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**Hemophilia & von Willebrand Disease**

*2013 Von Willebrand Disease and Rare Bleeding Disorders*

**Question 1:**

A 6 year old male is referred to you for easy bruising. Which of the following findings on his history is most consistent with von Willebrand disease?

1. Prolonged bleeding after circumcision.
2. Prolonged bleeding from the umbilical stump.
3. Calf muscle bleed.
4. Prolonged bleeding after dental extraction.(\*)
5. History of intracranial hemorrhage.

Explanation: It is important to understand the typical clinical features of von Willebrand disease that distinguish it from other factor deficiencies. Although the subtype of von Willebrand disease was not given in this vignette, the clinical features of type 1 and all type 2s are relatively similar though some type 2 variants have more frequent bleeding episodes. Type 3 von Willebrand disease behaves more like severe hemophilia and would present at a much younger age thus the vignette rules out type 3. VWD causes mucocutaneous hemorrhages and prolonged bleeding with surgery, but in particular with oral surgery. Thus the correct answer is D. Prolonged bleeding after circumcision is suggestive of hemophilia while prolonged bleeding from the umbilical stump is suggestive of FXIII deficiency. Muscle bleeds occur in hemophilia and intracranial hemorrhage can occur in any severe factor deficiency though it has more commonly been associated with FX and FXIII deficiency.

**Question 2:**

A 14 year old girl is referred to you for the recent onset of menorrhagia. Which of the following is most suggestive of von Willebrand disease?

1. Her periods are irregular with intervals ranging from 2 weeks to 2 months.
2. Menarche was at 12 years of age.
3. Her mother had excessive post-partum hemorrhage on 2 occasions.(\*)
4. She has 4 older sisters none of whom have any bleeding problems.
5. She has no other bleeding symptoms.

Explanation: This question is aimed at assessing your understanding of the clinical features of VWD. The correct answer is C. VWD is inherited in autosomal dominant fashion and post-partum hemorrhage is a common feature. Bleeding disorders per se don’t cause irregular periods—they cause excessive bleeding with periods and it is typical for girls with VWD who are going to have menorrhagia to present at menarche making A and B incorrect. Choice D is aimed at determining your understanding of the inheritance of VWD which is autosomal dominant (except for type 3), and while it would be possible to have 4 older sisters none of whom inherited the same gene, the likelihood is fairly low. Lastly, most patients with VWD have bleeding from more than one site, and while this is not absolute, it is more typical to have more than one site of bleeding.

**Question 3:**

The patient in the above scenario continues to have significant bleeding with each period and you determine that she requires treatment. You perform additional tests to determine which type of von Willebrand disease she has. Which of the laboratory results below would suggest that DDAVP won’t be effective?

1. A ristocetin cofactor level of 11%.
2. A factor VIII level of 55%.
3. Increased platelet aggregation with low dose ristocetin.(\*)
4. A normal platelet function analyzer-11 (PFA-100) assay.
5. Presence of all sizes of von Willebrand factor multimers.

Explanation: It is important to understand that DDAVP is generally only effective in type 1 VWD. While it may help patients with some variants of type 2, the fact that type 2 VWD represents a qualitative defect in VWD, the mere enhanced secretion from endothelial cells of an abnormally functional VWF is not in general going to be helpful. Increased aggregation with low dose ristocetin in what is known as the RIPA (ristocetin-induced platelet aggregation) assay is diagnostic of type 2B von Willebrand disease or in pseudo- or platelet-type VWD. The prescribing information for DDAVP specifically states that it is contraindicated in this type of VWD as it could lead to platelet aggregation, thrombocytopenia and worsen bleeding. Therefore the correct answer is C. A low level of ristocetin cofactor activity in and of itself does not mean DDAVP won’t be effective nor does a normal or borderline normal FVIII level. The PFA-100 is neither sensitive nor specific to VWD so a normal result (or even an abnormal result) doesn’t help in making a diagnosis and has no impact on determining if DDAVP would be effective. Choice E suggests a patient with type 1 VWD and DDAVP could be effective in such a patient.

**Question 4:**

A 10 month old male presents with a nosebleed that has been going on for 8 hours. He is found to have a hemoglobin of 45 g/L and receives a blood transfusion. His PT is 10.2 seconds (normal 9.7-11.2 seconds) and his PTT is 72 seconds (normal 22-36 seconds). You order factor assays and his factor VIII level is >1%. His factor IX level is normal. You order a dose of recombinant factor VIII of 40 IU/kg. His bleeding stops, however an hour later it starts again and is bleeding as profusely as it was before. Which of the following is the best next step?

1. Give a dose of a factor VIII/von Willebrand factor complex.
2. Send a factor VIII inhibitor titer.
3. Give an additional dose of recombinant factor.
4. Give fresh frozen plasma.
5. Give recombinant factor VIIa.

In this scenario, a male infant presents with symptoms consistent with a bleeding disorder and his laboratory evaluation is consistent with severe factor VIII deficiency. An appropriate dose of recombinant factor VIII is given and while the bleeding ceases temporarily, it begins again an hour after the infusion. This suggests that the recombinant factor VIII was not effective at controlling the bleeding. Although, at first glance this may meant the patient has an inhibitor, the vignette states that this is the child’s first symptom and thus his first dose of factor VIII thus making it highly unlikely (if not impossible) that he has an inhibitor. Inhibitors most often develop between the 5th and 20th exposure to factor VIII. Since the dose of recombinant factor VIII was appropriate, an additional dose is not likely to help. Fresh frozen plasma for a specific and severe factor deficiency for which alternative treatments are available is not indicated and is unlikely to be helpful. Recombinant factor VIIa is indicated for patients with inhibitors which this patient does not have at this point. Thus, the correct answer is A. This presentation strongly suggests type 3 VWD. The patient has a severe mucus membrane bleed which temporarily responds to recombinant factor VIII. The temporary response is due to a transient rise in the FVIII level which is not sustained due to the absence of VWF which acts as its carrier protein. Without VWF, FVIII is rapidly degraded.

**Question 5:**

An 8 year old female had severe bleeding following a tonsillectomy and adenoidectomy necessitating 2 blood transfusions. Otherwise, she had a history of easy bruising and occasional prolonged epistaxis. She is otherwise healthy. Which of the following would be most consistent with type 2M von Willebrand disease?

1. VWF Antigen—96%, ristocetin cofactor activity—26%, factor VIII activity—88%.(\*)
2. VWF Antigen—36%, ristocetin cofactor activity—31%, factor VIII activity—38%.
3. VWF Antigen—41%, ristocetin cofactor activity—44%, factor VIII activity—12%.
4. VWF Antigen—112%, ristocetin cofactor activity—65%, factor VIII activity—84%.
5. VWF Antigen—52%, ristocetin cofactor activity—47%, factor VIII activity—44%.

Explanation: Type 2M VWD is the result of a mutation in VWF which leads to decreased binding to platelets. The ristocetin cofactor activity measures precisely this function which in type 2M VWD would be diminished. The total amount of VWF present which is assessed by the VWF Antigen assay in type 2M is normal. The factor VIII binding function of VWF a type 2M patient is also normal. Therefore, in type 2M VWD, one has a normal VWF Antigen, a low ristocetin cofactor, and a normal factor VIII activity making A the correct answer. Choice B would be typical of type 1 VWD. Choice C would be consistent with type 2N VWD. In choice D, all the results are in the normal range while in choice E, the results are all borderline which could reflect a normal patient or one with type 1 VWD.

**Question 6:**

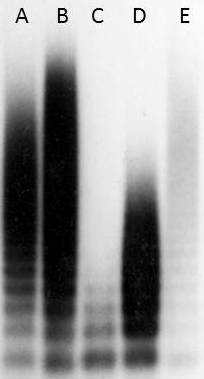
A 4 year old male presents with easy bruising and recurrent epistaxis. His labs are as follows: VWF Antigen—39%, ristocetin cofactor activity—37%, factor VIII activity—11%. What is the most likely phenotype of his parents?

1. Both are normal (no bleeding disorder).
2. The mother is a hemophilia carrier and the father is normal.
3. The mother is normal and the father has type 1 VWD.(\*)
4. The mother and father have type 1 VWD.
5. The mother has type 2A VWD and the father is normal.

Explanation: This child’s laboratory values are consistent with type 2N VWD. It is also conceivable that the patient has type 1 VWD and mild hemophilia. If we look at the second scenario first, it would require that his mother be a hemophilia carrier thereby passing the hemophilia gene to her son and the father would have to have type 1 VWD (alternatively, the mother could have both and pass both on to her son). None of the answer options allow for this possibility. Thus the patient has type 2N VWD. It is important to remember that in order to have this condition, one parent must have the type 2N mutation while the other parent has type 1 VWD. The type 2N by itself results in a modest reduction in factor VIII levels in that individual but not to the point of having bleeding symptoms. So, the parent with this mutation is phenotypically normal. The other parent generally has type 1 VWD. Thus, the correct answer is C. Choice A is incorrect because VWD is inherited in an autosomal dominant pattern (of note, patients with type 3—the recessive form arises from 2 parents with type 1 VWD) thus it is not possible for both parents to be normal. Choice B is incorrect because it could not explain the low VWF antigen and ristocetin cofactor in the patient. Choice D is not correct because the offspring of those parents could be normal or have type 1 or 3 VWD but not type 2N. Choice E is incorrect because the offspring of such a couple could have type 2A VWD but not type 2N.

**Question 8:**

In looking at the von Willebrand factor multimer analysis below, which pattern representing a form of VWD is most likely to respond to DDAVP? (\*)



Explanation: For the most part, the only type of VWD that consistently responds to treatment with DDAVP is type 1. Patients with type 1 VWD have a reduced amount of VWF but have a normal multimer pattern which is what is seen in column E. Column A is from normal plasma while column B is from a patient with thrombotic thrombocytopenic purpura (TTP) in which there are ultra-large multimers present. In column C, there is absence of large and intermediate molecular weight multimers consistent with type 2A while in column D, there is an absence of the large molecular weight multimers consistent with type 2B (or platelet-type) VWD.

**Question 9:**

You receive laboratory results on 5 unrelated patients on whom you sent von Willebrand factor antigen testing. All 4 are found to have a level of 48%. Which of the following is most likely to have a mutation in the von Willebrand factor gene?

1. 4 year old male with type O- blood.
2. 6 year old female with type AB+ blood.(\*)
3. 8 year old female with type B- blood.
4. 10 year old male with type O+ blood.
5. 12 year old male with type B+ blood.

Explanation: There are a variety of inherited and environmental factors that affect von Willebrand factor levels. Among the inherited factors outside the VWF gene, the most important contributor to the level of VWF antigen is blood type. Patients with type O blood have ~30% lower levels of circulating von Willebrand factor than those with type AB. Type A has the second highest levels and type B the third highest. Rh type has no influence. Thus in the 5 patients above, the one most likely to actually have low VWF as a result of a mutation in the VWF gene is choice B—the patient with type AB blood.

**Question 10:**

You are evaluating your database of patients with rare bleeding disorders which include patients with deficiencies of factors II, V, VII, X and XI. You identify a group of the same age and gender all of whom have levels of <5% of their respective factor. Which patient is likely to have the fewest episodes of bleeding?

1. Factor II.
2. Factor V.
3. Factor VII.
4. Factor X.
5. Factor XI.(\*)

Explanation: Deficiencies of factors II, V, VII, and X are similar in some ways to factor VIII or IX deficiency (hemophilia) in that the bleeding pattern is closely correlated to the degree of deficiency. Furthermore, these deficiencies at levels below 5% often present with severe bleeding symptoms such as intracranial, intra-abdominal, muscle or joint bleeds. Factor XI deficiency is unique to these in 2 ways. First, the bleeding symptoms are not closely correlated to the level measured in the blood such that patients with 20% levels can bleed worse than those with a <5% level. Secondly, patients with factor XI deficiency have fewer bleeding symptoms in general likely due to its relatively minor role in thrombin generation. It appears to only be necessary for severe hemostatic challenges such as surgery or trauma and hence such patients usually only bleed following surgery or trauma. Thus the correct answer is E.

**Question 11:**

A 2 week old is referred to you due to prolonged bleeding from the umbilical stump. You conduct a thorough evaluation and diagnose this child with severe FXIII deficiency. The bleeding from the umbilical stump has stopped. Which of the following is the most appropriate management for this patient?

1. Treat bleeds as needed.
2. Weekly infusions of fresh frozen plasma.
3. Weekly infusions of cryoprecipitate.
4. Monthly infusions of fresh frozen plasma.
5. Monthly infusions of cryoprecipitate.(\*)

Explanation: This question highlights 3 of the 4 critical aspects of factor XIII deficiency. First, factor XIII deficiency is notorious for causing intracranial hemorrhages resulting in significant morbidity and a risk for death. Second, factor XIII has the longest half-life of all the clotting factors averaging 7-10 days. Third, cryoprecipitate contains a high concentration of factor XIII. Of note, the 4th critical aspect is that it does not prolong the PT or the PTT. Given the high risk for intracranial hemorrhage combined with the long half-life makes this disorder a perfect scenario for life-long prophylaxis. Prophylaxis with cryoprecipitate once a month is very effective at preventing bleeding. [Note: a plasma-derived factor XIII concentrate called Corifact was approved by the FDA about 2 years ago, and is now the standard of care treatment and is given once a month to prevent bleeding. I am unsure whether or not the ABP question bank has caught up to this technology yet. If a similar question is asked on the Board Exam and the option in lieu of cryoprecipitate is Plasma-derived factor XIII concentrate, then that would be the correct answer.]

**Question 12:**

You are following a 9 year old patient with congenital afibrinogenemia who has approximately 7 bleeding episodes mostly following trauma and mostly large subcutaneous hematomas. The emergency room calls you as the patient is experiencing a sudden onset of spontaneous and severe abdominal pain. Which of the following should you be most concerned about?

1. Superior mesenteric artery thrombosis
2. Intussusception.
3. Splenic rupture.(\*)
4. Intestinal perforation.
5. Pancreatitis.

Explanation: Patients with afibrinogenemia are at risk for spontaneous rupture of the spleen for reasons that are understood. Thus, the correct answer is C. The other abdominal emergencies are not associated with afibrinogenemia or other bleeding disorders for that matter.

**Question 13:**

You are referred a male patient for evaluation of significant bleeding symptoms. The thrombin clotting time is significantly prolonged. This patient can have a deficiency of which of the following:

1. Fibrinogen.(\*)
2. Factor II.
3. Factor V.
4. Factor VII.
5. Factor XIII.

The thrombin clotting time (or thrombin time) measures the conversion of fibrinogen to fibrin and thus only requires there to be a normal amount and function of fibrinogen. Therefore the correct answer is A. Factors II, V and VII are “upstream” of thrombin and thus are bypassed when a thrombin time is done. Factor XIII although downstream from the formation for fibrin monomers is not required for the formation of the initial clot and thus is not required for a normal thrombin time.

**Question 14:**

You are referred a female patient for evaluation of her second idiopathic deep vein thrombosis. A thrombin time is done and is significantly prolonged. What would you do next with respect to the prolonged thrombin time?

1. Nothing. A prolonged thrombin time is not associated with thrombosis.
2. Order a fibrinogen activity.
3. Order a fibrinogen antigen.
4. Order a fibrinogen antigen and activity.(\*)
5. Order a reptilase time.

Explanation: Recurrent thrombosis in a patient with a prolonged thrombin time should raise the suspicion for dysfibrinogenemia. It is important to understand that congenital dysfibirnogenemia can be associated with either bleeding symptoms or thrombosis (thus choice A is incorrect). In order to diagnose dysfibrinogenemia, one must order a fibrinogen antigen and activity making D the correct answer. In general, the fibrinogen levels that are done clinically are measuring the function of fibrinogen. If a patient has a normal fibrinogen antigen and a low fibrinogen activity, they have dysfibrinogenemia. The reptilase time can be performed to assess fibrinogen function in patients who are receiving heparin since the thrombin time is affected by heparin. There is no mention that this patient is on heparin.

**Question 15:**

A 10 month old female presents with an increased number of bruises since she started crawling many of which are palpable. A laboratory evaluation demonstrates that she has congenital afibrinogenemia. At the age of 18 months, she has a fall landing on her head and a large hematoma has formed. She is brought to the emergency room. The next most appropriate step is:

1. Obtain a computed tomographic scan of her head.
2. Admit her for observation.
3. Administer fresh frozen plasma.
4. Administer cryoprecipitate.(\*)
5. Administer recombinant factor VIIa.

Explanation: Patients with afibrinogenemia can experience severe bleeding following trauma (they can also bleed spontaneously) and when dealing with a potential intracranial hemorrhage, the most important thing to do first is to administer replacement therapy. Since cryoprecipitate contains a high concentration of fibrinogen, this is the product of choice for replacing fibrinogen. Thus the correct answer is D. Obtaining a CT scan and/or admitting for observation are both reasonable and appropriate but not as the first step. Replacement therapy for head injuries in particular, should be given first followed by diagnostic testing. Fresh frozen plasma does not contain as much fibrinogen as cryoprecipitate and hence is not appropriate and recombinant factor VIIa has no role in the management of this condition. [Note: a plasma-derived fibrinogen concentrate called Riastap was approved by the FDA about one year ago, and is now the standard of care treatment for managing bleeding associated with afibrinogenemia/hypofibrinogenemia. I am unsure whether or not the ABP question bank has caught up to this technology yet. If a similar question is asked on the Board Exam and the option in lieu of cryoprecipitate is Plasma-derived fibrinogen concentrate, then that would be the correct answer.]

**Question 16:**

You are referred a 12 year old female by an orthopedic surgeon for spinal surgery to correct for scoliosis. Since this surgery involves a significant risk for major bleeding, the surgeon ordered pre-operative coagulation testing which demonstrates a significantly prolonged PTT. Which of the results below pose the highest risk for excessive bleeding during her surgery?

1. Factor VIII of 50%.
2. Factor XI of 20%.(\*)
3. Prekallikrein level of 15%.
4. High molecular weight kininogen level of 8%.
5. Factor XII of <1%.

Explanation: This question is examining your understanding of the contact activation factors which include factors XII, prekallikrein and high molecular weight kininogen. It is important to know that deficiencies in these factors will cause a prolonged (often markedly prolonged) PTT, however none of these deficiencies are associated with bleeding as they are not involved physiologically in thrombin generation. They are required however for the PTT assay (an artificial system) to be normal. On the other hand both factors VIII and XI are required for hemostasis. The correct answer is B since a factor XI level of 20% may be associated with excessive surgical bleeding whereas a factor VIII level of 50% will not (of note a FVIII level of 50% should not prolong the PTT).

**2015**

**Hemophilia and Von Willebrand Disease**

Guy Young, MD

1. A 6-year-old male is referred to you for easy bruising. Which of the following findings in his history is most consistent with von Willebrand disease (VWD)?

A. Prolonged bleeding after circumcision

B. Prolonged bleeding from the umbilical stump

C. Bleeding in the calf muscle

D. Prolonged bleeding after dental extraction

E. History of intracranial hemorrhage

2. A 14-year-old girl is referred to you for the recent onset of menorrhagia. Which of the following is most suggestive of VWD?

A. Her periods are irregular, with intervals ranging from 2 weeks to 2 months.

B. Menarche was at 12 years of age.

C. Her mother had excessive postpartum hemorrhage on two occasions.

D. She has four older sisters, none of whom have any bleeding problems.

E. She has no other bleeding symptoms.

3. The patient in question 2 continues to have significant bleeding with each period, and you determine that she requires treatment. You perform additional tests to determine which type of VWD she has. Which of the following laboratory results would suggest that DDAVP will *not* be effective?

A. A ristocetin cofactor level of 11%

B. A factor VIII level of 55%

C. Increased platelet aggregation with low-dose ristocetin

D. A normal platelet function analyzer-11 (PFA-100) assay

E. The presence of all sizes of von Willebrand factor multimers

4. A 10-month-old male presents with a nosebleed that has been going on for 8 hours. He is found to have a hemoglobin of 45 g/L and receives a blood transfusion. His prothrombin time (PT) is 10.2 seconds (normal 9.7–11.2 seconds), and his partial thromboplastin time (PTT) is 72 seconds (normal 22–36 seconds). You order factor assays, and his factor VIII level is >1%. His factor IX level is normal. You order a dose of recombinant factor VIII of 40 IU/kg. His bleeding stops; however, an hour later it starts again and is as profuse as it was before. Which of the following is the best next step?

A. Give a dose of a factor VIII/von Willebrand factor complex.

B. Send a factor VIII inhibitor titer.

C. Give an additional dose of recombinant factor.

D. Give fresh frozen plasma.

E. Give recombinant factor VIIa.

5. An 8-year-old female had severe bleeding following a tonsillectomy and adenoidectomy, necessitating two blood transfusions. Otherwise, she had a history of easy bruising and occasional prolonged epistaxis. She is otherwise healthy. Which of the following would be most consistent with type 2M VWD?

A. VWF antigen—96%, ristocetin cofactor activity—26%, factor VIII activity—88%

B. VWF antigen—36%, ristocetin cofactor activity—31%, factor VIII activity—38%

C. VWF antigen—41%, ristocetin cofactor activity—44%, factor VIII activity—12%

D. VWF antigen—112%, ristocetin cofactor activity—65%, factor VIII activity—84%

E. VWF antigen—52%, ristocetin cofactor activity—47%, factor VIII activity—44%

6. A 4-year-old male presents with easy bruising and recurrent epistaxis. His labs are as follows: VWF antigen—39%, ristocetin cofactor activity—37%, factor VIII activity—11%. What is the most likely phenotype of his parents?

A. Both are normal (no bleeding disorder).

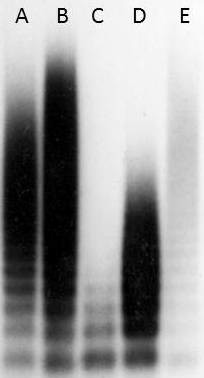
B. The mother is a hemophilia carrier and the father is normal.

C. The mother is normal and the father has type 1 VWD.

D. The mother and father have type 1 VWD.

E. The mother has type 2A VWD and the father is normal.

7. In looking at the VWF multimer analysis below, which pattern representing a form of VWD is most likely to respond to DDAVP?



8. You receive laboratory results on five unrelated patients for whom you orderedVWF antigen testing. All fiveare found to have a level of 48%. Which of the following patients is most likely to have a mutation in the VWF gene?

A. A 4-year-old male with type O- blood

B. A 6-year-old female with type AB+ blood

C. A 8-year-old female with type B- blood

D. A 10-year-old male with type O+ blood

E. A 12-year-old male with type B+ blood

9. You are evaluating your database of patients with rare bleeding disorders, which include patients with deficiencies of factors II, V, VII, X, and XI. You identify a group who are of the same age and gender, all of whom have levels of <5% of their respective factor. Which patient is likely to have the fewest episodes of bleeding?

A. Those with factor II deficiencies

B. Those with factor V deficiencies

C. Those with factor VII deficiencies

D. Those with factor X deficiencies

E. Those with factor XI deficiencies

10. A 2-week-old is referred to you because of prolonged bleeding from the umbilical stump. You conduct a thorough evaluation and diagnose this child with severe FXIII deficiency. The bleeding from the umbilical stump has stopped. Which of the following is the most appropriate management for this patient?

A. Treat bleeds as needed.

B. Give weekly infusions of fresh frozen plasma.

C. Give weekly infusions of cryoprecipitate.

D. Give monthly infusions of fresh frozen plasma.

E. Give monthly infusions of cryoprecipitate.

11. You are following a 9-year-old patient with congenital afibrinogenemia who has approximately seven bleeding episodes, mostly following trauma and mostly large subcutaneous hematomas. The emergency room calls you because the patient is experiencing a sudden onset of spontaneous and severe abdominal pain. Which of the following should you be most concerned about?

A. Superior mesenteric artery thrombosis

B. Intussusception

C. Splenic rupture

D. Intestinal perforation

E. Pancreatitis

12. You are referred a male patient for evaluation of significant bleeding symptoms. The thrombin clotting time is significantly prolonged. This patient can have a deficiency of which of the following?

A. Fibrinogen

B. Factor II

C. Factor V

D. Factor VII

E. Factor XIII

13. You are referred a female patient for evaluation of her second idiopathic deep vein thrombosis. A thrombin time is done and is significantly prolonged. What would you do next with respect to the prolonged thrombin time?

A. Nothing. A prolonged thrombin time is not associated with thrombosis.

B. Order a fibrinogen activity.

C. Order a fibrinogen antigen.

D. Order a fibrinogen antigen and activity.

E. Order a reptilase time.

14. A 10-month-old female presents with an increased number of bruises (many of them palpable) since she started crawling. A laboratory evaluation demonstrates that she has congenital afibrinogenemia. At the age of 18 months she has a fall, landing on her head, and a large hematoma has formed. She is brought to the emergency room. Which of the following is the most appropriate next step?

A. Obtain a computed tomographic (CT) scan of her head.

B. Admit her for observation.

C. Administer fresh frozen plasma.

D. Administer cryoprecipitate.

E. Administer recombinant factor VIIa.

15. A 12-year-old female is referred to you by an orthopedic surgeon for spinal surgery to correct for scoliosis. Because this surgery involves a significant risk for major bleeding, the surgeon ordered preoperative coagulation testing, which demonstrates a significantly prolonged PTT. Which of the following results poses the highest risk for excessive bleeding during her surgery?

A. Factor VIII of 50%

B. Factor XI of 20%

C. Prekallikrein level of 15%

D. High-molecular-weight kininogen level of 8%

E. Factor XII of <1%

16. Among the following patients’ lab values, which one is most likely to have a mutation in the VWF gene?

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient | vWF antigen | Ristocetin cofactor | FVIII activity | Blood type |
| A | 45 | 42 | 56 | O+ |
| B | 53 | 40 | 59 | O- |
| C | 58 | 50 | 60 | A+ |
| D | 59 | 56 | 53 | B- |
| E | 52 | 54 | 56 | AB+ |

Normal levels: vWF antigen: 52–110, Ristocetin cofactor: 48–110, FVIII activity: 50–150

A. Patient A

B. Patient B

C. Patient C

D. Patient D

E. Patient E

17. A patient you are treating for a VWD has a normal VWF antigen and factor VIII level but his ristocetin cofactor level is 18%. He presents to the emergency room with prolonged epistaxis lasting on and off for more than 12 hours. A CBC demonstrates a normal platelet count and a hemoglobin level of 80 mg/L (8mg/dl). He is complaining of a headache and is slightly tachycardic. On examination, blood is oozing slowly from the left nare. Which of the following is the most appropriate therapy to control his bleeding?

A. Intravenous desmopressin

B. Aminocaproic acid

C. Nasal packing

D. Cryoprecipitate

E. A factor VIII/VWF concentrate

18. An 8-year-old male presents with hematomas on the chest and extremities and a history of bleeding after tooth extraction. He has no history of joint bleeds. The maternal grandfather required a blood transfusion after a dental extraction. What is the most likely diagnosis?

A. Factor VIII deficiency

B. Glanzmann thrombasthenia

C. VWD, type 3

D. Factor XIII deficiency

19. A 2-month-old male with severe hemophilia A presents to the emergency department with lethargy. His past medical history is significant for bleeding with circumcision and prolonged bleeding with heel stick done for newborn screening. The infant’s maternal grandfather had a history of swollen joints and died in 1980. Which of the following is the most appropriate next step in the care of this patient?

A. Lumbar puncture

B. Computed tomography of the head

C. Administration of recombinant factor VIII

D. Administration of cryoprecipitate

E. Administration of recombinant factor VIIa

20. A 17-year-old male with severe hemophilia A and high-titer inhibitor presents to the clinic with lower abdominal pain and difficulty walking. He is treated with a factor VIII bypassing agent at home on an on-demand basis. On examination he walks hunched over and is unable to fully extend his hip; even slight extension causes pain. He has no history of fever or other constitutional symptoms. Which of the following is the most likely diagnosis?

A. Iliopsoas hemorrhage

B. Left knee hemarthrosis

C. Appendicitis

D. Gastrointestinal hemorrhage

21. A 13-year-old female presents to the clinic with a history of easy bruising and menorrhagia. She has never been treated for her symptoms. Her maternal grandfather has a history of “swollen joints” treated with “infusions.” Her mother required red cell transfusion after each of her deliveries. The following lab work was obtained: factor VIII activity = 55% (normal 74%–212%), VWF antigen = 97% (normal 45%–150%), VWF activity = 83% (45%–150%). Which of the following is the most appropriate next step in the evaluation of this patient?

A. Factor VIII genotyping

B. Factor VIII inhibitor assay

C. VWF exon 28 sequencing

D. von Willebrand type 2N testing

22. A 3-year-old boy with severe hemophilia B has received 11 treatments with recombinant factor IX. After his 12th dose he develops anaphylaxis. Which of the following is the most appropriate next test in the evaluation of this child?

A. Factor IX inhibitor assay

B. Factor IX assay

C. IgE level

D. C1 esterase inhibitor

23. A 2-year-old boy with severe hemophilia A presents to the emergency department after suffering a laceration of his frenulum. A factor VIII inhibitor assay is performed because he is still bleeding despite adequate factor VIII replacement. The titer is 200 Bethesda units/ml. Which of the following factor VIII gene mutations is most often associated with a FVIII inhibitor?

A. Missense mutation

B. Nonsense mutation

C. Large deletion

D. Inversion

E. Splice site mutation

24. A 1-week-old boy presents to your clinic for evaluation. His maternal uncle has mild hemophilia B with factor IX levels ~12% and mild bleeding symptoms. Factor IX testing done on the infant shows a factor IX level of <1%. Six months later, repeat testing shows a factor IX level of 14%. What is the most likely explanation for the discrepancy in factor IX levels between 1 week and 6 months of age?

A. Laboratory error at 1 week of life

B. Phlebotomy error at 1 week of life

C. Physiologically low levels of vitamin-K-dependent clotting factors at 1 week of life

D. Gene therapy received before 6 months of age

25. A 25-year-old woman who is an obligate hemophilia A carrier presents to the clinic for prenatal counseling at 35 weeks’ gestation. She is carrying a male fetus. She has previously declined prenatal diagnosis. What are the most appropriate recommendations at this time?

A. Prenatal diagnosis by fetal cord blood sampling

B. Prenatal diagnosis by amniocentesis

C. Prenatal diagnosis by chorionic villus sampling

D. Umbilical cord blood sampling at the time of delivery

26. A 3-year-old boy with moderate hemophilia A requires emergency surgery for an incarcerated hernia. Which of the following is the most appropriate preoperative management?

A. Administer desmopressin (DDAVP).

B. Administer aminocaproic acid.

C. Administer recombinant factor VIII.

D. Administer plasma-derived von Willebrand/factor VIII concentrate.

E. Proceed with surgery without special precaution.

27. A 3-year-old boy with moderate hemophilia A presents to the emergency department after sustaining a traumatic knee injury at school. His exam is consistent with an acute knee hemarthrosis. His weight is 15 kg. He receives 250 units of recombinant factor VIII in the emergency department. His knee does not improve. What is the most likely reason that the boy did not respond to the factor VIII replacement?

A. He has developed a factor VIII inhibitor.

B. He has a torn ligament and requires surgery.

C. The dose of factor VIII was too low.

D. He should have been given factor IX replacement.

28. A 13-year-old male with severe hemophilia A presents to the emergency department with acute onset of gross hematuria and flank pain. He also complains of headache and dizziness. A CT scan shows multiple renal calculi. Laboratory evaluation reveals a hemoglobin of 6g/dl. Which of the following is the most appropriate next step in the management of this patient?

A. Administer red cell transfusion.

B. Administer red cell transfusion and aminocaproic acid.

C. Administer red cell transfusion and tranexamic acid.

D. Administer red cell transfusion and recombinant factor VIII.

29. A 2-year-old male presents for his annual comprehensive care visit. He receives prophylactic factor VIII every other day. Prior inhibitor titers have been negative. An inhibitor titer is drawn as part of his annual screening labs; the result is 1.5 Bethesda units (BU). The child continues his prophylaxis and returns 1 week later for repeat testing. At that time the inhibitor is 1.0 BU. What is the most appropriate counseling to give to the family?

A. The child has an inhibitor and must start immune tolerance therapy.

B. The child has an inhibitor and must switch prophylaxis to recombinant factor VIIa.

C. The child has an inhibitor and must switch to plasma-derived factor VIII/von Willebrand factor containing product.

D. The child should continue his current prophylaxis, and the family should report any new bleeding symptoms.

30. A 12-year-old male presents with significant hemorrhage after tonsillectomy. He reports a history of easy bruising and epistaxis that have not required medical attention. Laboratory evaluation shows a hemoglobin of 8 g/dl (normal 11–13 g/dl), a PT of 11 seconds (normal 10.5–12.5), and a PTT of 32 seconds (normal 30–33). A platelet function assay (PFA) shows prolonged closure time with collagen/epinephrine and collagen/ADP cartridges. The family history is significant for a maternal uncle who had mild hemophilia B with a baseline factor IX of 35%. Which of the following is the most likely diagnosis in this child?

A. Glanzmann thrombasthenia

B. Storage pool disorder

C. Excessive aspirin ingestion

D. Mild hemophilia B

31. A male infant is born with a family history of severe hemophilia A in the paternal uncle. The family would like to proceed with circumcision. Which of the following is the most appropriate advice to give to the family?

A. Proceed with circumcision.

B. Proceed with circumcision after factor VIII replacement.

C. Send testing for factor VIII activity.

D. Send testing for factor VIII genotype.

32. A 2-year-old male with severe hemophilia presents after a frenulum laceration. He is bleeding despite factor replacement. You send inhibitor testing to the coagulation lab. The lab calls to tell you that upon mixing your patient’s plasma with control plasma, the factor VIII decreased from 100% to 6.25%. Which of the following is the corresponding Bethesda unit (BU) titer?

A. 6.25 BU

B. 62.5 BU

C. 3 BU

D. 4 BU

E. Factor XII of <1%

33. The parents of a 9-month-old boy diagnosed with severe factor VIII deficiency who has yet to receive any factor therapy ask you about his risk for developing an inhibitor. The patient is Caucasian and his factor VIII genotype reveals that he has the intron 22 inversion, the most common mutation found in severe hemophilia. His mother is a carrier and has two brothers with hemophilia, both of whom developed inhibitors. Testing VWD reveals a VWF antigen of 47% (normal range 50%–110%) and a ristocetin cofactor activity of 38% (normal range 55%–120%). Which of these findings put the child at increased risk for developing inhibitors?

A. His age

B. His Caucasian race

C. The intron 22 inversion

D. The family history

E. The low levels of VWF antigen and ristocetin cofactor activity

34. An 18-year-old male with mild hemophilia requires excision of two wisdom teeth. His baseline level of factor VIII is 8% and following a dose of intravenous desmopressin his level peaks at 28%. You are asked to develop a plan to prevent bleeding for this patient by the oral surgeon. Which of the following would be most appropriate?

A. Aminocaproic acid immediately prior to the procedure and for 2 weeks after

B. Desmopressin intravenously prior to the procedure

C. Desmopressin intravenously prior to the procedure followed by 2 weeks of aminocaproic acid

D. Factor VIII concentrate 40 IU/kg immediately prior to the procedure

E. Factor VIII concentrate 40 IU/kg immediately prior to the procedure followed by 2 weeks of aminocaproic acid

35. A 15-month-old with severe factor IX deficiency presents with his third episode of joint bleeding. At 12 months of age, he had a spontaneous bleed in his right elbow that was treated effectively with two doses of recombinant factor IX. At 14 months of age, he developed a right ankle bleed that was treated with one dose of recombinant factor IX. He now presents with a spontaneous bleed in his left ankle. Of note, he started walking at 13 months of age. This bleed is treated with another two doses of recombinant factor IX. Which of the following would be the most appropriate next step in his management?

A. Initiate prophylactic factor IX therapy with twice-weekly infusions of recombinant factor IX.

B. Continue observation and treat only when bleeding occurs.

C. Initiate a physical therapy evaluation to assess his gait.

D. Start intranasal desmopressin daily.

E. Refer the patient to a gene therapy clinical trial.

**Hemophilia and Von Willebrand Disease: Answers**

**Question 1**

**Answer:** D

**Explanation:** It is important to understand the typical clinical features of VWD that distinguish it from other factor deficiencies. The subtype of VWD was not given in this vignette, but the clinical features of type 1 and all type 2s are relatively similar (though some type 2 variants have more frequent bleeding episodes). Type 3 VWD behaves more like severe hemophilia and would present at a much younger age; the vignette therefore rules out type 3. VWD causes mucocutaneous hemorrhages and prolonged bleeding with surgery, but in particular with oral surgery. Thus the correct answer is D. Prolonged bleeding after circumcision is suggestive of hemophilia, while prolonged bleeding from the umbilical stump is suggestive of FXIII deficiency. Muscle bleeds occur in hemophilia, and intracranial hemorrhage can occur in any severe factor deficiency, though it has more commonly been associated with FX and FXIII deficiency.

**Question 2**

**Answer:** C

**Explanation:** This question is aimed at assessing your understanding of the clinical features of VWD. VWD is inherited in autosomal dominant fashion, and postpartum hemorrhage is a common feature. Bleeding disorders per se don’t cause irregular periods—they cause excessive bleeding with periods, and it is typical for girls with VWD who are going to have menorrhagia to present at menarche, making A and B incorrect. D is aimed at determining your understanding of the inheritance of VWD, which is autosomal dominant (except for type 3), and while it would be possible for someone with VWD to have four older sisters who had not inherited the same gene, the likelihood is fairly low. Last, although this is not *always* the case, *most* patients with VWD have bleeding from more than one site.

**Question 3**

**Answer:** C

**Explanation:** It is important to understand that DDAVP generally is effective in treating only type 1 VWD. Though it may help patients with some variants of type 2, type 2 VWD represents a qualitative defect in VWD, and the mere enhanced secretion from endothelial cells of an abnormally functional VWF is not in general going to be helpful. Increased aggregation with low-dose ristocetin in what is known as the RIPA (ristocetin-induced platelet aggregation) assay is diagnostic of type 2B VWD or of pseudo- or platelet-type VWD. The prescribing information for DDAVP specifically states that it is contraindicated in this type of VWD because it could lead to platelet aggregation or thrombocytopenia and worsen bleeding. Therefore, the correct answer is C. A low level of ristocetin cofactor activity in and of itself does not mean that DDAVP won’t be effective, nor does a normal or borderline-normal FVIII level. The PFA-100 is neither sensitive nor specific to VWD, so a normal result (or even an abnormal result) doesn’t help in making a diagnosis and has no impact on determining whether DDAVP would be effective. Answer E suggests a patient with type 1 VWD, and DDAVP could be effective in such a patient.

**Question 4**

**Answer:** A

**Explanation:** In this scenario, a male infant presents with symptoms consistent with a bleeding disorder, and his laboratory evaluation is consistent with severe factor VIII deficiency. An appropriate dose of recombinant factor VIII is given, and while the bleeding ceases temporarily, it begins again an hour after the infusion. This suggests that the recombinant factor VIII was not effective at controlling the bleeding. Although at first glance this may indicate that the patient has an inhibitor, the vignette states that this is the child’s first symptom and thus his first dose of factor VIII, making it highly unlikely (if not impossible) that he has an inhibitor. Inhibitors most often develop between the 5th and 20th exposure to factor VIII. Because the dose of recombinant factor VIII was appropriate, an additional dose is not likely to help. Fresh frozen plasma for a specific and severe factor deficiency for which alternative treatments are available is not indicated and is unlikely to be helpful. Recombinant factor VIIa is indicated for patients with inhibitors, which this patient does not have at this point. Thus the correct answer is A. This presentation strongly suggests type 3 VWD. The patient has a severe mucus membrane bleed that temporarily responds to recombinant factor VIII. The temporary response is due to a transient rise in the FVIII level, which is not sustained because of the absence of VWF, which acts as its carrier protein. Without VWF, FVIII is rapidly degraded.

**Question 5**

**Answer:** A

**Explanation:** Type 2M VWD is the result of a mutation in VWF, which leads to decreased binding to platelets. The ristocetin cofactor activity measures precisely this function, which in type 2M VWD would be diminished. The total amount of VWF present, which is assessed by the VWF antigen assay in type 2M, is normal. The factor VIII binding function of VWF in a type 2M patient is also normal. Therefore, in type 2M VWD, one has a normal VWF antigen, a low ristocetin cofactor, and a normal factor VIII activity, making A the correct answer. B would be typical of type 1 VWD. C would be consistent with type 2N VWD. In D, all the results are in the normal range, while in E, the results are all borderline, which could indicate a normal patient or one with type 1 VWD.

**Question 6**

**Answer:** C

**Explanation:** This child’s laboratory values are consistent with type 2N VWD. It is also conceivable that the patient has type 1 VWD and mild hemophilia. The second scenario (answer B) would require that his mother be a hemophilia carrier, thereby passing the hemophilia gene to her son, and the father would have to have type 1 VWD (alternatively, the mother could have both and pass both on to her son). None of the answer options allow for this possibility. Thus the patient has type 2N VWD. It is important to remember that to have this condition, one parent must have the type 2N mutation, while the other parent has type 1 VWD. The type 2N by itself results in a modest reduction in factor VIII levels in that individual, but not to the point of having bleeding symptoms. So the parent with this mutation is phenotypically normal. The other parent generally has type 1 VWD. Thus, the correct answer is C. A is incorrect because VWD is inherited in an autosomal dominant pattern (of note, patients with type 3—the recessive form—get it from two parents with type 1 VWD); thus it is not possible for both parents to be normal. B is incorrect because it does not explain the low VWF antigen and ristocetin cofactor in the patient. D is not correct because the offspring of those parents could be normal or could have type 1 or 3 VWD but not type 2N. E is incorrect because the offspring of such a couple could have type 2A VWD but not type 2N.

**Question 7**

**Answer:** E

**Explanation:** For the most part, the only type of VWD that consistently responds to treatment with DDAVP is type 1. Patients with type 1 VWD have a reduced amount of VWF but have a normal multimer pattern, which is what is seen in column E. Column A is from normal plasma, while column B is from a patient with thrombotic thrombocytopenic purpura (TTP), in which ultra-large multimers are present. In column C, there is an absence of large- and intermediate-molecular-weight multimers consistent with type 2A. In column D, there is an absence of the large-molecular-weight multimers consistent with type 2B (or platelet-type) VWD.

**Question 8**

**Answer:** B

**Explanation:** A variety of inherited and environmental factors affect VWF levels. Among the inherited factors outside the VWF gene, the most important contributor to the level of VWF antigen is blood type. Patients with type O blood have ~30% lower levels of circulating VWF than those with type AB. Type A has the second highest levels and type B has the third highest. Rh type has no influence. Thus in the five patients above, the one most likely to actually have low VWF as a result of a mutation in the VWF gene is choice B—the patient with type AB blood.

**Question 9**

**Answer:** E

**Explanation:** Deficiencies of factors II, V, VII, and X are similar in some ways to factor VIII or IX deficiency (hemophilia) in that the bleeding pattern is closely correlated to the degree of deficiency. Furthermore, these deficiencies at levels below 5% often present with severe bleeding symptoms such as intracranial, intra-abdominal, muscle, or joint bleeds. Factor XI deficiency is distinctive from these others in two ways. First, the bleeding symptoms are not closely correlated to the level measured in the blood, such that patients with 20% levels can bleed worse than those with a <5% level. Second, patients with factor XI deficiency have fewer bleeding symptoms in general, most likely because of its relatively minor role in thrombin generation. It appears to be necessary only for severe hemostatic challenges such as surgery or trauma, and hence such patients usually bleed only following surgery or trauma. Thus the correct answer is E.

**Question 10**

**Answer:** E

**Explanation:** This question highlights three of the four critical aspects of factor XIII deficiency. First, factor XIII deficiency is notorious for causing intracranial hemorrhages resulting in significant morbidity and a risk for death. Second, factor XIII has the longest half-life of all the clotting factors, averaging 7–10 days. Third, cryoprecipitate contains a high concentration of factor XIII. Fourth, factor XIII deficiency does not prolong the PT or the PTT. The high risk for intracranial hemorrhage, combined with the long half-life of factor XIII, makes this disorder a perfect scenario for lifelong prophylaxis. Prophylaxis with cryoprecipitate once a month is very effective at preventing bleeding.

Note: A plasma-derived factor XIII concentrate called Corifact was approved by the U.S. Food and Drug Administration (FDA) about 2 years ago and is now the standard-of-care treatment, given once a month to prevent bleeding. I am unsure whether the ABP question bank has caught up to this technology yet. If a similar question is asked on the board exam and the option in lieu of cryoprecipitate is plasma-derived factor XIII concentrate, then that would be the correct answer.

**Question 11**

**Answer:** C

**Explanation:** Patients with afibrinogenemia are at risk for spontaneous rupture of the spleen for reasons that are not understood. The other abdominal emergencies are not associated with afibrinogenemia (or, for that matter, with other bleeding disorders).

**Question 12**

**Answer:** A

**Explanation:** The thrombin clotting time (or thrombin time) measures the conversion of fibrinogen to fibrin and thus only requires there to be a normal amount and function of fibrinogen. Therefore, the correct answer is A. Factors II, V, and VII are “upstream” of thrombin and thus are bypassed when a thrombin time is done. Factor XIII, although downstream from the formation for fibrin monomers, is not required for the formation of the initial clot and thus is not required for a normal thrombin time.

**Question 13**

**Answer:** D

**Explanation:** Recurrent thrombosis in a patient with a prolonged thrombin time should raise the suspicion for dysfibrinogenemia. It is important to understand that congenital dysfibirnogenemia can be associated with either bleeding symptoms or thrombosis (thus A is incorrect). To diagnose dysfibrinogenemia, one must order a fibrinogen antigen and activity, making D the correct answer. In general, the fibrinogen levels that are done clinically are measuring the function of fibrinogen. If a patient has a normal fibrinogen antigen and a low fibrinogen activity, the patient has dysfibrinogenemia. The reptilase time can be performed to assess fibrinogen function in patients who are receiving heparin because the thrombin time is affected by heparin. There is no mention that this patient is on heparin.

**Question 14**

**Answer:** D

**Explanation:** Patients with afibrinogenemia can experience severe bleeding following trauma (they can also bleed spontaneously). When dealing with a potential intracranial hemorrhage, the most important thing to do first is to administer replacement therapy. Because cryoprecipitate contains a high concentration of fibrinogen, this is the product of choice for replacing fibrinogen. Thus the correct answer is D. Obtaining a CT scan and admitting her for observation are both reasonable and appropriate steps to take, but not as the first step. Replacement therapy for head injuries in particular should be given first, followed by diagnostic testing. Fresh frozen plasma does not contain as much fibrinogen as cryoprecipitate and hence is not appropriate, and recombinant factor VIIa has no role in the management of this condition.

Note: A plasma-derived fibrinogen concentrate called Riastap was approved by the FDA about 1 year ago and is now the standard-of-care treatment for managing bleeding associated with afibrinogenemia or hypofibrinogenemia. I am unsure whether the ABP question bank has caught up to this technology yet. If a similar question is asked on the board exam and the option in lieu of cryoprecipitate is plasma-derived fibrinogen concentrate, then that would be the correct answer.

**Question 15**

**Answer:** B

**Explanation:** This question is examining your understanding of the contact activation factors, which include factors XII, prekallikrein, and high-molecular-weight kininogen. It is important to know that deficiencies in these factors will cause a prolonged (often markedly prolonged) PTT; however, none of these deficiencies is associated with bleeding because they are not involved physiologically in thrombin generation. They are required, however, for the PTT assay (an artificial system) to be normal. On the other hand, both factors VIII and XI are required for hemostasis. The correct answer is B because a factor XI level of 20% may be associated with excessive surgical bleeding, whereas a factor VIII level of 50% will not (note that a FVIII level of 50% should not prolong the PTT).

**Question 16**

**Answer:** E

**Explanation:** It is important to know the effect of blood type on VWF levels and lab values. It is well-described that patients with type O blood have the lowest levels of VWF, while patients with type AB have the highest levels, and patients with types A and B fall in between. In this question, all of the laboratory values are purposefully in the borderline range. Importantly, as you look at the values, there is little to no difference between the patients, except for patient A who has somewhat lower levels. Given these values, the correct answer is E because this patient’s values, though similar to those of other patients, is for someone with type AB blood. Most laboratories only report one range of normal lab values and not blood-type specific values, thus the above represents a real-life scenario.

**Question 17**

**Answer:** E

**Explanation:** This patient has type 2M VWD based on the lab results provided. Specifically, the von Willebrand antigen and factor VIII level are normal, but the ristocetin cofactor activity is very low—disproportionately low as compared to the VWF antigen. This type of VWD is caused by a mutation in VWF which reduces its platelet binding function, hence the very abnormal ristocetin cofactor activity. In this vignette, the patient has had a rather severe and prolonged epistaxis as marked by the significant drop in his hemoglobin level which can be considered acute based on the history, symptom (headache), and sign (tachycardia). Given that, the most appropriate treatment is to administer VWF concentrate to achieve hemostasis. Desmopressin is not indicated in type 2M (and really all type 2) VWD because releasing more of his endogenous VWF into the circulation (which is the mechanism of action of desmopressin in VWD) won’t be effective because it is dysfunctional. Aminocaproic acid would be a good adjunctive therapy and should be prescribed to this patient once hemostasis is achieved but alone would likely not stop the bleeding. Nasal packing could be considered because pressure is an effective approach, but in this case, providing normal VWF would be a more appropriate treatment to stop the bleeding. Cryoprecipitate contains VWF, however, given the choice between cryoprecipitate and VWF concentrate, the better choice is always VWF concentrate because it has more concentrated )as its name indicates) and has reduced risks because it undergoes viral inactivation steps that cryoprecipitate does not.

**Question 18**

**Answer:** A

**Explanation:** This case demonstrates two common bleeding symptoms associated with hemophilia: bleeding after dental extraction and hematomas, which also are features of Glanzmann thrombasthenia and type 3 VWD. However, this vignette demonstrates an X-linked mode of inheritance, which is present only in factor VIII deficiency. The maternal grandfather also has factor VIII deficiency, and the boy’s mother is an obligate carrier. With any pregnancy, she has 50% chance that a male offspring will be affected. The other conditions are inherited in an autosomal recessive pattern.

**Question 19**

**Answer:** C

**Explanation:** This case demonstrates a life-threatening complication of severe hemophilia A, intracranial hemorrhage. In the event of any life-threatening hemorrhage, the first step is to give the appropriate factor replacement. Factor replacement should be given prior to any interventions or imaging studies. The most appropriate factor replacement for a boy with severe hemophilia A is recombinant factor VIII. Cryoprecipitate contains factor VIII but is associated with a higher rate of viral contamination. Recombinant factor VIIa should be reserved for individuals with known or suspected inhibitors.

**Question 20**

**Answer:** A

**Explanation:** This case illustrates the classic presentation of an iliopsoas muscle or retroperitoneal hemorrhage. This is a life-threatening hemorrhage. Patients with this bleed will feel more comfortable with a flexed hip and have pain with hip extension.

**Question 21**

**Answer:** A

**Explanation:** This girl is a hemophilia A carrier. Her maternal grandfather had hemophilia A, and her mother was an obligate carrier. With any pregnancy she has a 50% chance that a female offspring will be a carrier. Some hemophilia A carriers are symptomatic and may present with easy bruising, epistaxis, bleeding after surgery, menorrhagia, and/or postpartum hemorrhage. Factor VIII genotyping may be used to confirm the responsible genetic mutation. Factor VIII inhibitor testing would not be useful in this case because her factor VIII level is detectable, and the scenario is not consistent with acquired hemophilia or factor VIII inhibitor related to factor VIII replacement. VWF exon 28 sequencing should be reserved for suspected type 2M VWD; this girl has normal VWF activity, which rules out type 2M disease. The factor VIII level is higher than expected for type 2N VWD, and the inheritance pattern is not consistent with that diagnosis.

**Question 22**

**Answer:** A

**Explanation:** This case illustrates the well-known association between development of a factor IX inhibitor and anaphylaxis. This risk is highest within the first 10–20 exposure days. In this case, an inhibitor assay should be done to identify and quantify the inhibitor titer. A factor IX assay could be done to assess factor IX activity, but this assay is insufficient to determine the inhibitor titer. IgE level is a nonspecific test that is not relevant. C1 esterase inhibitor would be done in patients with angioedema and suspected C1 esterase inhibitor deficiency.

**Question 23**

**Answer:** C

**Explanation:** The risk of inhibitor correlates with the type of factor VIII mutation. The larger the gene disruption, the higher the risk of inhibitor. Individuals with large factor VIII gene deletions have the highest risk of inhibitor.

**Question 24**

**Answer:** C

**Explanation:** Like his uncle, this child has mild hemophilia B. This case demonstrates the difficulty in diagnosing mild hemophilia B at birth because of physiologically low levels of factor IX and other vitamin-K-dependent factors. Laboratory and phlebotomy errors can occur, and confirmatory testing should always be done, but these are not the best answers given the family history of mild hemophilia B. Gene therapy has been successful for some adults with hemophilia B, but gene therapy has not been established for infants with hemophilia B.

**Question 25**

**Answer:** D

**Explanation:** At this stage of pregnancy, the only acceptable answer is umbilical cord sampling at the time of delivery. Prenatal diagnostic testing must be done earlier in pregnancy: fetal cord blood sampling at 10–12 weeks’ gestation; chorionic villus sampling at 11–15 weeks’ gestation; and amniocentesis at 20–24 weeks’ gestation.

**Question 26**

**Answer:** C

**Explanation:** The child should be given recombinant factor VIII prior to emergency surgery to prevent bleeding complications. Recombinant factor VIII is preferred over plasma-derived factor VIII product because of the safety profile. DDAVP may be used in patients with mild hemophilia A if they have a documented response to a DDAVP challenge. Patients with moderate and severe hemophilia will not have enough factor VIII stores to have an appropriate response. Aminocaproic acid is not sufficient because it will not increase the factor VIII levels. It may be used as an adjunctive therapy for mucosal bleeding. Of note, postoperative management will also need to be coordinated depending on the postoperative surgical bleeding risk.

**Question 27**

**Answer:** C

**Explanation:** This case demonstrates the importance of knowing how to calculate factor VIII replacement and the appropriate factor correction for a knee hemarthrosis. For a traumatic knee hemarthrosis, 100% factor correction should be given. One unit/kg of factor VIII will raise the factor VIII level by 2%. Therefore, for a 100% correction, the dose would be 750 units. A dose of 250 units would provide only a 33% correction.

**Question 28**

**Answer:** D

**Explanation:** This case illustrates appropriate management of hematuria in hemophilia. In this case, the hematuria is related to renal calculi rather than trauma. It is important to remember that individuals with bleeding disorders may present with bleeding symptoms associated with another underlying condition such as renal calculi. The bleeding in this adolescent is significant enough to cause symptomatic anemia. Therefore, red cell transfusion should be administered. Additionally, treatment is required to stop the bleeding. Red cell transfusion will not replace any clotting factors. Antifibrinolytics, including aminocaproic acid and tranexamic acid, are contraindicated in the setting of hematuria because they may cause obstructive clots within the genitourinary system. Therefore, the best answer is to administer red cell transfusion in combination with recombinant factor VIII.

**Question 29**

**Answer:** D

**Explanation:** This child most likely has a transient inhibitor because his inhibitor remained at a low-titer (<5 BU) despite continuing prophylactic therapy. He can continue his current prophylaxis. If he has bleeding symptoms and does not respond to standard doses of factor replacement, additional inhibitor and pharmacokinetic studies will be warranted. Ifthis was a high-responding, high-titer inhibitor, then the child would need to discontinue factor VIII replacement and use a bypassing agent for prophylaxis and/or management of bleeds. Immune tolerance induction therapy would be recommended to eradicate the inhibitor.

**Question 30**

**Answer:** D

**Explanation:** Like his uncle, this child has mild hemophilia B. Clinicians should be aware that individuals with mild hemophilia A and B may have normal aPTT. In many laboratories, the aPTT will not prolong until the factor level is <30%. Given the prior history of bleeding and the family history of mild hemophilia B, the most likely diagnosis is hemophilia B, and a factor IX assay should be ordered. The PFA is mostly likely abnormal because of anemia. The PFA would be abnormal in Glanzmann thromboasthenia, but this is a rare autosomal recessive disorder that presents with severe mucosal bleeding in early childhood. Aspirin can also prolong the PFA but would be unusual in a child and would not explain prior bleeding symptoms.

**Question 31**

**Answer:** A

**Explanation:** In this case, the infant may undergo circumcision without special precaution. Based on the family history of hemophilia A on the father’s side, the child is not at risk for hemophilia because it is transmitted on the X chromosome, which would come from the maternal side. Because hemophilia A is not suspected, no testing or treatment is required. Of note, if the infant did have hemophilia A, factor replacement would be recommended prior to circumcision. Timing and risks of benefits of circumcision would need to be discussed with the family.

**Question 32**

**Answer:** D

**Explanation:** One BU inactivates 50% of plasma factor VIII activity in the incubation mixture. Therefore, a decrease in factor VIII activity from 100→50%→25%→12.5%→6.25% corresponds to 4 BU.

**Question 33**

**Answer:** D

**Explanation:** This question asks that you recognize the risk factors for the development of inhibitors. Although his age and his status as a previously untreated patient (no prior factor and known as PUPs) are important points that make close monitoring at the initiation of factor therapy important, they don’t per se increase the risk for inhibitors (all patients with hemophilia are PUPs at the early stages of their life). Race is an important risk factor for inhibitor development, however, it is patients of African descent that are at higher risk not Caucasians. The intron 22 inversion is the most common mutation found in severe hemophilia patients, however, it does not confer an increased (nor decreased) risk for the development of inhibitors. Levels of VWF are not known to influence the risk for inhibitor development. Family history is in fact the risk factor known to confer the highest risk for developing inhibitors with concordance among siblings as high as 90%.

**Question 34**

**Answer:** E

**Explanation:** Although this patient responds to desmopressin, his peak level of 28% is not sufficient for adequate hemostasis for a surgical procedure, including (and perhaps especially) dental extractions. Aminocaproic acid is an effective adjunctive therapy and helps maintain clot stability once a clot is formed but in and of itself doesn’t form clots. Therefore, answer A is incorrect. The most appropriate therapy is a factor concentrate to increase the level to at least 50% and, in this case, up to 80% (the recovery of factor VIII is 2%/IU/kg) followed by aminocaproic acid.

**Question 35**

**Answer:** A

**Explanation:** The most appropriate treatment for children with severe hemophilia with recurrent bleeding (especially recurrent joint bleeding) is prophylactic infusions of factor on a regular schedule to prevent bleeding episodes. Therefore, choice A is the correct answer. Observation after three joint bleeds by this age is inappropriate and will likely result in this patient continuing to have joint bleeds, putting him at risk for hemophilic arthropathy. Physical therapy to assess gait at this point and at this age is not indicated. Choice D is wrong for several reasons. First and foremost, desmopressin only works in factor VIII deficiency and only in a mild hemophilia patient. Second, desmopressin is relatively contraindicated at this age due to the risk for hyponatremia. Finally, it is not an effective treatment for prevention of bleeding in hemophilia. With respect to gene therapy, although clinical trials are under way, they are reserved only for adults.