**Inherited Bleeding Disorders**

**Guy Young**

1. An 8-year-old girl is referred to you for epistaxis and easy bruising. She has had an extensive evaluation by another hematologist, including a normal CBC, PT, PTT, factor XIII level, von Willebrand levels, and platelet function testing. She comes to your office for a second opinion, and you repeat all the testing, all of which is normal. She does not have hypermobility on physical exam.

Because of the recurrent epistaxis, which has a stop with pressure and start again pattern, you prescribe aminocaproic acid and ask the patient to follow up. At follow-up, the family reports that her epistaxis stopped completely. Each time the epistaxis resumes, it responds briskly to aminocaproic acid. In addition, her bruises resolve while she is on this treatment.

Which of the following is the most likely deficiency in this patient?

A. Factor XI

B. Factor XII

C. Factor XIII

D. Plasminogen activator inhibitor type 1 (PAI-1)

E. Plasminogen

**Explanation**

This patient does seem to have a bleeding disorder because she has recurrent bleeding from 2 different sites. Although an extensive “traditional” evaluation was negative, her impressive response to aminocaproic acid (an antifibrinolytic agent) suggests that she has excessive fibrinolysis. As its name implies, PAI-1 is an inhibitor of plasminogen activator (tPA). In its absence, tPA, which is present in relatively large amounts in the mucus secretions, is unchecked and leads to excessive breakdown of newly formed clots. With the typical minor traumas of day-to-day life, the small bleeds that begin in the nose or skin stop bleeding because there are no deficiencies of procoagulants, but the clots are quickly lysed because of the inability to fully inhibit tPA. Aminocaproic acid inhibits tPA and thereby prevents the rebleeding this girl is experiencing. The other answers cannot be correct because factor XI and factor XII deficiency would result in a prolonged PTT, and factor XII deficiency would not cause bleeding in any case. Factor XIII deficiency cannot be the cause because the patient’s factor XIII levels were normal, and, regardless, this would be an unusual presentation for factor XIII deficiency. If anything, plasminogen deficiency would cause thrombosis and not bleeding.

2. A 10-year-old boy coming from another country as a refugee arrives in your emergency department with severe anemia and is found to have had a ruptured spleen. He has never had any laboratory testing. There is no antecedent trauma. He has two brothers and two sisters, and one of his older sisters has had recurrent miscarriages. Both he and his sister have numerous bruises and, upon questioning, offer a history of large hematomas with minor trauma.

Which of the following is the most likely diagnosis?

A. Hemophilia A

B. Hemophilia B

C. Congenital afibrinogenemia

D. Factor XIII deficiency

E. Factor X deficiency

**Explanation**

As the name implies, bleeding disorders all result in excessive bleeding of a variety of forms and severities. Some have other unique features, two of which figure in this question: splenic rupture and recurrent miscarriages, which are not uncommon in patients with congenital afibrinogenemia. The other bleeding disorders listed are not associated with spontaneous splenic rupture, and most (other than factor XIII deficiency) are not associated with recurrent miscarriages.

3. You are asked to see an otherwise healthy 7-year-old boy with easy bruising, including in unusual locations such as the abdomen and back, and occasional epistaxis lasting 5 to 20 minutes occurring about once per month. He was seen by another hematologist, who did an extensive evaluation including PT, PTT, fibrinogen and factor XIII levels, PAI-1 level, von Willebrand disease testing on three occasions and platelet aggregation, electron microscopy, and flow cytometry. The family is seeking a second opinion.

Which of the following is the best next step?

A. Repeat all the tests listed above

B. Examine the patient for hypermobility

C. Check a pre-kallikrein level

D. Check a BUN and creatinine

E. Reassure the family that the patient does not have a bleeding disorder

**Explanation**

Based on the unusual pattern of bruising and the nosebleeds lasting in some cases up to 20 minutes, this patient probably has a bleeding disorder, so answer E would not be correct. Repeating the tests, including multiple rounds of testing for von Willebrand disease, is unlikely to reveal anything other than what was found by the previous hematologist. A low pre-kallikrein will prolong the PTT and is not associated with a bleeding diathesis, so answer C is incorrect. Renal dysfunction can result in these symptoms, but this is caused by platelet dysfunction and should be manifested in abnormal results on platelet aggregation testing. Furthermore, this child is otherwise healthy, so it would be rare for the presenting sign of renal dysfunction to be secondary to uremia-induced platelet dysfunction. Therefore, the correct answer is B. Hypermobility syndromes such as Ehler-Danlos can often present with mild bleeding symptoms, as this patient has, and can be easily diagnosed with a guided physical exam.

4. A 2-year-old with severe hemophilia A presents for his annual visits, and his parents report that in the last 3 months he has had three joint bleeds, with two occurring in the right ankle and one in the left elbow. He received six doses of factor to treat these bleeds and responded well. You decide to initiate prophylaxis with every-other-day factor infusions at 40 IU/kg/dose. A month after initiation, the patient returns to the clinic, and the family reports that he has two additional bleeds in his right ankle.

What should be the next step in his management?

A. Order a Bethesda assay to check for an inhibitor.

B. Increase the dosage or frequency of prophylaxis dosing.

C. Refer the patient to physical therapy.

D. Perform an MRI of the right ankle.

E. Refer the patient to orthopedic surgery.

**Explanation**

Any patient with hemophilia on prophylaxis who is having breakthrough bleeding that is frequent or unexpected should be evaluated for the presence of an inhibitor. In this case, the likelihood for an inhibitor is quite high, given that the patient is within his first 20 exposure days to factor VIII concentrates. Therefore, the correct answer is A. The patient is receiving adequate dosing for prophylaxis, so increasing the dosage or frequency is unlikely to help, and checking for an inhibitor should come first. An MRI may demonstrate the blood in the joint or hemosiderin, but this will not solve the problem of breakthrough bleeding during prophylaxis, nor will a referral to physical therapy or orthopedic surgery.

5. A 15-year-old girl with heavy menstrual bleeding presents to the hematology clinic, and after a detailed evaluation by adolescent medicine and hematology she, is found to have a bleeding disorder with the following labs:

PT: 10 seconds (normal 8-13 seconds)

PTT: 32 seconds (normal 24-38 seconds)

von Willebrand factor antigen: 93%

von Willebrand factor activity: 29%

Factor VIII activity: 84%

von Willebrand multimers: present in normal amounts

Platelet aggregation studies: normal platelet aggregation

Factor XIII activity: 103%

Which of the following combinations of medications would be effective for managing this patient’s heavy menstrual bleeding?

A. Desmopressin, aminocaproic acid, hormonal medication

B. Desmopressin, von Willebrand factor concentrates, hormonal medication

C. Factor VIII concentrates, von Willebrand factor concentrates, aminocaproic acid

D. von Willebrand factor concentrates, aminocaproic acid, hormonal therapy

E. Desmopressin, aminocaproic acid, hormonal therapy

**Explanation**

The laboratory tests confirm that this patient has type 2M von Willebrand disease (vWD). This result is based on the discrepancy between the von Willebrand factor antigen, which is normal, and the von Willebrand factor activity, which is very low. Typically, a ratio of activity to antigen that is 0.5 or less suggests type 2M vWD. A more current way to make a diagnosis is to test for mutations in exon 28 of the von Willebrand factor gene. Type 2M vWD is caused by a dysfunction in von Willebrand factor whereby it cannot properly bind to platelets. The key point in this question is to recognize that desmopressin is not effective in type 2M vWD because secreting more dysfunctional von Willebrand factor from the endothelial cells will not be helpful. Therefore, answers A, B, and E are incorrect. Factor VIII concentrates are not indicated in vWD, so answer C is also incorrect. Answer D includes the three main treatments for a girl with vWD and heavy menstrual bleeding, including replacing the missing von Willebrand factor, antifibrinolytic agents, and hormonal therapy.

6. You were asked to consult on a newborn on day of life 2 due to excessive bleeding after circumcision. The PTT is prolonged and the PT is normal. You order factor assays, and the results are as follows:

 Factor VIII: 8%

 Factor IX: 12%

 Factor XI: 15%

 Factor XII: 6%

What is the most likely diagnosis?

A. Factor VIII deficiency

B. Factor IX deficiency

C. Factor XI deficiency

D. Factor XII deficiency

E. All the factor levels are normal for age

**Explanation**

To evaluate for factor deficiencies in neonates, it is critical to know which factors are physiologically deficient and which are within the typical adult range. Most factors are physiologically deficient in neonates, particularly in the first week of life, but factor VIII and von Willebrand factor are normally higher in newborns than in adults, whereas factors IX and XI are normally lower. Factor XII also is lower in the newborn period, but this deficiency does not cause bleeding. Therefore, in this scenario, the correct diagnosis is factor VIII deficiency.

7. You are evaluating a 12-year-old girl who was admitted to the hospital for anemia (hemoglobin concentration of 85 g/L) who has had significant vaginal bleeding with the onset of menarche 3 weeks ago. Her family history includes several female relatives with von Willebrand disease (vWD).

Which of the following tests are necessary to detect the presence of type 2A vWD?

A. von Willebrand factor (vWF) antigen concentration

B. Ristocetin cofactor activity

C. Factor VIII activity

D. vWF multimer analysis

E. Ristocetin-induced platelet aggregation with low-dose ristocetin

**Explanation**

There are several types of vWD. Types 1 and 3 are caused by a partial or complete deficiency of vWF, whereas the type 2 variants are caused by specific functional defects in vWF. Although answers A, B, and C are important in the evaluation of type 2A vWD, they are not diagnostic, and determining the structure of the vWF multimers is the only way to reveal the diagnosis. In type 2A vWD, there is an absence of high- and medium-molecular-weight multimers (see figure). The ristocetin-induced platelet aggregation assay with low-dose ristocetin is important for the diagnosis of type 2B vWD.



8. A 1-year-old boy presents to the emergency department with irritability and vomiting, and a CT scan demonstrates a large intracranial parenchymal hemorrhage. The mother reports that his only other bleeding symptom was prolonged bleeding from the umbilical stump. The patient comes from a large pedigree with numerous male and female first- and second-degree relatives, but there is no history of excessive bleeding in any of them.

Which laboratory test pattern is most consistent with this history?

A. Normal PT and PTT

B. Prolonged PT, normal PTT

C. Normal PT, prolonged PTT

D. Prolonged PT, prolonged PTT

**Explanation**

This presentation is most consistent with factor XIII deficiency. The family history suggests a disorder inherited in an autosomal recessive pattern. The location of the two hemorrhages (intracranial and umbilical stump) are classic for factor XIII deficiency. Because factor XIII is not necessary to form the initial fibrin clot, which is the endpoint of the PT and PTT assays, both tests are normal in the presence of even severe factor XIII deficiency. Factor XIII activation results in the crosslinking of fibrin monomers, which can be assessed qualitatively in a clot solubility assay using either urea or acetic acid. Thus, the correct answer is A.

9. A 10-day-old boy is being seen in the emergency department due to lethargy and poor feeding. His anterior fontanel is full. A CT scan demonstrates an intraparenchymal hemorrhage. Coagulation tests are ordered with the following results: PT 37 seconds (normal 9.7 to 11.2 seconds) and PTT 66 seconds (normal 22 to 36 seconds).

This child may have which of the following factor deficiencies?

A. Factor VII

B. Factor VIII

C. Factor IX

D. Factor X

E. Factor XI

**Explanation**

The PT and PTT are screening tests performed to evaluate most clotting factors (factor XIII is not evaluated by these assays). It is critical to understand which assays are affected by each factor to make the correct diagnosis rapidly, particularly when treatment is warranted as soon as possible. In this scenario, both the PT and PTT are prolonged, which means that for a single factor deficiency, that factor would have to reside in the common pathway, which includes fibrinogen and factors II, V, and X. Therefore, the correct answer is D. Factor VII deficiency would not prolong the PTT, and deficiencies of factors VIII, IX, or XI would not prolong the PT.

10. You are seeing a patient who was transferred from another hospital for intracranial hemorrhage after a motor vehicle accident. In the previous hospital the patient received fresh frozen plasma, cryoprecipitate, and a platelet transfusion before any lab tests were ordered. The mother tells you that there are family members with a history of excessive bleeding but cannot be more specific. You are now asked to determine whether the patient has a bleeding disorder.

Which of the following tests must you wait the longest for to obtain a valid result?

A. Factor VIII level

B. Factor IX level

C. Factor X level

D. Factor XI level

E. Factor XIII level

**Explanation**

In this scenario, it is possible that the child has a factor deficiency that led to the intracranial hemorrhage. To request lab testing that you can rely on, you must know the half-life of the clotting factors (all of which were infused with the blood products the patient received) and, in this instance, which one has the longest half-life. The clotting factor with by far the longest half-life is factor XIII, approximately 10 days. The half-life of factor VIII is 8 to 12 hours, factor IX is 20 to 24 hours, factor X is approximately 40 hours, and factor XI is approximately 80 hours. Thus, after the transfusion of the blood products, it will take the longest for factor XIII to clear enough to assess the true level in the patient.

11. An 11-year-old boy with mild hemophilia is on vacation with his family in Zion National Park in southern Utah. While on a hike, he stumbles over a rock, and shortly thereafter he complains of pain in his right ankle. The trauma was fairly trivial. His family takes him to the regional medical center in St. George, where he is noted to have significant ankle swelling. The mother tells the physician that her son has hemophilia A, and her hematologist told her that such injuries require treatment with a factor VIII concentrate. The physician tells her they do not have factor VIII at this hospital, and the nearest hospital that has it is in Salt Lake City, which is a 6-hour drive away.

Which of the following is the best treatment option?

A. Driving the boy to Salt Lake City to receive factor VIII

B. Aminocaproic acid

C. Fresh frozen plasma

D. Desmopressin

E. A nonsteroidal antiinflammatory drug

**Explanation**

This patient probably has an acute trauma-related ankle hemarthrosis. The management for such a patient must include increasing the factor VIII level as quickly as possible. Among the options above, only answers A, C, and D will increase the factor VIII level, and only answers C and D can do so quickly. The best option for this patient would be to administer a dose of desmopressin. Most patients with mild hemophilia will have a significant and rapid rise in their factor VIII level after either an intravenous infusion or an intranasal dose. Fresh frozen plasma contains 1 IU/mL of factor VIII, and a 10-mL/kg infusion would increase the factor VIII level by about 10%. Nevertheless, fresh frozen plasma is no longer used to treat factor VIII deficiency. Because this hospital has a blood bank, presumably they also have cryoprecipitate, which would be a much better option for treating factor VIII deficiency because cryoprecipitate has a substantially higher concentration of factor VIII than plasma, making answer C incorrect. Aminocaproic acid is a useful adjunctive therapy in hemophilia but is not considered effective for managing hemarthrosis. A nonsteroidal antiinflammatory agent would generally be contraindicated when there is concern for hemarthrosis. Celecoxib could be used because it does not affect platelet function; however, it would not be the best treatment option.

12. A 2-year-old girl presents with prolonged oozing from her tongue after apparently biting it. Her platelet count is normal. Her PT is 68 seconds (normal range is 9 to 12 seconds), her aPTT is 123 seconds (normal range is 22 to 33 seconds), and her thrombin time is 58 seconds (normal range is 12 to 18 seconds).

Which of the following tests should be ordered next?

A. Factor XIII level

B. Fibrinogen level

C. Factor X level

D. Ristocetin cofactor activity

E. Pre-kallikrein level

**Explanation**

Although infrequently ordered, thrombin time is still available; it is a test that assesses the presence and function of fibrinogen. As its name implies, one adds thrombin to a plasma sample, which then takes a short time to clot in the presence of a normal amount of and function of fibrinogen. Therefore, the correct answer is B. All of the other choices would not result in a prolonged thrombin time. Factor XIII is not necessary for a normal result in any of the coagulation screening assays. Factor X is necessary for normal clotting in the PT and aPTT but not the thrombin time. Ristocetin cofactor activity assesses the platelet binding function of von Willebrand factor. Pre-kallikrein is a contact-activating factor necessary for a normal aPTT but not a normal PT or thrombin time. Of note, most laboratories perform a functional fibrinogen assay, making the thrombin time unnecessary for the evaluation of afibrinogenemia (it is simpler to just order a fibrinogen level); however, it is still an important screening test for dysfibrinogenemia, a condition (usually inherited) that can lead to either excessive bleeding or thrombosis depending on the mutation in the fibrinogen gene.

13. A 13-year-old girl develops menorrhagia at the onset of menarche, necessitating several packed red blood cell transfusions. She also needed a transfusion after a tonsillectomy and adenoidectomy when she was 5 years old, but the bleeding was never evaluated. She also has easy bruising and gingival bleeding daily when she brushes her teeth. She is referred to you by her pediatrician for an evaluation. There is a history of menorrhagia in her mother, although she never needed any transfusions. In addition, there is a history of epistaxis and postsurgical bleeding in her father. Her parents have normal aPTTs, but the patient has an abnormal screening laboratory test.

Which of the following is the most likely diagnosis?

A. Factor VII deficiency

B. Factor VIII deficiency

C. Factor IX deficiency

D. Factor XII deficiency

E. Factor XIII deficiency

**Explanation**

Clearly, there is an inherited bleeding disorder in this family, and it affects both parents. Given that the parents have normal aPTTs, it strongly suggests that the father does not have hemophilia (deficiency of factor VIII or IX). Furthermore, the bleeding and inheritance pattern suggests an autosomal recessive disorder. That makes answers B and C incorrect. Factor XII deficiency does not cause bleeding symptoms, making answer D incorrect. The presence of an abnormal screening test makes factor XIII deficiency very unlikely. Thus, this patient has factor VII deficiency. This disorder can be symptomatic in the heterozygous state (as in the parents) and is more severe in the homozygous state, which can be presumed to be the case for this patient given her more severe bleeding history. It is important to note that factor VII deficiency can result in all manner of bleeding; however, in the heterozygous state, factor VII deficiency will generally cause only mucocutaneous and postsurgical bleeding, whereas the homozygous or compound heterozygous state can result in more severe bleeding, including joint and muscle bleeding and, rarely, intracranial hemorrhage in addition to the mucocutaneous bleeding.

14. An 18-month-old boy with severe hemophilia A is being seen in the clinic for his second joint bleed in 3 months. The first one was in the right elbow and the second one is in the right ankle, for which he has received a total of three doses of recombinant factor VIII with a good response. He also has extensive bruising, especially on the lower extremity. He is an only child and recently was placed in daycare.

Which of the following is the best next step?

A. Order an inhibitor titer.

B. Check him for other bleeding disorders.

C. Start prophylaxis with factor VIII concentrates.

D. Get an MRI of his right ankle.

E. Suggest he not go to daycare.

**Explanation**

In general, patients with severe hemophilia will need prophylactic factor VIII therapy to prevent bleeding, and typically it is started after the first joint bleed or certainly after the second joint bleed. It can be started in the absence of joint bleeding, depending on the family’s preference. Therefore, answer C is correct. The child has responded well to factor for his two previous bleeds, so it is unlikely that he has an inhibitor at this point. The symptoms are classic for severe hemophilia, so there is no need to evaluate him for other diagnoses. There is no indication to get an MRI for an ankle bleed. MRIs are often done to detect chronic joint disease, which this child does not have at this point. With prophylaxis, there is no need to remove him from daycare, and often parents cannot do that for socioeconomic reasons.

15. A 4-year-old girl with a history of recurrent epistaxis and easy bruising is referred to you for evaluation. She is found to have a prolonged PTT and a factor VIII level that is less than 1%. Both parents have a history of excessive bleeding. She is admitted with a severe episode of epistaxis, and your colleague orders 40 IU/kg of recombinant factor VIII. Her epistaxis resolves initially but within an hour starts again at the same severity as before.

What is the best next step?

A. Infuse a von Willebrand factor concentrate.

B. Give another dose of recombinant factor VIII concentrate.

C. Call otorhinolaryngology to pack her nose.

D. Check for a factor VIII inhibitor.

E. Administer desmopressin.

**Explanation**

There are two key points in this scenario. First, the patient is a girl, which makes it highly unlikely she would have severe hemophilia because of the X-linked inheritance pattern. Second, both parents have a history of excessive bleeding, suggesting an autosomal recessive pattern of inheritance. Finally, she does not respond appropriately to a recombinant factor VIII concentrate. Such a patient probably has type 3 von Willebrand disease because they have exceedingly low, even unmeasurable factor VIII levels, but it is inherited in autosomal recessive pattern, meaning boys and girls are affected equally. Therefore, the next best step is to infuse a von Willebrand factor concentrate. More factor VIII an hour after the first dose will not help because in the absence of von Willebrand factor, the half-life of infused factor VIII is extremely low. Asking otorhinolaryngology to help is not out of the question, but it will not solve the underlying problem, which is absence of von Willebrand factor. She is unlikely to have an inhibitor, becuase she had some response to the infused factor VIII, and desmopressin, although helpful in type 1 von Willebrand disease, will not help in type 3 because it works by releasing von Willebrand factor from its storage area, and this patient does not have any von Willebrand factor to release.

16. A 12-year-old girl presents to your clinic with significant menstrual bleeding at the onset of menarche and is noted to have a hemoglobin of 9.9, although she is not symptomatic from her anemia. Her mother reports that she has a history of epistaxis when she was a child with some episodes lasting 30 minutes and that she also has heavy menstrual bleeding. Which of the following tests will lead to the most likely diagnosis?

A. Factor XI level

B. Factor X level

C. Factor XIII level

D. Ristocetin cofactor activity

E. Fibrinogen level

Explanation

Heavy menstrual bleeding at the onset of menarche is a common presentation for bleeding disorders in adolescent girls, and the most common bleeding disorder that results in such symptoms is von Willebrand disease (VWD). The diagnosis of VWD can be made with the ristocetin cofactor activity assay, making D the correct answer. While the other answers can all lead to a diagnosis of a bleeding disorder, deficiencies of Factor X and Factor XIII and fibrinogen are very rare. Factor XI deficiency is more common, especially among Ashkenazi Jews, but does not usually lead to bleeding symptoms in the absence of surgery or trauma.

17. A newborn male has severe bleeding after circumcision, resulting in the need for a blood transfusion. You are called to consult on this child, and you diagnose him with severe hemophilia A. Upon taking a family history, you note that no other family members have hemophilia, other bleeding disorders, or a bleeding diathesis. Which of the following is the most likely outcome of genotyping the Factor VIII gene?

1. No mutation will be found because there is no family history.
2. A missense mutation in the F8 gene will be identified.
3. An inversion mutation in the F8 gene will be identified.
4. A nonsense mutation in the F8 gene will be found.
5. A large deletion of the F8 gene will be found.

Explanation

By far the most common mutations in severe hemophilia A are inversion mutations, with an inversion of intron 22 being the most common, accounting for approximately 45% of the mutations in severe hemophilia, making C the correct answer. The other mutations in options B, D, and E all do occur but are much less common individually. Option A is incorrect because the lack of a family history does not mean this patient won’t have a mutation. On very rare occasions, no mutation in the F8 gene is found upon genotyping, but this is most likely technique-related, and with improved sequencing techniques, such instances are becoming even less common.