Hemophilia & von Willebrand Disease

2004

Valentino

1. A newborn infant with bleeding for 8 days following circumcision is evaluated for possible hemophilia. Of the following laboratory tests, which is most likely to be abnormal in the boy?
    a. Platelet count
    b. aPTT*
    c. PT
    d. Fibrinogen
    e. Bleeding time

2. A 6 year old boy is seen in consultation for bruising and epistaxis. The family history is remarkable for two maternal cousins with hemophilia. On physical examination, the child has large bruises primarily on the lower extremities, no petechiae, but crusted blood in both nares. The laboratory evaluation is normal including measurements of the PT, aPTT, bleeding times and fibrinogen. The most likely diagnosis is:
    a. Severe hemophilia A
    b. Mild hemophilia B*
    c. Lupus anticoagulant
    d. Immune thrombocytopenia
    e. Henoch-Schonlein purpura

3. What percentage of male children born to a women known to be a carrier of severe hemophilia A will have hemophilia?
    a. 0
    b. 25
    c. 50*
    d. 75
    e. 100

4. Among the genetic causes of severe hemophilia A, the most common is:
    a. Missense mutation
    b. Framshift mutation
    c. Nonsense mutation
    d. Large deletion
    e. Gene inversion*

5. A newly married couple requests information regarding prenatal diagnosis for severe hemophilia. The women has two brothers with severe hemophilia B, one complicated by inhibitor formation. What sampling method and at what gestational age should be recommended?
    a. Fetal cord blood sampling at 10-12 weeks gestation
    b. Chorionic villus sampling at 11-15 weeks gestation*
    c. Amniocentesis at 2024 weeks
    d. Umbilical cord blood sampling at the time of delivery

e. Maternal blood testing for factor IX activity prior to pregnancy

2006

Valentino

1. An eight year old boy is scheduled for elective surgery for placement of tympanostomy tubes due to recurrent episodes of otitis media. There is no family history of a bleeding disorder and the boy has no history of bruising or bleeding. Preoperative laboratory testing demonstrates the following results:

Prothrombin time	15.9 seconds	reference range,	9.5-11.5 seconds
aPTT	36 seconds		24-33 seconds
Platelet count	179,000		150-300,000

Of the following tests, which is most likely be abnormal on further testing of the boy?

f. Factor VIII:C
g. Ristocetin cofactor
h. Factor VII*
i. Fibrinogen
j. Bleeding time

2. Patients with von Willebrand disease are most likely to have which of the following combinations of test results:

	Clot retraction	Bleeding time	Platelet adhesion	ADP-induced platelet aggregation	Ristocetin-induced platelet agglutination
A*	Decreased	Prolonged	Decreased	Normal	Decreased
B	Normal	Normal	Normal	Normal	Normal
C	Normal	Normal	Decreased	Normal	Decreased
D	Normal	Prolonged	Decreased	Normal	Normal
E	Absent	Prolonged	Decreased	Absent	Normal

3. Patients with mild hemophilia are most likely to have which of the following combinations of clinical signs and symptoms:

	Petechiae	Purpura	Hemarthrosis	Bleeding after surgery	Mucous membrane bleeding
A	Absent	Absent	Absent	Absent	Absent
B	Absent	Present	Present	Present	Present
C*	Absent	Present	Absent	Present	Present
D	Absent	Present	Present	Present	Present
E	Present	Present	Absent	Present	Present

4. A newborn infant with bleeding for 8 days following circumcision is evaluated for possible hemophilia. Of the following laboratory tests, which is most likely to be abnormal in the boy?

k. Platelet count
l. aPTT*
m. PT
n. Fibrinogen
o. Bleeding time

5. Which combination of test results is most consistent with type 2B von Willebrand disease?

	Platelet count (150-300,000)	Bleeding time (3-9 min)	Factor VIII:C (50-150%)	Ristocetin cofactor activity (60-150%)	Ristocetin-induced platelet agglutination (normal)
A	Normal	7.5	143	121	Normal
B	43,000	9.5	87	74	Normal
C	221,000	14	38	23	Normal
D*	79,000	15	27	22	Reduced
E	427,000	20	122	144	Normal

6. A 6 year old boy is seen in consultation for bruising and epistaxis. The family history is remarkable for two maternal cousins with hemophilia. On physical examination, the child has large bruises primarily on the lower extremities, no petechiae, but crusted blood in both nares. The laboratory evaluation is normal including measurements of the PT, aPTT, bleeding times and fibrinogen. The most likely diagnosis is:
    a. Severe hemophilia A
    b. Mild hemophilia B*
    c. Lupus anticoagulant
    d. Immune thrombocytopenia
    e. Henoch-Schonlein purpura

7. What percentage of male children born to women known to be a carrier of severe hemophilia A will have hemophilia?
    a. 0
    b. 25
    c. 50*
    d. 75
    e. 100

8. Among the genetic causes of severe hemophilia A, the most common is:
    a. Missense mutation
    b. Framshift mutation
    c. Nonsense mutation
    d. Large deletion
    e. Gene inversion*

9. A newly married couple requests information regarding prenatal diagnosis for severe hemophilia. The woman has two brothers with severe hemophilia B, one

complicated by inhibitor formation. What sampling method and at what gestational age should be recommended?

a. Fetal cord blood sampling at 10-12 weeks gestation
b. Chorionic villus sampling at 11-15 weeks gestation*
c. Amniocentesis at 2024 weeks
d. Umbilical cord blood sampling at the time of delivery
e. Maternal blood testing for factor IX activity prior to pregnancy

10. A ten your old boy with severe Christmas disease has a swollen and warm left knee. There is no history of trauma. On physical examination, the knee is swollen but not tender and the range of motion is preserved. He has received three doses of recombinant factor IX concentrate at a dose of 50 IU/kg without improvement. The most appropriate next step is:
    a. Aspiration of the joint to decompress the hemarthrosis and exclude septic arthritis
    b. Measurement of the inhibitor titre as development of an immune response to recombinant factor IX is likely
    c. Continued regular administration of factor concentrate and physical therapy to treat chronic synovitis*
    d. Arthroscopy to repair a ruptured anterior cruciate ligament
    e. Splinting and rest to allow the acute hemarthrosis to resolve

11. Which of the following statements best describes the action of desmopressin (DDAVP) in controlling bleeding in patients with mild hemophilia?
    a. Induction of erythrocyte and platelet agglutination
    b. Inhibition of plasminogen
    c. Promotion of the interaction of collagen with platelet glycoprotein Ib/IX
    d. Release of von Willebrand factor from hepatocytes
    e. Activation of the factor X and the common pathway*

12. A two year old boy with severe hemophilia A develops an inhibitor after receiving the 7^{th} dose of anti-hemophilic factor concentrate. Which of the following statements best describes the genetics of inhibitor formation in sever hemophilia?
    a. Premature stop codon with no protein synthesis*
    b. Inversion 22
    c. Missense mutation resulting in the synthesis of a truncated factor VIII molecule
    d. Frameshift mutation
    e. Small deletion

13. Which of the following statements best describes the optimal treatment of life-threatening bleeding in a boy with severe hemophilia complicated by a high-responding inhibitor?
    a. Infusion of small doses of recombinant factor VIII concentrate
    b. Administration of platelet concentrates until the bleeding is controlled
    c. Infusion of large doses of monoclonal factor VIII concentrates
    d. Administration of agents that bypass the inhibitor to induce coagulation*

e. Conservative measures including analgesics and cold compresses

14. A 14 year old boy with severe hemophilia A and a history of 20 bleeds into the right knee is seen in consultation. What statement best describes the optimal treatment for the child?
    a. Administration of 50 IU/kg factor concentrate daily
    b. Administration of 25 IU/kg factor concentrate every other day*
    c. Surgical decompression of the joint
    d. Aspiration of the joint and application of a cast
    e. Rest and immobilization of the joint

15. A 17 year old girl is admitted to the hospital for severe anemia due to prolonged menstrual blood loss. Menarche was at age 12 years. Menses have been described as “not too bad” by the girl and her mother. During your consultation evaluation, you discover that she also has had frequent episodes of epistaxis, easy bruising and gum bleeding after exfoliation of deciduous teeth. The most informative laboratory test is likely to be which of the following:
    a. Ristocetin cofactor activity*
    b. Platelet count
    c. Prothrombin time
    d. aPTT
    e. Bleeding time

16. Which of the following statements is true regarding the 19 year old mother of a newborn boy with severe hemophilia A:
    a. Carrier testing and genetic counseling should be performed only if the boy develops an inhibitor to factor VIII
    b. Easy bruising and severe bleeding is likely to be present
    c. The likelihood that the mother is a carrier of the factor IX mutation is approximately 50%
    d. The probability that there is no family history of hemophilia is approximately 30%*
    e. The women should be counseled to undergo sterilization

17. Of the following, which statement is not characteristic of severe hemophilia
    a. Inherited deficiency of coagulation factor VIII
    b. Point mutations and gene deletions account for the majority of the defects identified
    c. Carriers of the mutation typically have clotting factor levels of 25-75%
    d. Plasma levels of factor VIII are temporarily increased following use of desmopressin*
    e. Thromboembolism, although clinical symptoms are uncommon, is a major complication of venous access devices

18. Which of the following statements is not true with regards to von Willebrand disease?
    a. Pattern of inheritance is autosomal
    b. Factor VIII:C activity is usually below the reference range.

c. The incidence of the disease is 1 per 10,000*
d. Evaluation of the multimeric structure of von Willebrand factor is helpful in the classification of variant forms of the disease
e. The von Willebrand factor gene is located on chromosome 12

19. Choose among the following sets of laboratory tests that is most likely for a patient with each subtype of von Willebrand disease

Set	Platelet count	Bleeding time	Factor VIII:C	vWF antigen
1	Normal	Increased	Reduced	Absent
2	Reduced	Increased	Reduced	Reduced
3	Normal	Normal	Normal	Normal
4	Normal	Increased	Normal	Reduced
5	Normal	Increased	Normal	Normal

a. Type 1 set 3
b. Type 2A set 4
c. Type 2B set 2
d. Type 2C set 5
e. Type 3 set 1

20. A 13 year old girl is referred for easy bruising and menorrhagia. Her father has a life-long history of easy bruising and bleeding after dental extraction and was diagnosed to have mild hemophilia. Which of the following diagnosis is most likely in this family?
    a. Mild hemophilia A
    b. Quebec platelet disorder
    c. von Willebrand Disease, type 2N*
    d. Congenital thrombocytopenia
    e. Factor XII deficiency

21. A ten your old boy with severe Christmas disease has a swollen and warm left knee. There is no history of trauma. On physical examination, the knee is swollen but not tender and the range of motion is preserved. He has received three doses of recombinant factor IX concentrate at a dose of 50 IU/kg without improvement. The most appropriate next step is:

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    b. Inhibition of plasminogen
    c. Promotion of the interaction of collagen with platelet glycoprotein Ib/IX
    d. Release of von Willebrand factor from hepatocytes
    e. Activation of the factor X and the common pathway*

23. A two year old boy with severe hemophilia A develops an inhibitor after receiving the 7^{th} dose of anti-hemophilic factor concentrate. Which of the following statements best describes the genetics of inhibitor formation in sever hemophilia?
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    c. Infusion of large doses of monoclonal factor VIII concentrates
    d. Administration of agents that bypass the inhibitor to induce coagulation*
    e. Conservative measures including analgesics and cold compresses

25. A 14 year old boy with severe hemophilia A and a history of 20 bleeds into the right knee is seen in consultation. What statement best describes the optimal treatment for the child?
    a. Administration of 50 IU/kg factor concentrate daily
    b. Administration of 25 IU/kg factor concentrate every other day*

c. Surgical decompression of the joint
d. Aspiration of the joint and application of a cast
e. Rest and immobilization of the joint

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    a. Ristocetin cofactor activity*
    b. Platelet count
    c. Prothrombin time
    d. aPTT
    e. Bleeding time

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    c. von Willebrand Disease, type 2N*
    d. Congenital thrombocytopenia
    e. Factor XII deficiency

2009

Hemophilia and von Willebrand Disease

Thomas C. Abshire, MD

1. A 10-year-old obese girl moves to your hemophilia treatment center for continued management of presumed von Willebrand Disease (VWD) and needs a tonsillectomy to control well-documented sleep apnea. Her main bleeding symptoms are occasional mouth bleeding and epistaxis, both managed with local control measures. The patient seems to remember that she did not respond very well to a DDAVP challenge. You ask for the medical records: normal CBC and platelet count, VWF: Ag = 45%, VWF:RCo: = 20%, FVIII = 55%, VWF multimers were normal. Repeat VWD testing performed at her center before moving were similar. Assuming that these values were both carefully performed and representative of the patient, what would you recommend *prior to* the upcoming surgery?
   A. Insist upon performing a low-dose, ristocetin-induced platelet aggregation to absolutely rule out type 2B VWD.
   B. Repeat all the VWD testing in your laboratory due to concern that the prior values, especially the VWF:RCo, were not carefully drawn and possibly affected by confounding variables.
   C. Send a sample for genetic testing (exon 28) for probable type 2M VWD.
   D. Send a sample for VWF propeptide assay, since this patient probably has type 1C VWD with accelerated VWF clearance.

Answer: D
Explanation: This girl probably has type 2M VWD, which would be confirmed by VWF exon 28 testing. Confounding effects on VWF testing should always be considered, but the consistency of the testing in this patient is suggestive of accuracy. Accordingly, surgery should proceed with a VWF/FVIII product given her history of bleeding, the prior laboratory testing which consistently demonstrated a 50% reduction in VWF:RCo to VWF:Ag ratio, and a low normal FVIII activity and normal VWF multimer pattern, as well as a lack of response to DDAVP. Type 1C VWD has both a low VWF:RCo and VWF:Ag (normal ratio). Type 2B VWD will have an abnormal VWF multimer pattern (loss of high molecular weight multimers) and often have a slightly low platelet count due to excessive binding of the VWF to platelets. Type 2N VWD (Normandy variant) will have a low FVIII activity in a range mimicking mild hemophilia (usually 10%-20%) but often normal to only slightly low VWF testing. Since the FVIII level is normal, it is not necessary to perform more specific FVIII binding testing.

2. A 15-month-old male with a known diagnosis of hemophilia A (FVIII deficiency) presents to the hemophilia treatment center with a new right knee bleed which does not appear to be responding to his usual FVIII dosing schedule. The father has been treating this bleed for 3 days (50 IU/kg of recombinant (r) FVIII per day). The boy has received 12 exposure doses to rFVIII in the past. You suspect an inhibitor to FVIII and send a Bethesda titer that is 25 BU. Your best next course of action would be to:
   A. Give high doses of rFVIII (200 IU/kg) to overwhelm the inhibitor.

B. Start low-dose immune tolerance at 50 IU/kg 3x/week immediately.
C. Administer activated prothrombin complex concentrates (aPCC) at 75 IU/kg three times daily until the knee bleed resolves.
D. Give recombinant (r) FVIIa at 90 mcg/kg every 2-3 hours for 3 doses or until the knee bleed resolves.
E. Do not treat the knee bleed with any factor concentrate, as previous treatment with rFVIII did not work and you would like to wait for the Bethesda titer to come down below 10 BU before initiating additional treatment.

Answer: D
Explanation: This patient presents in typical fashion for a new-onset high-titer inhibitor with a median FVIII exposure days (ED) = 10-12 ED. The bleed should be treated with rFVIIa as described below. The long-term options for this patient are to utilize immune tolerance therapy (ITT) once the inhibitor titer drops below 10 BU. Answers a. and b. are the treatment options for the current international ITT trial, which randomizes between high dose (200 IU/kg daily) and low-dose (50 IU/kg 3x/week) therapy. Although both dosing schedules are appropriate in the context of this randomized trial, it is best to not offer ITT until the BU drops below 10. If acute bleeds occur while waiting for the BU to drop to a lower level or while the patient is on ITT, the most appropriate treatment is to administer rFVIIa at a dose and interval as outlined in answer d. Although aPCC are another treatment option for inhibitor patients, the interval suggested in answer c. is not optimal unless there was close laboratory monitoring for possible DIC. Additionally, this child has never been exposed to plasma-derived FVIII and it would be best to utilize a bypassing agent that is recombinantly derived (rFVIIa). It would not be appropriate to avoid treating the bleed as suggested in answer e.

3. A 8-year-old African-American boy presents to your clinic for evaluation of nosebleeds. You determine that they occur almost weekly, can be from either nostril, and may last for 10-15 minutes before stopping with pressure. His gums bled when a few of his primary teeth came out. His mother had bleeding with her hysterectomy and he has a sister with heavy menses. On exam, he has 3-4 scattered 1- 2-cm bruises below his knees and several 2-cm bruises on his arms and trunk. Screening laboratory is a follows: PT 13.1 sec, aPTT 32 sec, PFA normal, CBC and platelet count normal, and fibrinogen 300 mg/dl. Based upon this information, which diagnosis is most likely?
    A. Bernard Soulier syndrome
    B. Mild factor FVIII deficiency
    C. Type 1 von Willebrand Disease (VWD)
    D. FXIII deficiency
    E. Type 2N VWD

Answer: C
Explanation: This young boy has a positive personal and family history of bleeding as well as findings on physical examination and therefore the diagnosis of a platelet vessel/VWF disorder such as type 1 VWD is likely. All the screening testing included are normal. Type 2N VWD is not likely due to the normal aPTT, which rules against the low FVIII associated with this type of VWD. Mild hemophilia A will also slightly prolong the

aPTT due to the low FVIII level. Bernard Soulier syndrome presents with more bleeding symptoms and often manifests a prolonged PFA and a low platelet count. Though FXIII deficiency has normal screening laboratory, its clinical presentation is similar to severe hemophilia and this boy has more mucosal bleeding symptoms.

4. An 18-month-old girl has known type 1 VWD. Her mother and brother also have type 1 VWD and are both responsive to DDAVP treatment for bleeding. The young girl presents to your clinic for management of continued nosebleeds and lethargy. She went to a local emergency room yesterday and was given an intravenous dose of DDAVP, 0.3 mcg/kg in 30 cc of normal saline over 15 minutes. On examination, she is afebrile, has dried blood at both nares, does not appear pale, but is slightly swollen in both lower legs. She is responsive to your exam and not irritable, but does appear somewhat lethargic. The most pressing need to address at present is:
   A. Draw a serum sodium due to concern about hyponatremia from the DDAVP.
   B. Administer a dose of VWF/FVIII product to stop the nosebleed.
   C. She is experiencing tachyphylaxis from the DDAVP and that is why she is still bleeding.
   D. Attend to her nosebleed with another dose of DDAVP.
   E. Immediately perform a lumbar puncture for evaluation of possible sepsis.

Answer: A
Explanation: This young girl probably has hyponatremia from intravenous DDAVP, causing lethargy and edema. Sending a stat serum sodium and instituting fluid restriction would be important. One should use caution in using DDAVP in children < 2 years of age. The girl's physical examination would suggests that she is not profoundly anemic from the nosebleeds, so giving a VWF/FVIII product would not be the first priority. Additional DDAVP should also not be given for the reason previously described. Though sepsis should always be considered in a small child presenting with lethargy, the history and physical exam would suggest hyponatremia as the etiology. Tachyphylaxis usually occurs after several doses of DDAVP.

5. A 6-year-old Caucasian male is undergoing an umbilical hernia repair. He has known type 1 VWD with VWF levels of 20% and a FVIII level = 25%. He is poorly responsive to DDAVP. He receives 60 IU/Kg of a VWF/FVIII product q12 h on the day of surgery and due to normal VWF and FVIII levels on day 2 of surgery, he is discharged from the hospital and his treatment schedule is changed to once a day for two days and then stopped after a total of 3 days of VWF/FVIII treatment. His mother contacts you on the 8th day post-op because he is bleeding from his surgical site; he has had no bleeding since the surgery. The most likely cause for his bleeding is:
   A. Development of a VWF inhibitor
   B. Inadequate levels of VWF on day 8 with new-onset mucosal bleeding
   C. Low levels of FVIII on day 8 with bleeding from wound remodeling at the surgical site
   D. Surgical cause for the bleeding

E. Inadequate replacement therapy for surgery; he should have received DDAVP since he has type 1 VWD

Answer: C
Explanation: The correct response illustrates how both VWF and FVIII levels need to be monitored closely after surgery. It is important to follow both levels, since low VWF levels appear to be more important in the immediate postoperative period and FVIII may play a greater role 5-7 days after surgery. Additionally, both VWF and FVIII may be more elevated after surgery than one would suspect due to release from storage sites in the endothelial cells. A surgical cause for the bleeding is not likely since the patient did not have bleeding until 1 week after the procedure. Inhibitors to VWF are extremely rare, especially in type 1 disease. Finally, the patient was a known poor responder to DDAVP, therefore this product appropriately was not given.

6. Patients with moderate hemophilia are most likely to have which of the following combinations of clinical signs and symptoms?

	Petechiae	Palpable purpura	Traumatic hemarthrosis	Bleeding after circumcision	Gum bleeding with brushing
a	Absent	Absent	Absent	Absent	Absent
b	Absent	Present	Present	Present	Absent
c	Present	Absent	Absent	Absent	Absent
d	Absent	Present	Present	Present	Present
e	Absent	Absent	Absent	Absent	Present

Answer: B
Explanation: Hemophilia has bleeding symptoms similar to other factor deficiency bleeding disorders such as postsurgical bleeding, deeper or delayed bleeding, and joint/muscle bleeding. Answer b. is most appropriate due to: palpable purpura, traumatic joint bleeding, and post-surgical bleeding. Petechiae is more likely in platelet disorders (and not likely in VWD) and mouth/gum bleeding with tooth brushing is not likely in most cases of ITP unless the platelet count is very low or there is an associated platelet dysfunction. Accordingly, patient a. is normal, subject c. has acute ITP, and patients d. and e. have type 3 and type 1 VWD, respectively.

7. An 8-year-old boy with severe hemophilia B has a swollen and slightly warm left knee. He has a prior history of multiple joint and muscle bleeds and recently has had four bleeds into this joint over the last 6 months. The boy has received approximately 40 doses of FIX since birth. He is not on prophylaxis and the family has treated each of his prior bleeds with two infusions of recombinant FIX at 60 IU/kg. There is no history of trauma. On physical examination, the knee is swollen (2+/3 synovial changes) but not tender or erythematous and the knee extension is decreased by 15 degrees. He has received two doses of recombinant FIX prior to coming to clinic without much improvement. The most appropriate next step is:
   A. Aspiration of the joint to decompress the hemarthrosis and exclude septic arthritis

B. Measurement of a FIX inhibitor titer, as development of an antibody to factor IX is likely
C. Place the child on prophylaxis with recombinant FIX at a dose of 60IU/kg 2-3 x per week for 3 months and then re-evaluate the joint
D. Immediate arthroscopic synovectomy to remove the abnormal synovium
E. Obtain an X ray and then ice and splint the joint and allow the joint to rest and the hemarthrosis to resolve

Answer: C
Explanation: This young boy with severe hemophilia B has a knee target joint. He has not been on prophylaxis, but, at this juncture, treating him with recombinant FIX 2-3x per week (secondary prophylaxis) may help avoid surgery and if the family decides to continue prophylaxis, may avoid many of the joint/muscle bleeds he has sustained in his lifetime. This is the most appropriate choice. He might eventually need arthroscopic surgery, but this choice would not be appropriate in the acute setting or until you had tried limited prophylaxis. Joint aspiration may be helpful but is controversial since the patient has a more chronic synovitis picture and has no clinical evidence for septic arthritis. RICE therapy (rest, ice, compression, and elevation) without factor replacement is not an appropriate therapy in hemophilia management. Development of an inhibitor at his age and after 40 doses of FIX without any accompanying danger signal (surgery, trauma, etc.) is unlikely.

8. A 2-year-old boy with 1% FVIII has had minimal bleeds in his lifetime. He has received recombinant FVIII treatment approximately 10 times for mostly traumatic muscle bleeds, oral bleeding, and one bleed into his left ankle. He now presents with a second bleed into his right ankle; the first bleed occurred 1 month ago and was treated with three doses of recombinant FVIII at conventional doses and his symptoms resolved completely. His examination reveals 1+/3 synovitis but normal range of motion. His exam is otherwise normal. Plain films of the ankle show soft tissue changes and no bony abnormalities. Which of the following would be the best management choice at this time?
   A. Continue with aggressive target joint replacement therapy (three infusions of recombinant FVIII over 4 days) around each joint bleed, but don't start prophylaxis.
   B. Consider sending a Bethesda titer since he has had about 10 infusions of recombinant FVIII and he will most likely develop an inhibitor.
   C. Arrange for your orthopedic surgeon to schedule the patient for an arthroscopic synovectomy.
   D. Strongly consider a radionuclide synovectomy because the patient is too young for arthroscopic surgery and radionuclide synovectomy carries little risk and is more effective at eliminating the abnormal synovium.
   E. Start the patient on conventional primary prophylaxis with recombinant FVIII at 20-25 IU/kg Monday and Wednesday and 40-50 IU/kg on Friday.

Answer: E
Explanation: This case illustrates the proper indication for initiating primary prophylaxis in a patient with severe hemophilia. The majority of the developed world institutes prophylaxis in a child with hemophilia before the age of 30-36 months. In the United

States, many clinicians will start prophylaxis after the patient has declared himself as a "bleeder" but no later than after 1-2 bleeds into one joint. There is debate about which dose should be utilized to initiate prophylaxis, with some opting for a once-weekly approach (Canada) and some staying with a conventional 3x/week approach (Sweden). Waiting on prophylaxis (choice a) might lead to further joint bleeding and damage as the patient has declared himself to be a "bleeder." Development of an inhibitor is a possibility, but the patient appears to have responded in the past to conventional recombinant FVIII and he probably is having routine Bethesda titer assessments in his comprehensive clinic. Development of an inhibitor should be considered if he doesn't respond to factor with this new joint bleed. The patient is a bit young for arthroscopic surgery (technical barriers) and radionuclide synovectomy, although technically easier, is not without potential side effects. Either synovectomy option should not be considered until the patient has failed prophylaxis.

9. A 5-year-old boy with hemophilia A is due for a molar dental extraction. He has responded to recombinant FVIIII in the past and you need to devise a treatment plan for the upcoming procedure. He weighs 20 kg. Which of the following choices characterizes the best treatment plan?
   A. Avoid any treatment (factor replacement and antifibrinolytic therapy) since molar extractions are unlikely to cause bleeding.
   B. Do not give recombinant FVIII but give aminocaproic acid, 2 grams, 30 minutes prior to the procedure and then withhold further dosing of antifibrinolytics.
   C. Do not give recombinant FVIII and administer aminocaproic acid, 1 gram every 12 hours for 2 days.
   D. Give a dose of recombinant FVIII at 950 IU 30 minutes prior to the procedure along with 2 grams of aminocaproic acid every 6-8 hours for 3-7 days.
   E. Administer one dose of recombinant FVIII at 950 IU 30 minutes prior to the procedure and hold on any additional antifibrinolytic therapy or factor replacement.

Answer: D
Explanation: Preventive treatment of bleeding in dental extractions is important. One should only need to administer one dose of recombinant FVIII at 20-25 IU/Kg along with antifibrinolytic therapy, 100 mg/kg/dose, given every 6-8 hours for 3-7 days. All of the other answers are inadequate due to lack of treatment (with both factor and antifibrinolytics) or inadequate dosing.

10. A 5-day-old infant presents to your clinic for evaluation of a large 4 x 4 cm bruise with a underlying palpable hematoma on the left thigh secondary to a hepatitis B immunization in the nursery prior to discharge. He was circumcised without excessive bleeding or prolonged oozing. He sports a 3 x 3 cm right-sided cephalohematoma from a forceps delivery. His exam is otherwise normal. The father accompanies his new baby and although he personally has no bleeding symptoms, he thinks that there might be a bleeding history on his wife's side of the family with excessive bruising and menorrhagia in his wife and her sister (maternal aunt) and a

history of bruising and postoperative bleeding in the maternal grandfather. Which diagnosis is most likely the cause of the newborn's bleeding symptoms?

A. Moderate (2%) hemophilia A
B. Type 1 VWD
C. FXIII deficiency
D. Maternal ITP
E. Type 3 VWD

Answer: A
Explanation: Hemophilia can be varied in its presentation. Several of this newborn's bleeding episodes (large palpable hematoma and cephalohematoma) point towards a factor deficiency as a cause for the bleeding. Patients with hemophilia do not need to have circumcision related bleeding. The family history is consistent with hemophilia since both the mother and her sister (maternal aunt) appear to be symptomatic carriers and their father (maternal grandfather) has bleeding similar to other older moderate hemophiliacs. This family history could be consistent with type 3 VWD, but the father is asymptomatic (both parents should have type 1 VWD). The child and family history is not consistent with type 1 VWD. Additionally, newborns rarely bleed in the first week of life from type 1 VWD since the VWF is often elevated around delivery. Maternal ITP might cause a low platelet count in the baby, but the bleeding symptoms, if present, are almost always mucosal in nature. FXIII deficiency often presents with more severe bleeding manifestations, especially delayed bleeding from surgery (circumcision) as well as bleeding from the umbilical cord and a more pronounced cephalohematoma.

2011

Hemophilia and von Willebrand Disease

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1. A 10-year-old obese girl moves to your hemostasis treatment center for continued management of presumed von Willebrand Disease (VWD) and needs a tonsillectomy to control well-documented sleep apnea. Her main bleeding symptoms are occasional mouth bleeding and epistaxis, both managed with local control measures and aminocaproic acid. The patient seems to remember that she did not respond very well to a DDAVP challenge. You ask for the medical records and they demonstrate: normal CBC and platelet count, VWF: Ag = 45%, VWF:RCo: = 20%, FVIII = 55%, VWF multimers = normal. Repeat VWD testing performed at her treatment center before moving were similar to her first testing results. Assuming that both VWD tests were carefully performed and representative of the patient, what would you recommend *prior to* the upcoming surgery?
   A. Insist upon performing a low-dose, ristocetin-induced platelet aggregation to absolutely rule out type 2B VWD.
   B. Repeat all the VWD testing in your laboratory due to concern that the prior values, especially the VWF:RCo, were not carefully drawn and possibly affected by confounding variables.
   *C. Send a sample for genetic testing (exon 28) for probable type 2M VWD.

D. Send a sample for VWF propeptide assay, since this patient probably has type 1C VWD with accelerated VWF clearance.

Answer: C
Explanation: This girl probably has type 2M VWD, which would be confirmed by VWF exon 28 testing. Confounding effects on VWF testing should always be considered, but the consistency of the testing in this patient is suggestive of accuracy. Accordingly, surgery should proceed with a VWF/FVIII product given: a) her history of mucosal bleeding, b) the prior laboratory testing which consistently demonstrated a 50% reduction in VWF:RCo to VWF:Ag ratio, c) a low normal FVIII activity d) normal VWF multimer pattern, and e) a lack of response to DDAVP. Type 1C VWD has both a low VWF:RCo and VWF:Ag (normal ratio of approximately 1:1). Type 2B VWD will have an abnormal VWF multimer pattern (loss of high molecular weight multimers) and often have a slightly low platelet count due to excessive binding of the VWF to platelets. Type 2N VWD (Normandy variant) will have a low FVIII activity in a range mimicking mild hemophilia (usually 10%-20%) but often normal to only slightly low VWF testing. Since the FVIII level is normal, it is not necessary to perform more specific FVIII binding testing to rule out Type 2N VWD.

2. A 15-month-old male with a known diagnosis of hemophilia A (FVIII deficiency) presents to the hemophilia treatment center with a new right knee bleed which does not appear to be responding to his usual FVIII dosing schedule. The father has been treating this bleed for 3 consecutive days (50 IU/kg of recombinant (r) FVIII per day). The boy has received 12 exposure doses to rFVIII in the past. You suspect an inhibitor to FVIII and send a Bethesda titer which confirms the inhibitor, 25 BU. Your best next course of action would be to:
   A. Give high doses of rFVIII (200 IU/kg) to overwhelm the inhibitor.
   B. Start low-dose immune tolerance at 50 IU/kg 3x/week immediately.
   C. Administer activated prothrombin complex concentrates (aPCC) at 75 IU/kg three times daily until the knee bleed resolves.
   *D. Give recombinant (r) FVIIa at 90 mcg/kg every 2-3 hours for 3 doses and monitoring for clinical improvement and then less frequently until the knee bleed resolves. If rFVIIa is given for longer periods of time, monitoring for DIC is prudent.
   E. Do not treat the knee bleed with any factor concentrate, as previous treatment with rFVIII did not work and you would like to wait for the Bethesda titer to come down below 10 BU before initiating additional treatment.

Answer: D
Explanation: This patient presents in typical fashion for a new-onset high-titer inhibitor with a median FVIII exposure days (ED) = 10-12 ED. The bleed should be treated with rFVIIa as described below. The long-term options for this patient are to utilize immune tolerance therapy (ITT) once the inhibitor titer drops below 10 BU. Answers A. and B. present the upper and lower range of possible treatment options for a patient with an inhibitor. Although both dosing schedules for ITT might be appropriate, it is best to not offer ITT until the BU drops below 10. If acute bleeds occur while waiting for the BU to drop to a lower level or while the patient is on ITT, the most appropriate treatment is to

administer rFVIIa at a dose and interval as outlined in answer D. Although aPCC are another treatment option for treating acute bleeds in inhibitor patients, the interval suggested in answer C. is not optimal unless there was close laboratory monitoring for possible DIC. Additionally, this child has never been exposed to plasma-derived FVIII and it would be best to utilize a bypassing agent that is recombinantly derived (rFVIIa). Answer E is not appropriate as the acute bleed is not treated.

3. A 8-year-old African-American boy presents to your clinic for evaluation of nosebleeds. You determine that they occur almost weekly, can be from either nostril, and may last for 10-15 minutes before stopping with pressure. His gums bled when a few of his primary teeth came out. His mother had bleeding with her hysterectomy and the patient has a sister with heavy menses. On exam, he has 3-4 scattered 1- 2-cm bruises below his knees and several 2-cm bruises on his arms and trunk. Screening laboratory is a follows: PT 13.1 sec, aPTT 32 sec, PFA normal, CBC and platelet count normal, and fibrinogen 300 mg/dl. Based upon this information, which diagnosis is most likely?
    A. Bernard Soulier syndrome
    B. Mild factor FVIII deficiency
    *C. Type 1 von Willebrand Disease (VWD)
    D. Severe FXIII deficiency
    E. Type 2N VWD

Answer: C
Explanation: This young boy has a positive personal and family history of bleeding as well as findings on physical examination of mucosal bleeding, therefore the diagnosis of a probable platelet vessel/VWF disorder such as type 1 VWD is most likely. All the screening testing included are normal. Although the PFA may be abnormal in type 1 vWD, normal values are frequently encountered. Type 2N VWD is not likely due to the normal aPTT, (low FVIII associated with type 2N VWD would give a prolonged aPTT in most laboratories). Mild hemophilia A will also slightly prolong the aPTT due to the low FVIII level. Bernard Soulier syndrome usually presents with more bleeding symptoms then presented in this case and will often manifest a markedly prolonged PFA as well as a low platelet count. Although FXIII deficiency has normal screening laboratory, its clinical presentation is similar to severe hemophilia and this boy has more mucosal bleeding symptoms than the delayed and deeper bleeding often accompany factor deficiency bleeding..

4. An 18-month-old girl has known type 1 VWD. Her mother and brother also have type 1 VWD and are both responsive to DDAVP treatment for bleeding. The young girl presents to your clinic for management of continued nosebleeds and lethargy. She went to a local emergency room yesterday and was given an intravenous dose of DDAVP, 0.3 mcg/kg in 30 cc of normal saline over 15 minutes. On examination, she is afebrile, has dried blood at both nares, does not appear pale, but is slightly swollen in both lower legs. She is responsive to your exam and not irritable, but does appear somewhat lethargic. The most pressing management need to address at present is:
    *A.Draw a serum sodium due to concern about hyponatremia from the DDAVP.

B. Administer a dose of VWF/FVIII product to stop the nosebleed.
C. Address the tachyphylaxis issue from the DDAVP and treat her bleeding with a VWF/FVIII containing concentrate.
D. Attend to her nosebleed with another dose of DDAVP.
E. Immediately perform a lumbar puncture for evaluation of possible meningitis/sepsis.

Answer: A
Explanation: This young girl probably has hyponatremia from intravenous DDAVP, causing fluid retention and lethargy. Sending a stat serum sodium and instituting fluid restriction are essential. Additionally, if she developed a seizure, the patient might need rapid correction of her sodium. One should use caution in giving DDAVP in children < 2 years of age. The girl's physical examination would suggest that she is not profoundly anemic from the nosebleeds, so giving a VWF/FVIII product would not be the first priority. Additional DDAVP should also not be given for the reason previously described. Though meningitis/sepsis should always be considered in a small child presenting with lethargy, the history and physical exam would suggest hyponatremia as the etiology. Tachyphylaxis usually occurs after several doses of DDAVP and is not the main management problem in this setting.

5. A 6-year-old Caucasian male is undergoing an umbilical hernia repair. He has known type 1 VWD with VWF activity and antigen levels = 20% and a FVIII level = 25%. He is poorly responsive to DDAVP. He receives 60 IU/Kg of a VWF/FVIII product pre-and 8 hours post surgery and due to normal VWF and FVIII levels on day 2 of surgery, he is discharged from the hospital and his treatment schedule is changed to once a day for two days and then stopped after a total of 3 days of VWF/FVIII treatment. His mother contacts you on the 8^{th} day post-op because he is bleeding from his surgical site; he has had no other bleeding since the surgery. The most likely cause for his bleeding is:
   A. Development of a VWF inhibitor
   B. Inadequate levels of VWF on day 8 with new-onset mucosal bleeding
   *C. Low levels of FVIII on day 8 with bleeding from wound remodeling at the surgical site
   D. Surgical cause for the bleeding
   E. Inadequate replacement therapy for surgery; he should have received DDAVP since he has type 1 VWD

Answer: C
Explanation: The correct answer is illustrative of how both VWF and FVIII levels need to be monitored closely after surgery. It is important to follow both levels, since low VWF levels appear to be more important in the immediate postoperative period and FVIII may play a greater role 5-7 days after surgery. Additionally, both VWF and FVIII may be more elevated after surgery than one would expect due to release from storage sites in the endothelial cells. A surgical cause for the bleeding is not likely since the patient did not have bleeding until 1 week after the procedure. Inhibitors to VWF are extremely rare, especially in type 1 disease. Finally, the patient was a known poor responder to DDAVP, therefore this product appropriately should not have been given.

6. Patients with moderate hemophilia are most likely to have which of the following combinations of clinical signs and symptoms?

	Petechiae	Palpable purpura	Traumatic hemarthrosis	Bleeding after circumcision	Gum bleeding with brushing
A.	Absent	Absent	Absent	Absent	Absent
*B.	Absent	Present	Present	Present	Absent
C.	Present	Absent	Absent	Absent	Absent
D.	Absent	Present	Present	Present	Present
E.	Absent	Absent	Absent	Absent	Present

Answer: B
Explanation: Hemophilia has bleeding symptoms similar to other factor deficiency bleeding disorders such as postsurgical bleeding, deeper or delayed bleeding, and joint/muscle bleeding. Answer B. is most appropriate due to: palpable purpura, traumatic joint bleeding, and post-surgical bleeding. Petechiae is more likely in platelet disorders (and not likely in VWD) and mouth/gum bleeding with tooth brushing is not likely in hemophilia or in most cases of ITP unless the platelet count is very low or there is an associated platelet dysfunction. Accordingly, patient A.. is normal, subject C. has acute ITP, patient D. has type 3 VWD (due to low FVIII activity of 1-5%) and patient E. type 1 VWD.

7. An 8-year-old boy with severe hemophilia B has a swollen and slightly warm left knee. He has a prior history of multiple joint and muscle bleeds and recently has had four bleeds into this joint over the last 6 months. The boy has received approximately 40 doses of FIX since birth. He is not on prophylaxis and the family has treated each of his prior bleeds with two infusions of recombinant FIX at 60 IU/kg. There is no history of trauma. On physical examination, the knee is swollen (2+/3 synovial changes) but not tender or erythematous and the knee extension is decreased by 15 degrees. He has received two doses of recombinant FIX prior to coming to clinic (one per day x 2 days) without much improvement. The most appropriate next step is:
   A. Aspiration of the joint to decompress the hemarthrosis and exclude septic arthritis
   B. Measurement for a FIX inhibitor titer, as development of an antibody to factor IX is likely
   *C. Place the child on prophylaxis with recombinant FIX at a dose of 60IU/kg 2-3 x per week for 3 months and then re-evaluate the joint
   D. Immediate arthroscopic synovectomy to remove the abnormal synovium
   E. Obtain an X ray and then ice and splint the joint and allow the joint to rest and the hemarthrosis to resolve

Answer: C
Explanation: This young boy with severe hemophilia B has a knee target joint. He has not been on prophylaxis, but, at this juncture, treating him with recombinant FIX 2-3x per week (secondary prophylaxis) may help avoid surgery and if the family decides to continue prophylaxis, may avoid many of the joint/muscle bleeds he has sustained in his

lifetime. This is the most appropriate choice. He might eventually need arthroscopic surgery, but this choice would not be appropriate in the acute setting or until you had tried limited prophylaxis. Joint aspiration may be helpful but is controversial since the patient has a more chronic synovitis picture and has no clinical evidence for septic arthritis. RICE therapy (rest, ice, compression, and elevation) without factor replacement is not an appropriate therapy in hemophilia management. Development of an inhibitor at his age and after 40 doses of FIX without any accompanying danger signal (surgery, trauma, etc.) is unlikely.

8. A 2-year-old boy with 1% FVIII has had minimal bleeds in his lifetime. He has received recombinant FVIII treatment approximately 10 times for mostly traumatic muscle bleeds, oral bleeding, and one bleed into his left ankle. He now presents with a second bleed into his right ankle; the first bleed occurred 1 month ago and was treated with three doses of recombinant FVIII at conventional doses and his symptoms resolved completely. His examination reveals 1+/3 synovitis but normal range of motion. His exam is otherwise normal. Plain films of the ankle show soft tissue changes and no bony abnormalities. Which of the following would be the best management choice at this time?
   A. Continue with aggressive target joint replacement therapy (three infusions of recombinant FVIII over 4 days) around each joint bleed, but don't start prophylaxis.
   B. Consider sending a Bethesda titer since he has had about 10 infusions of recombinant FVIII and he will most likely develop an inhibitor.
   C. Arrange for your orthopedic surgeon to schedule the patient for an arthroscopic synovectomy.
   D. Strongly consider a radionuclide synovectomy because the patient is too young for arthroscopic surgery and radionuclide synovectomy carries little risk and is more effective at eliminating the abnormal synovium.
   *E. Start the patient on conventional primary prophylaxis with recombinant FVIII at 20-25 IU/kg Monday and Wednesday and 40-50 IU/kg on Friday.

Answer: E
Explanation: This case illustrates the proper indication for initiating primary prophylaxis in a patient with severe hemophilia. The majority of the developed world institutes prophylaxis in a child with hemophilia before the age of 30-36 months. In the United States, many clinicians will start prophylaxis after the patient has declared himself as a "bleeder" but no later than after 1-2 bleeds into one joint. There is debate about which dose should be utilized to initiate prophylaxis, with some opting for a once-weekly approach (Canada) and some staying with a conventional 3x/week approach (Sweden). Waiting on prophylaxis (choice A) might lead to further joint bleeding and damage as the patient has declared himself to be a "bleeder." Development of an inhibitor is a possibility, but the patient appears to have responded in the past to conventional recombinant FVIII and he probably is having routine Bethesda titer assessments in his comprehensive clinic visits. Development of an inhibitor should be considered if he doesn't respond to factor with this new joint bleed. The patient is a bit young for arthroscopic surgery (technical barriers) and radionuclide synovectomy, although technically easier, is not without potential side effects. Either synovectomy option should

not be considered until the patient has failed prophylaxis and has a continued abnormal exam and MRI.

9. A 5-year-old boy with hemophilia A is due for a molar dental extraction. He has responded to recombinant FVIIII in the past and you need to devise a treatment plan for the upcoming procedure. He weighs 20 kg. Which of the following choices characterizes the best treatment plan?
   A. Avoid any treatment (factor replacement and antifibrinolytic therapy) since molar extractions are unlikely to cause bleeding.
   B. Do not give recombinant FVIII but give aminocaproic acid, 2 grams, 30 minutes prior to the procedure and then withhold further dosing of antifibrinolytics.
   C. Do not give recombinant FVIII and administer aminocaproic acid, 1 gram every 12 hours for 2 days.
   *D. Give a dose of recombinant FVIII at 500 IU 30 minutes prior to the procedure along with 2 grams of aminocaproic acid every 6-8 hours for 3-7 days.
   E. Administer one dose of recombinant FVIII at 950 IU 30 minutes prior to the procedure and hold any additional factor replacement or antifibrinolytic therapy.

Answer: D
Explanation: Preventive treatment of bleeding in dental extractions is important. One should only need to administer one dose of recombinant FVIII at 20-25 IU/Kg along with antifibrinolytic therapy, 100 mg/kg/dose, given every 6-8 hours for 3-7 days. All of the other answers are incorrect due to lack of treatment (with both factor and antifibrinolytics) or inappropriate or inadequate dosing.

10. A 5-day-old infant presents to your clinic for evaluation of a large 4 x 4 cm bruise with a underlying palpable hematoma on the left thigh secondary to a hepatitis B immunization in the nursery prior to discharge. He was circumcised without excessive bleeding or prolonged oozing. He demonstrates a 3 x 3 cm right-sided cephalohematoma from a forceps delivery. His exam is otherwise normal. The father accompanies his new baby and although the father personally has no bleeding symptoms, he thinks that there might be a bleeding history on his wife's side of the family with excessive bruising and menorrhagia in his wife and her sister (maternal aunt) and a history of bruising and postoperative bleeding in the maternal grandfather. Which diagnosis is most likely the cause of the newborn's bleeding symptoms?
    *A. Moderate (2%) hemophilia A
    B. Type 1 VWD
    C. FXIII deficiency
    D. Maternal ITP
    E. Type 3 VWD

Answer: A
Explanation: Hemophilia can be varied in its presentation. Several of this newborn's bleeding episodes (large palpable hematoma and cephalohematoma) point towards a factor deficiency as a cause for the bleeding. Patients with hemophilia will not always manifest circumcision-related bleeding. The family history is consistent with hemophilia

since both the mother and her sister (maternal aunt) appear to be symptomatic carriers and their father (maternal grandfather) has bleeding similar to other older moderate hemophiliacs. This family history could be consistent with type 3 VWD, but the father is asymptomatic (both parents should have type 1 VWD). The child and family history is not consistent with type 1 VWD. Additionally, newborns rarely bleed in the first week of life from type 1 VWD since the VWF is often elevated around delivery. Maternal ITP might cause a low platelet count in the baby, but the bleeding symptoms, if present, are almost always mucosal in nature. FXIII deficiency often presents with more severe bleeding manifestations then demonstrated in this case, especially delayed bleeding from surgery (circumcision) as well as bleeding from the umbilical cord and a more pronounced cephalohematoma and probable intracranial hemorrhage.

11. A six year Spanish-American male with severe hemophilia B comes to the ER after falling two stories from an open window. He lost consciousness and has an obvious hematoma on the back of his head. While the nurse is arranging a stat CT scan, you are calculating his dose of recombinant FIX. He weighs 20 kg. Given that recombinant FIX dosing is higher than plasma derived FIX, the best approximate dose would be ?

* A. 2800 U
B. 3600 U
C. 1800 U
D. 1400 U

Answer: A
Explanation: This child needs prompt attention to infusion of FIX prior to any intervention. One should correct any patient with hemophilia to a level of 100% for a life threatening hemorrhage. 1 U/kg of FIX will raise the FIX level by 1 %. However, the recovery of recombinant FIX is about 30-40 % less than for plasma derived FIX in children and accordingly, one should utilize the following formula to achieve a FIX level of 100% = 100 U x 20 kg x 1.4 = 2800 U, so the correct answer is A.

12. A newly married couple requests information regarding prenatal diagnosis for severe hemophilia. The woman has two brothers with severe hemophilia A, one complicated by inhibitor formation. If the family would like to know both whether the baby might have hemophilia and if there is a risk for the baby developing an inhibitor, what sampling method/testing procedure and at what gestational age should testing be performed?

A. Fetal cord blood sampling for FVIII activity at 18-20 weeks gestation
B. Chorionic villus sampling for inversion 22 detection at 11-15 weeks gestation
C. Amniocentesis for RFLP testing at 20-24 weeks
D. Umbilical cord blood sampling at the time of delivery
E. Maternal blood testing for factor VIII activity prior to a planned pregnancy

Answer: B

Explanation: The best combination of testing/gestational age for both detection of severe hemophilia and whether there might be a risk for an inhibitor development would involve testing for inversion 22. Fetal cord blood sampling for FVIII assessment occurs at 18-20 weeks and can tell whether the baby has hemophilia but usually is not utilized to detect a mutation which might signal the future development of an inhibitor. RFLP testing might be more informative since other family members are known who have hemophilia but this should not be performed as late as 20-24 weeks. Umbilical cord sampling at birth will detect hemophilia but will not inform regarding inhibitor risk. Additionally, maternal testing for carrier status by utilizing FVIII and VWF testing can be performed to detect a carrier but needs to be confirmed at least once and does not inform about the child.

13. Patients with Type 2 von Willebrand disease (VWD) will have a dysfunctional protein, often manifested by a reduced functional assessment of the VWF protein (ristocetin cofactor) compared to the VWF antigen. Which combination of test results listed below would best help differentiate type 2B from other types of VWD or other bleeding disorders?

	Platelet count (150-300,000)	Platelet Function (PFA))	VWF Multimers	Ristocetin cofactor activity (60-150%)	Ristocetin-induced platelet aggregation: (Low dose)
A	Normal	Normal	Normal	121	Normal
B	35,000	Nl-Slightly prolonged	Normal	74	Normal
C	221,000	Prolonged	Loss of High and medium MW multi	20	Absent
*D	79,000	Prolonged	Loss of High MW multi	22	Increased
E	427,000	Markedly Prolonged	Normal	144	Normal

Answer: D
Explanation: The best test to differentiate type 2B VWD from other bleeding disorders is to perform a low dose ristocetin induced platelet aggregation test. This is the only type of VWD that manifests increased aggregation to the antibiotic ristocetin and this test distinguishes type 2B VWD from other bleeding disorders. This is the result of increased affinity of the *VWF* to platelet GP Ib/IX. The genetic defect is in exon 28 of the VWF. Answer A is normal, B is chronic ITP, C is type 2A VWD (where there is no aggregation to ristocetin, low or high dose) and E is Glanzmann's thrombasthenia. Platelet type VWD is not an answer with this question but is similar to type 2B VWD in laboratory

presentation. However, this condition is a *platelet* defect in GPIb/IX and not the VWF, therefore the two conditions can be distinguished by exon 28 testing.

14. The vast majority of hemophilia gene mutations are known (90-95%) for severe hemophilia A. Which gene mutation is the most common genetic abnormality for those with mild hemophilia A?

A. Frameshift mutation
*B. Missense mutation
C. Nonsense mutation
D. Large deletion
E. Inversion 22

Answer: B
Explanation: 85% of mild hemophilia is the result of a missense mutation. The other gene mutations listed characterize the vast majority of genetic abnormalities found in severe hemophilia A (combined > 90% of severe FVIII gene mutations).

15. A 10 year old boy with mild hemophilia A (FVIII = 15%) comes to the Emergency Department at 9 pm Sunday evening for evaluation of left hip/thigh pain. He has rarely had bleeding episodes in the past and does not infuse on his own. He was playing "capture the flag" with some other boys last night and somehow remembers stepping into a hole. He did not have much pain last night but but his pain has increased throughout the day and now he is unable to bear weight on his left leg. On exam, his vital signs are stable and he is unable to stand on his left leg and lays on the table with his hip flexed and his thigh externally rotated. He has some paresthesias down the lateral aspect of his thigh. You are able to both internally and externally rotate his hip but cannot extend his hip. His weight is 35 Kg. A stat CBC shows: WBC 7.2K, Plt 267K and Hgb 9.0 g/dl. Which test is most appropriate to diagnose this condition and how should this condition be treated?

A. Don't perform any imaging test as it is Sunday evening and difficult to call in the radiologist. Also, this is probably a "pulled muscle" and since he has mild hemophilia, the muscle strain will probably heal on its own.
B. Perform an ultrasound of the hip and give 875 U of recombinant FVIII.
*C. Perform a CT scan of pelvis/hip and give 1750 U of recombinant FVIII bolus followed by 875 U Q12 hours for 10-14 days.
D. Perform a CT scan of the abodomen/pelvis/hip and give 1750 U of recombinant FVIII and then follow the patient clinically to see how he does and whether he will need additional factor infusions.
E. Give a 1750 U of recombinant FVIII and a RBC transfusion for the anemia, schedule an ultrasound of the abdomen/pelvis and hip tomorrow morning and contact orthopedics about scheduling a hip aspiration first thing tomorrow.

Answer: C

Explanation: The correct answer is to treat this iliopsoas bleed (classic history and physical exam findings) as an emergent bleed, correcting to 100% FVIII (50 U/kg or 1750 U). The best imaging test to perform emergently is a CT scan of the abdomen/pelvis/hip to differentiate from a hip bleed, although the exam (able to internally and externally rotate the hip, essentially rules a hip bleed out). Some Centers utilize ultrasound to diagnose the acute bleed but this level of expertise might not be available off hours. Certainly, follow up with an ultrasound until bleed resolution is an appropriate imaging modality. Treatment should be for 10-14 days of FVIII, keeping the trough FVIII level above 50% (similar to surgery) and then gradual reduction to daily FVIII and then every other day prophylaxis until complete imaging and exam evidence of bleed resolution. It may take 1-3 months for the patient to get back to his normal state. The other choices are either not understanding the bleeding aspect of a muscle strain (A), lack of appropriate dose and duration of factor use (B), lack of correct duration of treatment (D) or inappropriate use of a RBC transfusion (the patient is hemodynamically stable) and inappropriate timing of the imaging study (not done that evening).

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?

A. Prolonged bleeding after circumcision.
B. Prolonged bleeding from the umbilical stump.
C. Calf muscle bleed.
D. Prolonged bleeding after dental extraction.(*)
E. 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?

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 post-partum hemorrhage on 2 occasions.(*)
D. She has 4 older sisters none of whom have any bleeding problems.
E. 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?

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. 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?

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.

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 5^{th} and 20^{th} 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?

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%.

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:

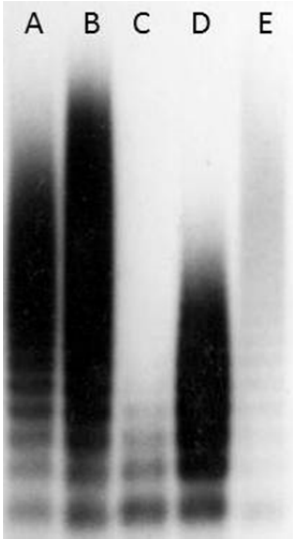
A 4 year old male presents with easy bruising and recurrent epistaxis. His labs are as follows: VWF Antigen—39%, ristocetin cofactor activity—37%, factor VIII activity—11%. What is the most likely phenotype of his parents?

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.

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?

A. 4 year old male with type O- blood.
B. 6 year old female with type AB+ blood.(*)
C. 8 year old female with type B- blood.
D. 10 year old male with type O+ blood.
E. 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?

A. Factor II.
B. Factor V.
C. Factor VII.
D. Factor X.
E. 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?

A. Treat bleeds as needed.
B. Weekly infusions of fresh frozen plasma.
C. Weekly infusions of cryoprecipitate.
D. Monthly infusions of fresh frozen plasma.
E. 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 4^{th} 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?

A. Superior mesenteric artery thrombosis
B. Intussusception.
C. Splenic rupture.(*)
D. Intestinal perforation.
E. 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:

A. Fibrinogen.(*)
B. Factor II.
C. Factor V.
D. Factor VII.
E. 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?

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.

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:

A. Obtain a computed tomographic scan of her head.
B. Admit her for observation.
C. Administer fresh frozen plasma.
D. Administer cryoprecipitate.(*)
E. 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?

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%.

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).