or prions. For these reasons, some physicians and consumers have a greater level of confidence in recombinant than in plasma-derived concentrates. The first generation rFVIII concentrates are formulated in human albumin. rFIX and the recently introduced second generation recombinant factor VIII products are formulated in sucrose. It should be borne

in mind that recombinant factor concentrates are not pharmaceuticals but are biological products derived from mammalian cell cultures.

The pharmacokinetics of factor VIII are complex. Clearance is increased in the presence of active bleeding, recent surgery, and blood group O, and is inversely correlated with vWF concentration and age.<sup>4,6</sup> The type of concentrate may also be a factor, as the recovery of recombinant factor VIII in children was superior to that of plasma-derived factor VIII.<sup>7</sup> One should aim for peak post-infusion factor VIII levels of approximately 0.30 to 1.0 IU/ml, depending on the severity of bleeding.<sup>8</sup> These levels can typically be achieved with administration of 15-50 IU/kg of either plasma-derived or recombinant factor VIII concentrate. For non-threatening episodes, clinical monitoring is sufficient, but for life- or limb-threatening hemorrhage or for peri-operative prophylaxis plasma concentrations should be measured. Most mild bleeding episodes respond to a single dose of factor VIII, but one or more follow-up treatments at 12-24 hour intervals may be necessary. For severe bleeding or following major surgery or trauma, therapeutic factor VIII concentrations (nadir levels > 0.50 IU/ml) should be maintained for 5 to 14 days. This can be achieved by intermittent injection every 6 to 12 hours, or preferably by continuous infusion, typically at a rate of 1-4 IU/kg/hr. Short-term prophylactic regimens may be indicated thereafter, for example following central nervous system (CNS) bleeding, or to allow vigorous rehabilitation and physical therapy following orthopedic procedures.

Treatment considerations are similar for factor IX, but with allowance for different pharmacokinetics. The biological half-life of factor IX is approximately 24 hours, roughly double that of factor VIII, but the in vivo recovery is less, varying in recent reports from 0.010 IU/ml per IU/kg for a chromatographically purified concentrate<sup>9</sup> to 0.017 IU/ml per IU/kg for an immunoaffinity purified product.<sup>10</sup> The recovery of recombinant factor IX concentrate is considerably poorer than that of plasma-derived factor IX, and is strikingly age-related, being as low as 0.0066 IU/ml per IU/kg in very young patients,<sup>9</sup> although there is evidence that the correlation is primarily with body weight rather than age.<sup>11</sup> For severe bleeding in hemophilia B patients, an initial dose of 75 to 100 IU/kg of high purity or recombinant factor IX concentrate will usually achieve the desired plasma level of greater than 0.75 IU/ml, following which intermittent injections or continuous infusion can be given.

Adjunctive measures may increase the efficacy or reduce the need for replacement therapy. Simple measures such as rest, immobilization by splinting or other means, selected anti-inflammatory agents (avoiding those that impair platelet function), and the application of cold are valuable additional modalities. Fibrin sealants or topi-

cal bovine thrombin may be useful in surface bleeding or following dental extraction. These products may provoke antibodies to bovine thrombin and/or factor V (a contaminant in some preparations), which can crossreact with their human counterparts, sometimes causing bleeding. Gelatin, microfibrillar collagen, and oxycellulose are often used as hemostatic matrices in the surgical setting. For oral or gastrointestinal bleeding, the use of an antifibrinolytic lysine analog (aminocaproic or tranexamic acid) is often very effective and may dramatically reduce the need for follow-up clotting factor infusions.<sup>12</sup> Oral doses for adults are 6 g for aminocaproic acid and 25 mg/kg for tranexamic acid, given three to four times daily. Tranexamic acid is preferred by many patients because of better gastrointestinal tolerance, but it is not available in the US. Both drugs may also be given intravenously, and tranexamic acid has also been used as an oral rinse for dental bleeding.<sup>13</sup>

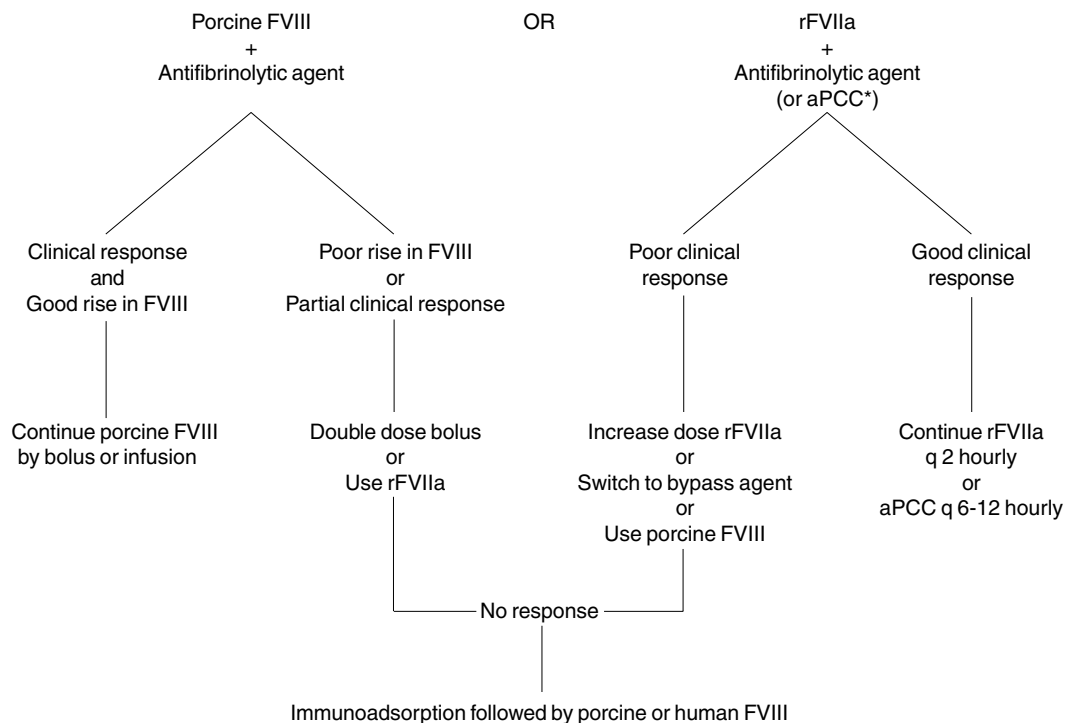
### Acquired Hemophilia

Acquired hemophilia, or acquired autoimmune factor VIII deficiency, is often unrecognized, is difficult to treat, and may be life-threatening. It is a rare disorder, but the often quoted incidence figure of “one per million” may be an underestimation due to under-reporting, failure of accurate diagnosis in cases with fatal outcomes, and

spontaneous remissions. Most affected individuals are elderly, and some have associated autoimmune or malignant disease. Acquired hemophilia also occurs in postpartum women, in whom the natural history is probably distinct, with a greater tendency to spontaneous resolution.<sup>14</sup>

When the diagnosis of acquired hemophilia is established, treatment should be guided by both the clinical situation and the titer of the inhibitor antibody. A suggested treatment algorithm is presented in **Figure 2**. If possible both anti-human and anti-porcine factor VIII inhibitor titers should be measured. Factor VIII autoantibodies in acquired hemophilia are usually incompletely inhibitory, so that factor VIII levels are usually detectable and may be as high as 10-20% of normal values. However, bleeding is much more severe in these patients than in congenital hemophiliacs with similar factor VIII levels. An explanation for this paradoxical observation remains elusive.

Patients with acquired hemophilia occasionally respond to desmopressin, but this is unreliable. Its use is counter-productive if it delays more predictably effective therapy for serious hemorrhage. Human factor VIII is rarely effective in the presence of an inhibitor antibody unless the titer is less than approximately 5 BU. Extracorporeal immunoadsorption using a staphylococ-



**Figure 2. Management of severe internal (life- or limb-threatening) bleeding in acquired hemophilia.**

\* aPCC are used as first line therapy by some hematologists, but it is generally preferable to avoid human plasma-derived products where there are effective alternatives, especially in previously unexposed patients. Concurrent use of antifibrinolytic agents with aPCC should be avoided because of the risk of thrombosis.

Abbreviations: FVIII, factor VIII; rFVIIa, recombinant activated factor VIIa; aPCC, activated prothrombin complex concentrate

cal A affinity matrix may be used to transiently lower anti-factor VIII antibody levels, allowing short-term treatment with factor VIII in otherwise refractory patients.<sup>15</sup>

As factor VIII inhibitor antibodies are usually relatively species-specific, most newly diagnosed acquired hemophilia patients have low or undetectable titers of anti-porcine factor VIII. These patients can usually be successfully treated with factor VIII concentrate prepared from pooled porcine plasma.<sup>16</sup> This product is attractive in that it specifically replaces the deficient protein, and treatment can be monitored by using standard factor VIII assays, either PTT-based or chromogenic. As a foreign protein, porcine factor VIII is itself immunogenic, but neutralizing antibodies may not arise for seven to ten days in previously unexposed patients, by which time the bleeding episode may have been satisfactorily controlled. Transfusion reactions and thrombocytopenia are additional adverse effects, but these are rarely severe enough to interrupt treatment. Porcine factor VIII is conventionally given by intermittent bolus injection, but evidence suggests that administration by continuous infusion is safe and effective.<sup>17</sup> No transmission of a porcine virus to a human recipient has been known to occur with this concentrate. The dose required to achieve therapeutic factor VIII levels is typically 50 to 100 IU/kg in previously untreated patients, but the requirements may rise if an alloantibody response to porcine factor VIII develops during the course of treatment.

The alternative therapeutic approach is the use of inhibitor bypassing agents, which lead to fibrin clot formation independent of factor VIII. Prothrombin complex concentrates (PCC), formerly used to treat hemophilia B, were the first successful bypassing agents. Two deliberately activated derivatives (aPCCs) were subsequently introduced (FEIBA and Autoplex). They are more effective than standard PCCs,<sup>18</sup> but the response is unpredictable, and clinically relevant laboratory monitoring is not available. aPCCs have a good safety record when they are used intermittently in low-risk patients, and they are suitable for self-administration at home in some inhibitor patients. Thrombotic complications including myocardial infarction and disseminated intravascular coagulation are a concern, but these have generally occurred when PCCs or aPCCs are given in intensive high dose schedules or to patients with extensive crush injury or advanced liver disease.<sup>19</sup> The recommended dose is 50-100 units/kg, given at intervals of not less than 8 hours. It should be understood that the units in which the aPCCs are calibrated are not conventional coagulation factor activity units. It is prudent to avoid the concurrent use of antifibrinolytic agents with aPCCs.

An alternative of at least equal and possibly greater efficacy is recombinant factor VIIa (rFVIIa). This agent

has the advantages in principle that are associated with recombinant as opposed to plasma-derived proteins. Animal models,<sup>20</sup> *in vitro* studies<sup>21</sup> and phase 1 clinical trials<sup>22</sup> encouragingly showed that recombinant factor VIIa causes little activation of coagulation. However, thrombotic events have been reported in treated patients,<sup>23-26</sup> and as is the case with aPCC, the true incidence of such complications is still uncertain. Prospective, randomized studies are needed to compare the thrombogenicity as well as the efficacy of rFVIIa and aPCCs. One such study is currently underway. The recommended dose of rFVIIa is 90 µg/kg, and owing to its short half-life further doses must be given every 2 to 4 hours until hemostasis is achieved.

There is sufficient experience with the use of adjunctive antifibrinolytic agents with rFVIIa to recommend this combination as being safe and effective.<sup>27</sup> rFVIIa has a short plasma half-life, which may be a logistical disadvantage in some settings, and may encourage the use of additional unnecessary doses of this costly agent before the response to the first treatment can be evaluated. Some hematologists have given rFVIIa by continuous infusion, but this mode of administration must be considered experimental.<sup>28</sup> As for aPCCs, no laboratory marker has been established to guide therapy. Some clinicians follow plasma factor VII activity, which rises to supra-physiological levels during treatment,<sup>24</sup> but the validity of using this as a surrogate marker for the clinical response has not been rigorously validated.

In most patients with acquired hemophilia immunomodulation should be instituted concomitantly with hemostatic therapy. There is no consensus on the optimal regimen. Combination treatment with agents of demonstrated efficacy should be given.<sup>29</sup> These include intravenous immune globulin, corticosteroids, and alkylating agents. Immunoabsorption is probably also of value when the initial anti-factor VIII titer is high.<sup>30</sup> In women who develop factor VIII inhibitors post-partum and in whom bleeding is well controlled and not acutely threatening it may be possible to withhold immunosuppression, as the autoantibodies in this setting tend to resolve spontaneously.

### **von Willebrand's Disease**

Type 1 vWD, the most common subtype, is caused by partial quantitative deficiency of vWF. It is characterized by impaired platelet adhesion to exposed subendothelium in high shear vessels and by enhanced clearance of factor VIII, leading to variable and mild factor VIII deficiency. The clinical expression is mild to moderate bleeding, primarily from mucocutaneous sites. It may be difficult to establish a diagnosis of type 1 vWD for several reasons.<sup>31</sup> Functional and antigenic vWF levels in affected individuals overlap with normal ranges,

and they fluctuate with ABO blood group, age, thyroid function, and pregnancy. In addition, there is no single definitive functional assay, and genotypic testing for this highly heterogeneous disorder is not yet feasible.

Most patients with type 1 vWD respond to desmopressin. It may be given by intravenous or subcutaneous injection or by intranasal spray. The latter two routes are suitable for self-treatment at home. The dose of the injectable form is 0.03 µg/kg, but we do not exceed a dose of 20 µg. For convenience, subcutaneous injection of the contents of a 1 ml vial of the 15 µg/ml formulation is often effective for adult patients. The intranasal dose is 150 µg for children and 300 µg for adults, equivalent to 1 and 2 sprays respectively. The response to desmopressin is highly variable, reflecting the heterogeneity of type 1 vWD. However, the response in any one person is relatively constant. Therefore a test infusion in the non-bleeding state is advisable in order to identify patients who are candidates for treatment. Patients in whom intranasal treatment is under consideration should be retested by this route. Adverse effects, such as headache and flushing, are usually mild and transient. As desmopressin has antidiuretic activity,<sup>32</sup> patients should be advised to modestly restrict fluid intake within 24 hours of administration. More careful attention must be given to this adverse effect in infants and in post-operative patients. There have been a few reports of acute arterial thromboembolic events (myocardial infarction or stroke) following the use of desmopressin in elderly patients with established vascular disease.<sup>33,34</sup> It would be prudent to avoid this drug in such patients. The vWF response to repeated doses of desmopressin declines if the treatment interval is less than 48 hours, but this effect is less marked in vWD than in mild hemophilia.<sup>35</sup> The response to 3 to 4 consecutive daily doses is usually adequate.

Most bleeding episodes in vWD are from mucosal or cutaneous sites. Potentially avoidable hysterectomies have been performed in many women with unrecognized or poorly managed vWD.<sup>36</sup> For management of menor-

rhagia, desmopressin and/or aminocaproic or tranexamic acid given at the onset of menses may be effective.<sup>37,38</sup> Patients should be counseled that in some cases 2 to 3 daily doses of desmopressin and a 3 to 5 day course of antifibrinolytic therapy may be required. Oral contraceptive agents are often effective in managing menorrhagia in patients with type 1 vWD. As low doses of estrogen have little effect on vWF levels, its efficacy presumably results from its effect on the endometrium.

On rare occasions, patients with type 1 vWD may require transfusional replacement therapy. In these unusual situations, concentrates containing both factor VIII and the full range of vWF multimers are recommended. The classes of available agents are shown in **Table 6**. Administration of these products to vWF patients leads to "synthesis" of factor VIII (release of the clotting factor into the circulation). Based on studies in severe (type 3) vWD patients, these infusions result in a very long apparent factor VIII half-life, approximately 40 hours, compared with approximately 12 hours for vWF antigen and activity.<sup>39</sup> The FDA now requires that plasma products approved for use in vWD be labeled in terms of vWF, and hematologists are starting to become familiar with prescribing and monitoring therapy in ristocetin cofactor (RCof) units. The recommended dosage is 40-80 RCof units/kg depending on the severity of bleeding. For severe hemorrhage or major surgery, repeat doses may be given at 8-12 hour intervals until hemostasis is secured. Therapy may be monitored by the RCof assay, aiming for nadir levels of  $\geq 0.5$  IU/ml. Excellent correction of the deficient factor VIII activity will also be achieved by this schedule. In some situations, such as post-operatively and in the presence of soft tissue hemorrhage, it appears that correcting factor VIII deficiency is more important than correcting vWF.<sup>40</sup> However, much of the experience leading to this conclusion was gained using products containing both factor VIII and vWF, and the latter was generally monitored by the skin bleeding time, which is no longer accepted as a valid marker of the therapeutic response. If

**Table 6. Therapeutic agents for von Willebrand disease (vWD).**

Agent	Comments
<b>Desmopressin (DDAVP)</b>	Useful in most cases of type 1 disease, occasionally in type 2 (may worsen thrombocytopenia in type 2B)
<b>Antifibrinolytic agents</b>	For mucosal or cutaneous bleeding; tranexamic acid is better tolerated orally than aminocaproic acid
<b>Combination oral contraceptives</b>	Used only for menorrhagia
<b>vWF/VIII concentrates</b>	Now commonly labeled and prescribed in von Willebrand factor (vWF) (ristocetin cofactor) units
<b>High purity vWF concentrate</b>	In clinical trials
<b>Cryoprecipitate</b>	Recommended only if lyophilized concentrates are not available
<b>Fibrin sealants or topical thrombin</b>	Often useful in surface bleeding and dental extraction; risk of antibodies to thrombin and/or factor V
<b>Platelet concentrates</b>	Specific replacement of platelet vWF in severe deficiency; rarely necessary
<b>Recombinant factor VIIa</b>	Theoretically useful; has been used in acquired vWD

one's treatment aim is to maintain factor VIII levels, less frequent dosing with VIII/vWF concentrates (typically once a day) will be needed, because of the prolonged half-life of factor VIII in vWD patients. The available literature suggests that these less intensive treatment regimens are usually successful.<sup>41,42</sup>

A very high purity vWF concentrate containing little factor VIII is available in Europe, and a recombinant vWF product is under development. Although cryoprecipitate is effective, it is no longer preferred for treatment of vWD, as it is not virally attenuated. High purity and most intermediate purity factor VIII concentrates are generally not suitable for patients with vWD. The former are devoid of vWF, and most of the latter products are deficient in the hemostatically effective high molecular weight vWF multimers.

### Factor XI Deficiency

Factor XI deficiency, the least rare of the non-hemophilic congenital coagulation factor deficiencies, should be considered in any patient with unexpected bleeding, especially among Jews, in whom two of the causative mutations occur with high prevalence. Spontaneous bleeding is rare. The factor XI gene is autosomal, and menorrhagia is a frequent presenting symptom in women.<sup>43,44</sup> The clinical expression factor XI deficiency correlates poorly with the plasma factor XI concentration, but most individuals whose levels are below 0.15 IU/ml will experience excessive bleeding after trauma or surgery.<sup>42</sup> Some patients with less severe deficiency (factor XI levels as high as 60-70% of normal) have a bleeding tendency.

There is anecdotal evidence that some patients with partial factor XI deficiency respond to desmopressin.<sup>45</sup> It is unclear whether this response is due to modest increments in factor XI or to more substantial increases in vWF and factor VIII. In any event, desmopressin may be considered for minor bleeding episodes in mildly affected patients. Antifibrinolytic agents are frequently effective for surface or mucosal bleeding, and their use may avoid the necessity of administering plasma products for procedures such as dental extraction. However many severely factor XI deficient patients require replacement therapy. Plasma is suitable for this purpose. As a non-concentrated product, plasma can achieve only modest increments in factor XI levels, but in most cases it is sufficient to secure hemostasis. The concentration of factor XI is normal in pooled solvent/detergent treated plasma, and use of this product obviates the risk of transmission of lipid-enveloped viruses.<sup>46</sup> Virally inactivated factor XI concentrates derived from human plasma are available from European manufacturers.<sup>47</sup> These concentrates allow efficient replacement therapy, but they have thrombogenic potential.<sup>48</sup> It is therefore recommended to avoid peak therapeutic factor XI levels greater than 0.70 IU/ml, to use them with great caution in patients with atherothrombotic vascular disease, and to consider the concurrent use of thromboprophylaxis.<sup>49</sup> Individual doses should not exceed 30 IU/kg, with an expected factor XI yield of approximately 0.02 IU/ml per IU/kg. The half disappearance time is variable but quite long, approximately two days on average.

**Table 7. Available clotting factor concentrates. Plasma-derived except where noted as recombinant. Not all these concentrates are available in all countries.**

Concentrate	Comments
*Factor VIII	Intermediate and high purity preparations available
*Factor VIII, recombinant	Stabilized in albumin or sucrose; full-length or B-domain deleted
*Factor VIII, porcine	For factor VIII inhibitor patients
Prothrombin complex (PCC)	Calibrated in factor IX units; variable concentrations II, X, and VII
*Factor IX	High purity, for hemophilia B
*Factor IX, recombinant	Full length, stabilized in sucrose
*Activated prothrombin complex (APCC)	For factor VIII or IX inhibitor patients
*Factor VIIa, recombinant (rFVIIa)	For factor VIII or IX inhibitor patients; may develop wider indications
*von Willebrand factor (vWF)	VIII/VWF or single component VWF (see Table 6)
*Factor XI	Co-purified with AT III; heparin added
Factor VII	For congenital VII deficiency; factor VIIa is an alternative
Factor XIII	Suitable for long-term prophylaxis
Fibrinogen	Virally inactivated alternative to cryoprecipitate

\*See text for more complete discussion of these products.

## Concluding remarks

Bleeding that is unprovoked, is of unexpected volume, or occurs from unexpected or multiple sites suggests the possibility of a new onset or previously unrecognized systemic bleeding disorder. A high index of suspicion is necessary to recognize threatening acquired syndromes such as factor VIII inhibitor autoantibodies, but it is not unusual for mild congenital bleeding disorders to remain undiagnosed until relatively late in life. Such syndromes can remain subclinical until hemostasis is further compromised by events such as trauma, surgery, instrumentation, menarche, parturition, organ dysfunction, or drug effect. The management of patients with unexpected bleeding should be based on the clinical scenario and on the results of screening or specific laboratory tests. Only in exceptional circumstances should it be necessary to administer plasma as non-specific replacement therapy in the absence of a diagnosis. The classes of available concentrated clotting factor concentrates are listed in **Table 7**. In general, plasma products should be given judiciously, and the use of pharmaceuticals to reduce or avoid their use is encouraged. The diagnosis of a congenital bleeding disorder may lead to family screening studies and antenatal testing, and in patients found to have acquired hemophilia a search for associated autoimmune or malignant disease is mandatory, except for those in whom the inhibitor has arisen post-partum. Patients who receive plasma derivatives or who may need them in the future should be screened for antibodies to HIV and hepatitis C, and they should be offered vaccination against hepatitis B and A if they are seronegative for these viruses.

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