

Blood Coagulation Overview and Inherited Hemorrhagic Disorders

2002

Abshire

- 1) Thrombin is one of the key proteins in the coagulation cascade and has both procoagulant and anticoagulant properties. Which one of the following is an important anticoagulation function:
 - a. Activation of factors V and VIII
 - b. Factor XIII activation
 - c. Stimulation of the thrombin activated fibrinolytic inhibitor (TAFI)
 - d. Complex with thrombomodulin (TM).

- 2) The endothelial cell lining blood vessels possesses several important anticoagulation functions . Which one of the following is one of its' important hemostasis (procoagulant) functions?
 - a. Production of nitric oxide (NO)
 - b. Activation of thrombomodulin (TM)
 - c. Release of plasminogen activator inhibitor (PAI-I)
 - d. Release of TPA
 - e. Interaction of heparin sulfate with anti-thrombin III (AT III)

- 3) A term well infant is born without complications after a normal pregnancy and initial nursery stay. Upon drawing the metabolic screen, the baby is noted to have prolonged oozing from the heelstick sample. CBC, plt ct, PT, a PTT and fibrinogen were normal. Family history is negative. He returns for the 2 week check and the mother notices that the umbilical cord has been oozing for 4 days. A screening test for factor XIII deficiency is ordered and the baby's clot does not dissolve in 5 M urea. The euglobulin lysis time (ELT) was less than one hour. The most likely diagnosis is:
 - a. Factor XIII heterozygous deficiency
 - b. Homozygous antiplasmin deficiency
 - c. Mild hemophilia B (Factor IX deficiency)
 - d. von Willebrand Disease
 - e. Tissue plasminogen activator (TPA) excess.

- 4) The newborn's coagulation system is both similar and quite different from a child's. Which clotting parameter in the neonate is most similar to that of a two year old child?
 - a. Protein C activity
 - b. Thrombin time
 - c. Fibrinogen level
 - d. von Willebrand Factor (vWF)
 - e. Factor XII

- 5) A five year old female has recurrent strep pharyngitis and enlarged tonsils. Her pediatrician consults with an ENT surgeon who recommends tonsillectomy and

adenoidectomy. She comes to see you for a pre-op assessment. History reveals a recent strep infection one week ago; she is still on penicillin. Family history confirms maternal menses lasting 5 days (changing pads 4 x/day) and a brother with a few scattered (1 cm) bruises on the lower extremity. The patient has nosebleeds, 1-2 x per month during the winter season which stop with pressure. Laboratory reveals: normal CBC, plt count, PT 12 sec, a PTT 48 sec (10 sec prolonged), fibrinogen 200 mg/dl. 1:1 mixing studies of the aPTT show a correction (immediately) of only 3 secs. What is the best test to confirm the diagnosis?

- a. Obtain a more detailed family bleeding history
 - b. Repeat the aPTT
 - c. Perform a phospholipid neutralization of the aPTT
 - c. Perform Factors VIII, IX, XI assays
- 6) A three year old boy has a raised, erythematous confluent rash on the lower extremities. He complains of right knee pain and mild abdominal pain. His CBC, platelet count, PT and aPTT are normal. The most likely diagnosis is?
- a. von Willebrand disease (vWD)
 - b. Rocky Mountain spotted fever (RMSF)
 - c. Non-accidental trauma
 - d. Henoch-Schönlein purpura
- 7) All clotting factors are produced in the liver and some are produced in other locations. Which one of the following are synthesized in megakaryocytes?
- a. Factor VIII
 - b. Factor XI
 - c. Factor IX
 - d. Factor II
- 8) Joint bleeding is a hallmark of the hemophilias (Factor VIII and IX deficiency). Which one of the less common factor deficiencies also is known to have joint bleeding?
- a. Factor II
 - b. Factor V
 - c. Factor XI
 - d. Factor XII
 - e. Factor X
- 9) A term, appropriate weight female is born after uncomplicated pregnancy and delivery. The mother is a vegetarian and is breast feeding her child. The mother argues, against your advice, to not give the usual 0.5 mg Vit K prior to discharge. At two months of age, the infant has 3 days of watery diarrhea. She presents 2 days later

with an intracranial hemorrhage. Laboratory tests include a normal CBC and platelet count but PT and a PTT both >100 secs. The most likely cause for this condition?

- a. The mother was on anti-convulsants (Dilantin) during pregnancy and did not tell you.
 - b. The mother is a vegetarian
 - c. Undiagnosed cystic fibrosis
 - d. Breast feeding
 - e. Lack of vitamin K at birth and diarrhea
- 10) An 11 month male presents to the ER oozing from a torn frenulum. He is known to have moderate (3%) Factor VIII level and has never been treated. The most appropriate treatment would be?
- a. Place ice on his frenulum
 - b. Give IV DDAVP 0.3 ug/kg in 30 cc normal saline
 - c. Give a 250 unit vial of a virally inactivated plasma derived FVIII product.
 - d. Give a 250 unit vial of recombinant FVIII.
- 11) A six year old Hispanic 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. 2500 U
 - b. 5000 U
 - d. 1250 U
 - e. 500 U
- 12) Which is the most likely side effect of DDAVP in a two year male with type 1 vWD who will have PE tubes placed and adenoidectomy for recurrent otitis media?
- a. Lack of response to DDVAP (tachyphylaxis)
 - b. Thrombosis
 - c. Hyponatremia and seizure
 - c. Excessive urination.
- 13) The most appropriate treatment for an eight year male with severe FVIII deficiency and weekly bleeding into his right elbow is the following:
- a. Infusion of 20 u/kg x one dose recombinant FVIII for each bleed
 - b. Rest, ice and elevation of the elbow
 - c. Avoidance of all strenuous activity

- d. Begin secondary prophylaxis, 20 u/kg on Monday, Wednesday, and 40 u/kg on Friday and re-evaluate in 3 months.

14) Type 2 N von Willebrand Disease (vWD) is distinguished from type 2M vWD by the following lab testing:

- a. Abnormal multimeric pattern
- b. Markedly reduced FVIII activity in comparison to the vW Factor antigen/ristocetin cofactor.
- c. Inappropriately low ristocetin cofactor when compared to the vW Factor antigen
- d. Abnormal response to low dose ristocetin.

2004

Abshire

15) Thrombin is one of the key proteins in the coagulation cascade and has both procoagulant and anticoagulant properties. Which one of the following is an important anticoagulation function of thrombin:

- d. Activation of factors V and VIII
- e. Factor XIII activation
- f. Stimulation of the thrombin activatable fibrinolytic inhibitor (TAFI)
- * d. Form a complex with thrombomodulin (TM).

16) The endothelial cells of blood vessels possess several important anticoagulation and procoagulant functions. Which one of the following is an important procoagulant functions?

- a. Production of nitric oxide (NO)
- c. Activation of thrombomodulin (TM)
- * c. Release of plasminogen activator inhibitor (PAI-1)
- d. Release of TPA
- e. Interaction of heparin sulfate with anti-thrombin III (AT III)

17) A term well infant male is born without complications after a normal pregnancy and initial nursery stay. The baby is noted to have prolonged oozing from the heelstick metabolic screen. To assess a potential coagulopathy, a CBC, plt ct, PT, a PTT and fibrinogen were sent and the results were all normal. Family history is negative for any bleeding disorder. He returns for the 2 week check and the mother states that the umbilical cord has been oozing for 4 days. A screening test for factor XIII deficiency is ordered and this test shows that the baby's clot does not dissolve in 5 M urea. The euglobulin lysis time (ELT) is very short (less than one hour). The most likely diagnosis is:

- b. Factor XIII heterozygous deficiency
- * b. Homozygous antiplasmin deficiency
- c. Mild hemophilia B (Factor IX deficiency)
- d. von Willebrand Disease

- e. Tissue plasminogen activator (TPA) excess.
- 18) The newborn's coagulation system is both similar and quite different from that of a child's. Which coagulation factor or clotting test in the neonate is most similar to that of a two year old child?
- c. Protein C activity
 - d. Thrombin time
 - * c. Fibrinogen level
 - d. Factor II
 - e. Factor XII
- 19) A five year old female has recurrent strep pharyngitis and enlarged tonsils. Her pediatrician consults with an ENT surgeon who recommends a tonsillectomy and adenoidectomy. She comes to see you for a pre-operative assessment. History reveals a recent strep infection one week ago and she is still on penicillin. Family history confirms maternal menses lasting 5 days (changing pads which are partially soaked 4 x/day) and a brother with a few scattered (1 cm) bruises on the lower extremity. The patient has nosebleeds, 1-2 x per month during the winter season, associated with upper respiratory infections, which stop with pressure. Laboratory findings on this patient reveal: normal CBC and plt count, PT 12 sec, a PTT 48 sec (10 sec prolonged), fibrinogen 200 mg/dl. 1:1 mixing studies of the prolonged aPTT show a correction (immediately) of only 3 secs and a similarly prolonged aPTT at one hour. Which would be the best test to order to confirm the suspected diagnosis?
- d. Obtain a more detailed family bleeding history
 - e. Repeat the aPTT
 - * c. Perform a phospholipid neutralization of the aPTT
 - f. Perform Factors VIII, IX, XI assays
- 20) A three year old boy has a raised, erythematous confluent rash on the lower extremity. He complains of right knee pain and mild abdominal pain. His CBC, platelet count, PT and aPTT are normal. The most likely diagnosis is?
- d. von Willebrand disease (vWD)
 - e. Rocky Mountain spotted fever (RMSF)
 - f. Non-accidental trauma
 - * d. Henoch-Schönlein purpura
- 21) All clotting factors are produced in the liver and some are also produced in other locations. Which one of the following coagulation factors are found in megakaryocytes?
- b. Factor VIII
 - * b. Factor XI
 - c. Factor IX
 - d. Factor II

22) Joint bleeding is a hallmark of the hemophilias (Factor VIII and IX deficiency). Which one of these less common factor deficiencies is also known to present with joint bleeding?

- e. Factor II
- f. Factor V
- g. Factor XI
- h. Factor XII
- * e. Factor X

23) A 9 year old Greek male with homozygous β -thalassemia is receiving his regular q 3 week transfusion. Mid-way through the transfusion he develops fever, chills, hypotension and gross hematuria and extensive bleeding from his mouth. Initial Lab: WBC 21,000 (60% P, 15% B, 29%L), Hgb 4.5 gm/dl, platelet 75,000/mm³, PT 30 secs, aPTT 55 sec, fibrinogen 70 mg/dl, D-Dimer 4500. You presume a hemolytic transfusion reaction and secondary DIC. Which of the following is the most appropriate choice for initial therapy?

- * a. Give normal saline, antibiotics, red blood cells and fresh frozen plasma.
- c. Give normal saline, AT III infusion, red cells and platelet transfusion
- d. Give aminocaproic acid, red blood cells and platelet transfusion
- e. Administer low dose heparin, normal saline bolus, red cell transfusion and cryoprecipitate.

24) A term, appropriate weight female is born after uncomplicated pregnancy and delivery. The mother is a vegetarian and is breast feeding her child. The mother argues, against your advice, to not administer the usual 0.5 mg Vit K prior to her baby's discharge. At two months of age, the infant has 3 days of watery diarrhea. She presents 2 days later with an intracranial hemorrhage. Laboratory shows a normal CBC and platelet count but an extremely elevated PT and a PTT; both which are >100 secs. The most likely cause for this condition?

- e. The mother was on anti-convulsants (Dilantin) during pregnancy and did not tell you.
- f. The mother is a vegetarian
- g. Undiagnosed cystic fibrosis
- h. Breast feeding
- * e. Lack of vitamin K at birth and diarrhea causing impaired Vitamin K absorption at 2 months

Match the diagnoses from the following list with the correct screening coagulation laboratory tests

[need scrambled list of possible diagnoses, letters a – k]

Diagnoses Based upon Screening Laboratory

Case #	Diagnosis	Plt ct (10 ³ /mm ³)	PFA (sec)	PT (sec)	aPTT (sec)	TCT (sec)	Fib (mg/dl)
1.	_____	300	nl	10	75	12	300
2.	_____	250	nl	27	30	11	250
3.	_____	200	inc	11	42	12	260
4.	_____	350	nl	10	29	10	200
5.	_____	160	-	20	43	17	40
6.	_____	10	-	28	>120	>60	10
7.	_____	90	inc	25	40	19	85
8.	_____	275	inc	12	31	11	270
9.	_____	360	-	>60	>120	13	265
10.	_____	5	nl-inc	11		29	12 255
11.	_____	265	-	15	>120	>60	200

Answers:

1. Hemophilia
2. FVII def
3. VWD
4. FXIII def (or α_2 AP)
5. DIC- hypoxia
6. DIC- severe
7. Liver disease
8. Platelet dysfunction
9. Vitamin K def
10. ITP
11. Heparin

2006

Abshire

1) A term well infant male is born without complications after a normal pregnancy and initial nursery stay. At the two week well baby check, the mother notes that the child has slept more than usual over the last 24 hours. Exam confirms lethargy and left sided weakness. A head CT scan demonstrates a right-sided cerebral hemorrhage. History is negative for head or other trauma nor has the patient ever displayed heelstick or other bleeding symptoms. Family history is likewise negative. A CBC with platelet count, PT, a PTT and fibrinogen are all normal and plasma is saved prior to empiric treatment with Fresh Frozen Plasma. The screening test for factor XIII deficiency is ordered and this test shows that the baby's clot dissolves readily in 5 M urea. The most likely diagnosis is:

- a. Severe factor XIII deficiency
- b. Severe hemophilia B (factor IX deficiency)
- c. von Willebrand Disease
- d. Tissue plasminogen activator (TPA) excess.

Correct answer: a

Educational Objective: Recognize those conditions which can cause bleeding despite normal screening laboratory.

This child has an unexplained intracranial hemorrhage which should cause the clinician to worry about factor deficiency bleeding. The correct answer, Factor XIII deficiency is characterized by head bleeding or delayed bleeding (e.g. persistent oozing from the umbilical stump). The fact that the family history is negative does not rule out a bleeding disorder, particularly in those conditions that are autosomal recessive. Further specific testing as noted in the question are essential in determining a diagnosis. The screening test for factor XIII deficiency suggests that this clot stabilizing factor is not present since there is lysis of the clot in 5 M urea. Severe hemophilia, either A or B is ruled out by a normal aPTT. Von Willebrand Disease (vWD) is a possibility but as the prototypical platelet-vessel type of bleeding disorder, usually does not present with delayed or deep bleeding such as an intracranial hemorrhage. Finally, TPA excess is not a bleeding disorder. The inhibitor of TPA, plasminogen activator inhibitor-1 (PAI-1) and the inhibitor for plasmin (alpha 2 antiplasmin), however, both present with deep bleeding similar to hemophilia and with normal screening laboratory.

2) A two year old male has recurrent sinusitis, otitis media and loud snoring at night. His pediatrician consults with an ENT surgeon who recommends placement of PE tubes and an adenoidectomy and orders a CBC, PT and an aPTT. The boy has been maintained on almost continuous antibiotics. Laboratory findings reveal: normal CBC and platelet count, PT 12 sec (normal range), aPTT 48 sec (10 sec prolonged). You are consulted at 4 pm the day prior to the surgery. Patient and family history is completely negative for any bleeding symptoms. The laboratory performs a fibrinogen level on the frozen specimen and it is normal (200 mg/dl). You redraw a new specimen and perform a 1:1 mixing study. The prolonged aPTT shows no correction either immediately or at one hour. You recommend to the surgeon to proceed with the surgery but would like to order a confirmatory test. Which test would best confirm the suspected diagnosis?

- g. Obtain a more detailed family bleeding history
- h. Repeat the aPTT
- c. Perform a phospholipid neutralization of the aPTT
- d. Perform factor VIII, IX, XI assays

Correct answer: c

Educational Objective: Benign nature of post-infectious lupus anticoagulant (LA) in children.

This case is a classic example of the lupus anticoagulant (LA) in children and its benign nature. It is important to realize that these patients do not bleed and encourage your surgical colleagues to proceed with surgery. Post-infectious LA are usually directed against anionic phospholipids. The family and personal bleeding history are clearly normal, making an inherited bleeding disorder unlikely. The LA in children is usually defined by a recent history of infections(usually viral) or after administration of

antibiotics. This is often seen in children who present to the ENT surgeon for possible adenoidectomy or PE tube placement due to repeated sinus, ear or other upper respiratory infections. The surgeon will usually perform a PT/aPTT and prolongation of the aPTT will prompt further evaluation from the hematologist. Repeating the aPTT to rule against a laboratory error might be helpful but if still prolonged, will not shed further light on the diagnosis. In this case, lack of correction of the aPTT immediately and at one hour strongly suggests an inhibitor. A specific factor inhibitor (e.g. fVIII) is suggested by partial but not complete correction of the aPTT immediately upon incubation and then prolongation to the original aPTT result or to a greater degree at one hour. If that was the evident in this case, specific factor testing (answer d.) should be ordered. The best confirmatory test of a LA would be to demonstrate the phospholipid nature of the LA by performing a phospholipid neutralization of the aPTT. If this test is positive, you have established the diagnosis of a LA.

3) A term, appropriate weight female is born after uncomplicated pregnancy and delivery. The mother is breast feeding her child and refuses all immunizations and medications, including Vitamin K. The baby appears to be thriving until 6 weeks of age, when she has several days of watery diarrhea. The mother continues breast feeding. Two days later, the child presents to the emergency room with profuse GI bleeding and scattered, large ecchymoses. She appears 5% dehydrated and has decreased capillary refill. Laboratory shows a low Hgb (5 g/dl) but a normal WBC and platelet count. PT and aPTT are both extremely elevated; (>100 secs) but the fibrinogen is normal (300 mg/dl). The most likely cause for this condition?

- i. The mother was on anti-tuberculosis drugs during pregnancy and did not inform you.
- j. Undiagnosed malabsorption such as cystic fibrosis
- k. Breast feeding
- l. The mother is a vegetarian and did not tell you
- e. Lack of vitamin K at birth and diarrhea causing impaired Vitamin K absorption at 6 weeks

Correct answer: e

Educational Objective: Recognize the factors underlying Vitamin K deficiency in children.

This child has late onset hemorrhagic disease of the newborn (HDN). If the mother were on an anti-tuberculosis drugs during pregnancy, then possibly these medications could have contributed to **early** HDN but would be an unlikely culprit this far removed from birth. Undiagnosed cystic fibrosis could certainly contribute to malabsorption and resultant loss of fat soluble vitamins including vitamin K but would be lower on the differential in this patient given she is thriving at 6 weeks. Breast feeding can contribute to vitamin K deficiency but is extremely rare as a sole cause, without other contributing factors. The mother being a vegetarian could contribute to vitamin B12 deficiency but this deficiency would not present this early in infancy. Also, vitamin K is readily available in green leafy vegetables. The correct answer to this case of late onset HDN is:

e: not receiving vitamin K at birth, breast feeding and recent diarrhea decreasing vitamin K absorption.

4) A 10 year African-American female with homozygous sickle cell disease and history of a stroke is in your clinic to receive her regular RBC transfusion (q 3-4 weeks) to suppress Hgb S production. Her trough Hgb prior to the transfusion is usually 9-10 gm/dl. Mid-way through this transfusion she develops fever, chills, hypotension, gross hematuria and extensive bleeding from her mouth. Initial laboratory: WBC 28,000 (65% P, 20% B, 15%L), Hgb 3.5 gm/dl, platelet 75,000/mm³, PT 30 secs, aPTT 55 sec, fibrinogen 40 mg/dl, D-Dimer 10,000. You presume a hemolytic transfusion reaction and secondary DIC. Which of the following is the most appropriate choice for initial therapy?

- a. Give normal saline, antibiotics, fresh frozen plasma and as matched red blood cells as possible.
- b. Give normal saline, AT III concentrates, platelet transfusion and as matched red blood cells as possible.
- c. Give aminocaproic acid, platelet transfusion and as matched red blood cells as possible.
- d. Administer normal saline bolus, low dose heparin, cryoprecipitate and as matched red blood cells as possible.

Correct answer: a

Educational Objective: Understand how to recognize and manage DIC in children.

The main causes of disseminated intravascular coagulation (DIC) in children are: infections (e.g. meningococemia), malignancy (e.g. M3 AML), massive tissue damage (e.g. shock, burns), vascular disorders (e.g. hemangioma) and immunologic (e.g. transfusion reaction). Treatment should be focused on eliminating the inciting cause (probable minor blood group reaction) and providing general supportive care (such as normal saline for the hypotension and antibiotics for a possible infectious cause of the presenting symptoms in this case) and blood product/component therapy support (if the laboratory or clinical findings warrant such support). The correct answer in this case is:

- a. All of the other treatment options surround some element of controversy. AT III concentrates are a possible adjunct to supportive care but until clinical trials better define the role of ATIII in DIC, this treatment modality should be reserved for conditions where the AT III level is documented to be low. Antifibrinolytic therapy such as aminocaproic acid can be very helpful in DIC where there is excessive fibrinolysis (e.g. snake bites and some cases of leukemia) but should not be used routinely in the management of DIC due to bleeding risk. Finally, certain infections (such as meningococcal disease) and malignancy are sometimes associated with excessive thrombin generation presenting with laboratory and/or clinical evidence of thrombosis (sometimes accompanied by bleeding). In this setting, low dose heparin has been utilized to interrupt excessive thrombin formation but should not be considered standard of care in most cases of DIC.

5) A nine year Asian (Taiwanese) boy is referred to your clinic for mild bruising. History suggests that this bruising is on both the arms and the legs, usually small in size (1 x 1 cm) and sometimes spontaneous. There is also a history of gum bleeding with tooth brushing. Family history is negative for any bleeding disorder. You perform a bleeding screen with the following results: Plt ct 90,000/mm³, PFA increased for both col/epi and col/adp, PT 25 sec, aPTT 40 sec, thrombin time 24 sec (7 sec prolonged) and fibrinogen 85 mg/dl. Which diagnosis most likely explains these laboratory values?

- a. Disseminated intravascular coagulation
- b. Vitamin K deficiency
- c. Heparin overdose
- d. von Willebrand Disease type 2B
- e. Liver disease

Correct answer: e.

Educational Objective: Know the coagulation laboratory screening values for liver disease

This Taiwanese boy has previously undiscovered hepatitis B infection with liver disease. The laboratory testing best fits liver disease manifested by abnormal coagulation testing in all screening parameters: slightly low platelet count, elevated PFA due to the platelet dysfunction of liver disease, a more prolonged PT compared to the PTT due to concomitant decreased absorption of vitamin K dependant factors and a slightly low fibrinogen level and prolonged thrombin time reflective of this as well as the dysfibrinogen of liver disease. DIC usually has more severe abnormalities, vitamin K deficiency or heparin overdosing do not have a low platelet count or low fibrinogen, and heparin overdose would have a much more prolonged PTT and thrombin time. VWD type 2B can present with thrombocytopenia but does not have any of the other laboratory abnormalities present in this case.

6) You are called to the NICU to consult on a term baby boy with an intracranial hemorrhage (ICH). The pregnancy was normal and the baby was born vaginally without instrumentation. Birth weight was 9 #, 12 oz. The mother has no known health problems and her only medications were prenatal vitamins. The baby had some respiratory distress immediately after birth and had an umbilical venous catheter (UVC) placed for administration of antibiotics and fluids and was placed on 40% oxygen. CXR showed "wet lungs". Four hours after the UVC is placed, the baby could not be aroused. Head ultrasound showed a large intraventricular hemorrhage. You recommend the following laboratory tests: WBC 13,000, Hgb 15 g/dl, Plt count 200,000/mm³, PT 16 sec (ULN 15 sec), PTT > 120 sec, Fibrinogen 250 mg/dl, Thrombin Time > 60 sec. What recommendations would you give at this point?

- a. Give Fresh Frozen Plasma (FFP) 15 cc/kg
- b. Infuse packed red blood cells (PRBC) at 10 cc/kg
- c. Administer 250 units of recombinant FVIII

- d. Give 2 mg of IV Vitamin K
- e. Administer 5 mg IV protamine slowly over one minute

Correct answer: e

Educational Objective: Know the clinical presentation and treatment of heparin overdosing

The purpose of this question is to recognize the clinical situations where one should consider heparin overdosing as a cause of bleeding. In this case, the historical data does not help you much to discern the cause of this ICH. Several conditions must be considered including hemophilia, DIC, vitamin K deficiency and heparin overdose. The laboratory in this case helps pinpoint the cause of the bleeding. The baby has slight anemia as a result of the head bleed. Giving packed red blood cells for this mild anemia would not be the first treatment option. The platelet count is normal as is the fibrinogen level. The PT is only slightly prolonged but the PTT and thrombin time are elevated to the point that they will not clot. These results rule against hemophilia and the use of rFVIII (massively elevated PTT as well as thrombin time), vitamin K deficiency and administration of parenteral vitamin K (only slight elevated PT; in vitamin K deficiency both the PT and PTT are very elevated) and DIC and the use of FFP (normal platelet count and fibrinogen level). The best answer is heparin overdosing, the result of inadvertent administration of 5000 units of heparin via the UVC and the best treatment would be to reverse the heparin with protamine.

7) The newborn's coagulation system is both similar and quite different from that of a child's. Which coagulation factor or test in the neonate is different from that of a two year old child?

- a. Factor V
- b. Thrombin time
- c. Fibrinogen level
- d. Platelet count

Correct answer: b.

Educational Objective: Know how the newborn coagulation system is different from that of a child

The newborn's coagulation system is very different from that of a child. In particular, the vitamin K dependant clotting factors (factors II, VII, IX and X) as well as the contact factors (prekallikrein, HMWK, factor XI and XII) and Protein C are all low in the newborn compared to the child. Additionally, the newborn has a mild dysfunctional fibrinogen due to increased sialic acid which is reflected in a prolonged thrombin time (correct answer in this case). All of the other responses for this question, factors V, fibrinogen and the platelet count are all similar to the child. Factor VIII and VWF are elevated in the newborn compared to the child and are not included as answers to this question.

8) Thrombin is one of the key proteins in the coagulation cascade and has both procoagulant and anticoagulant properties. Which one of the following is an important anticoagulation function of thrombin:

- a. Activation of factors V and VIII
- b. Factor XIII activation
- c. Stimulation of the thrombin activatable fibrinolytic inhibitor (TAFI)
- d. Forms a complex with thrombomodulin (TM)
- e. Platelet activation

Correct answer: d

Educational Objective: Understand the dual roles of thrombin in the coagulation cascade (coagulation and anticoagulation)

Thrombin is one of the key players in the coagulation cascade. Small amounts of thrombin generated from the activation of the FVII-TF pathway will in turn activate FV, FVIII, FXI and FXIII as well as cleave Fibrinogen to Fibrin. Thrombin also activates platelets and one of the inhibitors to fibrinolysis (TAFI). Its anticoagulant properties include release of Tissue Plasminogen Activator (TPA) for the endothelial cells and complexes with thrombomodulin to activate Protein C. Therefore, thrombin acts to both propagate and inhibit its production.

9. Screening tests are important, along with the medical history, to help discern the cause of a bleeding disorder. Which one of the following diagnoses is correctly paired with its screening test?

- a. Glanzmann thrombasthenia and a normal Platelet Function Analyzer (PFA) test
- b. Factor VII level of 35% and a normal PT of 14 seconds (ULN 15 sec)
- c. Factor IX level of 50% and a prolonged aPTT of 45 seconds (ULN 38 sec)
- d. Antiplasmin deficiency and a normal Euglobulin Lysis Time (ELT) (normal < 60 seconds)
- e. Fibrinogen level of 75 mg/dl and a normal thrombin time of 16 seconds (ULN 17 sec)

Correct answer: d.

Educational Objective: Understand the role of the screening tests in the diagnosis of a bleeding disorder

Antiplasmin deficiency presents with a moderately severe bleeding disorder due to unchecked plasmin degradation of a fibrin clot. The screening test for fibrinolysis, the ELT, is very short in this disorder and reflects excessive plasmin lysis of the clot in a short period of time (< 60 minutes). The other choices have mismatched screening

values. Glanzmann thrombasthemia is a severe platelet function defect due to deficiency of GPIIb/IIIa on the platelets and lack of binding to fibrinogen. The disorder does not respond clinically to addition of collagen and ADP, two of the agonists utilized in the PFA test. A factor VII level of 35% will give a prolonged PT of several seconds (PT = 17-18 seconds). A 50% Factor IX level is normal in every laboratory and should give a normal aPTT. Finally, hypofibrinogenemia of 75 mg/dl will produce a prolonged thrombin time of 21 – 22 seconds.

10. A 16 year adolescent comes to your clinic for pre-operative evaluation for wisdom tooth extraction. She is from Poland and of Jewish ancestry. She has a known factor XI level of 30%. Her bleeding history is significant for bruising on her extremities, gum bleeding when brushing her teeth and a history of oozing when her baby teeth came out, and menses which last 8 days, requiring 8-10 pads per day, usually completely soaked with blood. She has never had surgery and has never received treatment for her factor XI deficiency. What is most important to consider in planning her upcoming procedure?

- a. Plan on empirically giving FFP 15cc/kg before the extraction
- b. Plan on giving aminocaproic acid 100mg/kg pre-extraction and then q 6-8 h for 7 days with close monitoring of bleeding symptoms
- c. Insist on a complete family history from all her relatives to get a better picture of her bleeding risk
- d. Empirically give a platelet transfusion before the wisdom tooth extraction
- e. Insist on repeating the factor XI level as lower levels are usually associated with worse bleeding.

Correct Answer: b.

Educational Objective: Know how to diagnosis and manage factor XI deficiency

This is a challenging case due to the difficulty of pinpointing bleeding risk in a factor XI patient. Factor XI levels are notoriously unreliable in predicting bleeding and a more reliable indicator is the patient or family history of bleeding. In this case, insisting on a detailed family history of bleeding is not that important since the child has already declared herself to be a “bleeder”. For these reasons, answers c and e are not the best answer. Once you decide to go through with the extraction, the best course of action is to give aminocaproic acid, since this antifibrinolytic is often all that is needed for the prevention of oral bleeding. This teenager has never been treated, so empiric use of FFP or a platelet transfusion may be unnecessary. I would reserve the use of these two therapeutic modalities for intra or post-operative bleeding which does not respond to aminocaproic acid. FFP is used to replace plasma factor XI and a platelet transfusion is used for those few patients who are low in platelet levels of factor XI.

2009

Blood Coagulation Overview and Acquired Hemorrhagic Disorders
Clifford M. Takemoto, MD

1. A 2-year-old boy is admitted to the PICU with transaminitis and a direct hyperbilirubinemia. The platelet count is 90,000 per cu mm. The PT is 45 seconds and the aPTT is 68 seconds. What laboratory testing can help distinguish the coagulopathy of liver failure versus DIC?
 - A. FVII
 - B. FV
 - C. FVIII
 - D. FXI
 - E. Fibrinogen

Answer: C

Explanation: While all these factors are synthesized in the liver, FVIII is also expressed from endothelial cells. In the setting of liver failure, FVIII activity is usually normal or increased, while the other factors are decreased. In contrast, with severe DIC, all of the listed factors, including FVIII, are depressed secondary to consumption of the factors. The platelet count can be depressed in both liver failure and DIC. Thus, the determination of FVIII activity may help to distinguish the coagulopathy of liver failure versus DIC.

2. A full-term infant boy was born at home via a midwife, and the parents elected not to administer hepatitis B vaccine or vitamin K. The child is breastfed at home and was well until 3 months of age, when he developed diarrhea. The baby is noted to be lethargic with bleeding from the mouth and ecchymotic lesions. A head CT shows an intracranial bleed. The hemoglobin is 7 gm/dl and the platelets are 360,000 per cu mm. The PT/aPTT is 63 sec and > 100 sec. The most appropriate management is:
 - A. FFP
 - B. FFP and IV vitamin K
 - C. IV vitamin K
 - D. Cryoprecipitate
 - E. Cryoprecipitate and IV vitamin K

Answer: B

Explanation: This case highlights the risk factors and presentation of vitamin K deficiency bleeding (VKDB). Early VKDB presents in the first 1 to 2 weeks of life and is manifested by prolongation of both PT and aPTT. Symptoms include ecchymosis, gastrointestinal bleeding, and intracranial hemorrhage. Late VKDB occurs from 2 weeks to as late as 6 months. Intramuscular vitamin K prophylaxis is protective against VKDB; orally administered vitamin K is protective against early VKDB, but not for late VKDB. Risk factors include exclusively breastfed infants who have received inadequate vitamin K prophylaxis. Another risk factor for VKDB is fat malabsorption. Administration of vitamin K intravenously carries a small risk of anaphylaxis, but can restore activity of vitamin K-dependent coagulation factors (by gamma-carboxylation) in 4 to 6 hours. Thus, vitamin K deficiency with mild bleeding symptoms may be managed with vitamin

K administration alone. However, with life-threatening bleeding, both FFP and vitamin K are indicated. FFP alone without vitamin K will only be of transient benefit. Cryoprecipitate is enriched for fibrinogen, vWF, FVIII, and FXIII; all of these factors are not vitamin K dependent, and thus their activity is not expected to be deficient in this patient.

3. A 15-month-old boy on the general pediatric service is being treated with IV antibiotics for osteomyelitis. He is noted to have mild bruising over the lower extremities. Family history is notable for mild FIX deficiency in a paternal uncle. Laboratory evaluation from a peripheral venepuncture shows a platelet count of 353,000 per cu mm and a PT of 11.5 seconds and an aPTT of 52 seconds. What is the most appropriate recommendation for additional work up in this patient?
- A. DIC screen
 - B. Platelet aggregation testing
 - C. FIX activity
 - D. aPTT Mixing study
 - E. von Willebrand screen

Answer: D

Explanation: This child has minimal bleeding symptoms with an isolated prolongation of the aPTT. The differential diagnosis includes a coagulation factor deficiency of the intrinsic pathway (FVIII, FIX, FXI, FXII), a circulating inhibitor (lupus anticoagulant), or heparin contamination. An appropriate first screen is an aPTT mixing study. Correction of the aPTT with normal plasma suggests a coagulation factor deficiency and further investigation of specific factors would then be warranted. Failure to correct the aPTT would be consistent with a lupus anticoagulant or heparin. In the majority of children, lupus anticoagulants are benign and transient, but they can be associated with thromboembolic disease. Bleeding can also rarely be associated with lupus anticoagulants, but in those cases, the PT and aPTT are often prolonged due to depletion of prothrombin. Heparin effect can be investigated with a thrombin time that will be prolonged with heparin. A reptilase time will be normal with heparin. DIC usually results in prolongation of the PT initially, followed by prolongation of the aPTT. Some individuals with vWD will have isolated prolongation of the aPTT, but the prolongation tends to be mild. The family history of FIX deficiency in the paternal uncle does not increase the risk of FIX deficiency in this patient. Platelet aggregations may reveal a platelet dysfunction, but will not provide an explanation for the prolonged aPTT.

4. A 16-year-old girl was diagnosed with a DVT at an outside hospital and was initially treated with heparin, then transitioned to warfarin. She and her family come to your clinic now a month later for a second opinion about thrombophilic risk factors. Which of these thrombophilic tests will not be affected by warfarin?
- A. Protein C
 - B. Antithrombin
 - C. Protein S
 - D. DRVVT

Answer: B

Explanation: Both protein C and protein S are vitamin K dependent, as well as the serine proteases, FII, FVII, FIX, and FX. Thus protein C and S activity will be depressed on warfarin. The DRVVT is a PTT-based test that is sensitive to prolongation by antiphospholipid antibodies. However, due to depletion of vitamin K-dependent procoagulant factors, the DRVVT often is prolonged on warfarin. Antithrombin is not vitamin K-dependent, and the activity should not be affected by warfarin.

5. A 4-month-old boy with an expanding violaceous chest wall mass is seen in the emergency room. A PT and aPTT are > 100 seconds and > 200 seconds, respectively. The fibrinogen is 50 mg/dl, the platelets are 20,000 per cu mm, and the D-dimers are elevated at > 50 ng/dl. Which of the following is expected to be elevated in this condition?
- A. Antithrombin
 - B. Protein S
 - C. Protein C
 - D. FVIII
 - E. PAI-1

Answer: E

Explanation: This case illustrates a patient with DIC associated with a hemangioendothelioma, termed Kasabach-Merritt syndrome. The cardinal feature of DIC is activation of systemic coagulation resulting in microvascular fibrin deposition. Consumption of procoagulants factors and platelets result in bleeding risk. In addition, the activity of natural anticoagulant proteins, such as antithrombin, protein C, and protein S, are decreased. This, coupled with impaired fibrinolytic mechanisms, contribute to microvascular thrombosis. Increased PAI-1 (an inhibitor of plasmin generation) expression from vascular endothelial cells is thought to be the major mechanism of impaired fibrinolysis in DIC.

6. A 9-year-old girl with relapsed ALL is undergoing evaluation for bone marrow transplant. She developed a catheter-associated thrombosis during chemotherapy and had undergone a thrombophilic work-up. Which of the following thrombophilic conditions would be potentially corrected with bone marrow transplantation from an unaffected donor?
- A. FV leiden
 - B. Prothrombin 20210 mutation
 - C. Antithrombin deficiency
 - D. Protein C deficiency
 - E. Antiphospholipid antibody syndrome

Answer: E

Explanation: Factor V, Factor II, antithrombin, and protein C are primarily produced in the liver. The prothrombin G20210A describes is a single-nucleotide change (G to A) in the 3' untranslated region (nucleotide 20210) of the prothrombin (Factor II) gene. FV Leiden is a point mutation in the Factor V gene that results in resistance to cleavage by

activated protein C . While the majority of Factor V is produced in the liver, it is notable that a fraction of FV (~20%) is expressed from platelets. Antiphospholipid antibody syndrome arises from dysregulation of the immune system with production of abnormal antiphospholipid-dependent antibodies from lymphocytes. When these antibodies interfere with aPTT-based tests (resulting in prolongation), they are termed lupus anticoagulants. Antibody specificity may also be demonstrated against cardiolipin (anti-cardiolipin antibodies, ACA) or beta 2 glycoprotein I (B2GPI). How these antibodies predispose to thrombosis is not entirely clear, but may involve platelet activation with microparticle formation or endothelial dysfunction. Bone marrow transplantation would be expected to ablate the recipient's immune system and reconstitute with donor immune system.

7. A 2-week-old girl with congenital heart disease is admitted the PICU with a newly diagnosed atrial thrombus. She is treated with systemic thrombolysis with tPA, but there is no evidence of clot lysis. A possible etiology is:
- A. Plasminogen deficiency
 - B. Protein C deficiency
 - C. Antithrombin deficiency
 - D. FV Leiden homozygote
 - E. Antiphospholipid antibodies

Answer: A

Explanation: The inactive proenzyme, plasminogen, is converted to the active serine protease, plasmin, by t-PA or u-PA. Plasmin degrades fibrin clot into fibrin split products and D-Dimers. Plasminogen in neonates is lower than in adults, and rare patients have been identified with plasminogen deficiency. Low plasminogen activity may result in impaired fibrinolysis with t-PA. Chronic thrombi are also often resistant to thrombolysis. Protein C deficiency, antithrombin deficiency, FV Leiden, and antiphospholipid antibodies are all prothrombotic risk factors, but do not significantly impair fibrinolysis.

8. A 14-year-old girl with SLE is admitted with a swollen left leg and chest pain. She is diagnosed with a lower extremity DVT and pulmonary emboli. She is also noted to have generalized edema and 4+ protein in the urine. She is started on an UFH drip, but requires very high doses to maintain a therapeutic aPTT. You suggest a possible reason for this:
- A. Antithrombin deficiency
 - B. Antiphospholipid antibodies
 - C. Protein C deficiency
 - D. FV Leiden homozygote
 - E. Prothrombin 20210 mutation

Answer: A

Explanation: UFH is monitored by prolongation of the aPTT, but the pharmacokinetics can be affected by many factors. The anticoagulant effect of heparin is mediated by antithrombin. Thus, antithrombin deficiency is a potential etiology for heparin resistance. Deficiency of antithrombin can be either congenital or acquired. Acquired antithrombin

deficiency can be seen in conditions such as nephrotic syndrome due to urinary loss of antithrombin, which was the case in this patient. Asparaginase therapy and liver disease are also associated with acquired antithrombin deficiency. Congenital antithrombin deficiency is seen in about 2 to 4 individuals in 100,000 in the general population. Another etiology for heparin resistance is elevated FVIII secondary to inflammation. Antiphospholipid antibodies are a risk factor for thrombosis and can be seen in patients with SLE. However, these antibodies would be expected to prolong the aPTT. Protein C deficiency, FV leiden, and the prothrombin mutation would not be expected to alter heparin metabolism.

9. A 5-year-old boy undergoes a preoperative evaluation for elective tonsillectomy and adenoidectomy. There is no family history of bleeding. The aPTT is elevated at 48 seconds and the PT normal at 10.5 seconds. He is referred to you clinic for further work-up. You order the following studies:

	<u>Patient</u>	<u>normal</u>
aPTT	48 seconds	(23-34)
1:1 mix	42.5 seconds	(23-34)
DRVVT	68 seconds	(27-45)
1:1 mix	55 seconds	(27-45)
DRVVT	38 seconds	(27-45)
	after neutralization with phospholipid	

What is the most appropriate management plan?

- A. FFP prior to surgery
- B. Start aspirin therapy
- C. Postpone elective surgery and recheck aPTT in 2 to 3 months
- D. Refer to rheumatology for work-up of lupus

Answer: C

Explanation: The mixing studies indicate that the etiology of the aPTT prolongation is due to an inhibitor rather than factor deficiency. The correction of the DRVVT after neutralization with phospholipid demonstrates that the antibodies are phospholipid dependent. Antibodies that inhibit aPTT-based tests (such as the DRVVT) and are phospholipid dependent are called lupus anticoagulants (LA). In the majority of children, these antiphospholipid antibodies are benign and transient. In some cases, however, they may be a risk factor for thrombosis, particularly if they are identified in association with an autoimmune disease such as lupus. In the absence of clinical findings suggestive of an underlying autoimmune disease, an extensive workup or anticoagulation is not indicated. Significant bleeding does not appear to be a common association, except in the instances when both PT and aPTT are prolonged. In these cases, the antibody appears to target and deplete prothrombin. In this healthy child, the LA is likely to be benign and transient, but the risks of bleeding with surgical challenges have not been extensively assessed. If the surgery is elective, a reasonable approach would be to postpone the surgery and

determine if the LA resolves over several months. If the patient is to proceed with surgery, then administration of FFP or platelets only as needed for bleeding would be appropriate (rather than prophylactic given), as FFP would not be expected to correct the aPTT, and the added bleeding risk posed by the LA is likely minimal to none.

10. You are consulted for a 15-year-old girl with a preoperative PT and aPTT of 17 sec and 52 sec prior to scoliosis surgery. The CBC is normal with a platelet count of 275,000 per cu mm. The fibrinogen activity is low at 82 mg/dl. The D-dimer is not elevated. Liver function tests are normal. A thrombin time is elevated at 65 seconds. She reports easy bruising and heavy menses, but no other symptoms of excessive bleeding. There is no family history of bleeding, but her father reports a history of DVT at age 25 years. The appropriate next step for this patient is:
- A. CT of abdomen and pelvis for occult vascular lesion causing Kasabach-Merritt syndrome
 - B. Obtain a fibrinogen antigen
 - C. ADAMTS-13 activity
 - D. Heparinase of plasma for evaluation of heparin contamination
 - E. 5 mg of vitamin K by mouth for 3 days, then repeat the PT and aPTT

Answer: B

Explanation: The low fibrinogen activity will result in prolongations of the PT and aPTT. Fibrinogen is not a vitamin K-dependent factor, so vitamin K deficiency is not the etiology of this picture. DIC will result in consumption of the fibrinogen, but the D-dimer is not elevated and the platelet count is normal, making the diagnosis of DIC (associated with Kasabach-Merritt syndrome) unlikely. Fibrinogen is produced by the liver, and can be decreased in liver disease; however, this patient has normal liver functions tests. The thrombin time is elevated with decreased fibrinogen activity. Other reasons for elevations in thrombin time include heparin and fibrin split products (with DIC). Heparin however does not cause a decrease in fibrinogen activity. Deficiency of ADAMTS-13 is a cause of congenital TTP, which is characterized by a microangiopathic hemolytic anemia but does not cause depression of fibrinogen.

The fibrinogen antigen in this patient was 246 mg/dl, which was discordant with the activity of 82 mg/dl. This finding indicates the diagnosis of dysfibrinogenemia. Fibrinogen is composed of 3 protein chains that are encoded by separate genes; primary disorders of fibrinogen arise from mutations in these genes. Dysfibrinogenemia can result in either bleeding symptoms or thrombotic symptoms. The father in this case also had the diagnosis of dysfibrinogenemia. Other clinical phenotypes associated with fibrinogen chain mutations include afibrinogenemia (absence of fibrinogen antigen) and hypofibrinogenemia (low fibrinogen activity and antigen). Bleeding symptoms can be managed with cryoprecipitate.

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Questions

1) An 18 year old girl with cystic fibrosis develops pneumonia and is admitted for IV antibiotics through a PICC line. She is clinically stable, but develops a prolonged episode of epistaxis. The ward team obtains laboratory testing which showed a platelet count of 342,000 per cu mm, an aPTT of 30 seconds and an elevated PT of 18.4 seconds. She receives 3 oral doses of vitamin K of 5 mg and a repeat aPTT is 28.5 seconds and the PT remains elevated at 14.9 seconds. The team consults you for the elevated PT. You tell them the likely reason for the persistent elevation of PT is:

- a. Heparin contamination from sample drawn through the PICC line
- b. congenital FVII deficiency
- c. A circulating inhibitor
- *d. malabsorption of vitamin K
- e. Disseminated Intravascular Coagulation (DIC)

Explanation: An isolated PT elevation is most commonly caused by FVII deficiency. The etiology of FVII deficiency may be congenital or acquired due to vitamin K deficiency, liver synthetic dysfunction, or consumption (as in DIC). While vitamin K deficiency, liver disease and DIC can all prolong both PT and aPTT, early in the course, the PT is usually prolonged before the aPTT due to the short half life of FVII. Thus DIC is possible, but less likely with a normal platelet count and stable clinical appearance. Congenital FVII deficiency is also possible and would not improve with vitamin K administration, but rare (1 in 1,000,000). Heparin contamination in samples drawn from central lines are a common cause of elevated aPTT, however, the PT is usually not significantly prolonged. Circulating inhibitors (lupus anticoagulants) most commonly prolong the aPTT and not the PT. Due to the pancreatic insufficiency with cystic fibrosis, malabsorption of fat-soluble vitamins such as vitamin K is common and would explain the lack of response to oral vitamin K.

2) A 14 year old boy with newly diagnosed ALL is admitted with a severe headache and diagnosed with a cerebral sinus venous thrombosis. He was treated during induction therapy with glucocorticoids, L-asparaginase, doxorubicin and VCR. Which of the following thrombotic risks are findings associated with asparaginase?

- a. Elevated aPTT
- b. Elevated FVIII activity
- * c. decreased antithrombin activity
- d. elevated fibrinogen activity
- e. decreased PAI-1 activity

Explanation: Asparaginase treatment results in decreased protein synthesis of multiple coagulation factors. Common findings associated with asparaginase treatment include low fibrinogen, elevated PT/aPTT, and decreased antithrombin levels. Asparaginase may be associated with either hemorrhage or thrombosis which is thought to be related to the relative depression of procoagulant and anti-coagulant proteins. Of the anticoagulant proteins, antithrombin depression is common and may be a risk for thrombosis. Elevated FVIII is a risk factor for thrombosis in general, but not specifically related to asparaginase. Elevated aPTT can be seen with asparaginase secondary to a decrease in several procoagulant factors, but is not a risk for thrombosis. Low fibrinogen is commonly seen rather than elevation, and would be considered a bleeding risk rather than thrombotic risk. Similarly, low PAI-1 would be a risk factor for bleeding.

3) A pediatrician refers a 2 year old girl to your clinic for extensive bruising. Initial work up shows a normal platelet count, normal PT/aPTT, and platelet aggregation studies. The mother also has a history of significant bruising and used to work at a circus as a contortionist. A referral is made to the Department of Social Services for concern of abuse. Which of the following next work up do you consider?

- a. obtain alpha 2 antiplasmin activity to evaluate for increase levels
- b. obtain PAI-1 activity to evaluate for increased levels

- c. recommend that she be placed into foster care
- * c. refer to genetics for work up of connective tissue disease
- d. send platelets for electron microscopy evaluation

Explanation: Individuals with connective tissue disease may present with easy and significant bruising. Increased flexibility is common and many of these disorders are inherited in an autosomal dominant fashion; the history suggests the possibility that the mother also carries the diagnosis of a connective tissue disease. The platelet count, PT/aPTT and platelet function assays are normal in these disorders. Deficiencies (rather than elevations) of alpha 2 antiplasmin and PAI-1 may present with bleeding with normal platelet and coagulation screens also, but are extremely rare. FXIII deficiency is another rare disorder that may present with bleeding and normal bleeding screens. Electron microscopy can evaluate for storage pool defects, but these would be expected to show abnormalities on platelet aggregation studies. Abuse should always be considered with abnormal bruising without apparent etiology, and an appropriate referral had been already made.

4) A 2 year old boy is admitted to the PICU with transaminitis and a direct hyperbilirubinemia. The platelet count is 90,000 per cu mm. The PT is 45 seconds and the aPTT is 68 seconds. What laboratory testing can help distinguish the coagulopathy of liver failure versus DIC?

- a. D-dimer
- b. fibrinogen
- *c. FVIII
- d. FVII
- e. FV

Explanation: While all these factors are synthesized in the liver, FVIII is also expressed from endothelial cells. In the setting of liver failure, FVIII activity is usually normal or increased, while the other factors are decreased. In contrast, with severe DIC, all of the listed factors, including FVIII, are depressed secondary to consumption of the factors. The platelet count can be depressed in both liver failure and DIC. D-dimers are cleared in the liver, so will be elevated in both liver failure and DIC. Thus, the determination of FVIII activity may help to distinguish the coagulopathy of liver failure versus DIC.

5) A fullterm infant girl was born at home via a midwife, and the parents elected not to administer hepatitis B vaccine or vitamin K. The child is breast fed at home and was well until 3 months of age when he developed diarrhea. The baby is noted to be lethargic with bleeding from the mouth and ecchymotic lesions. A head CT shows an intracranial bleed. The hemoglobin is 7 gm/dl and the platelets are 360,000 per cu mm. The PT/aPTT is 63 sec and >100 sec. Most appropriate management:

- a. FFP
- b. IV vitamin K
- d. Cryoprecipitate
- * c. FFP and IV vitamin K
- e. rFVIIa

Explanation: This case highlights the risk factors and presentation of vitamin K deficiency bleeding (VKDB). Early VKDB presents in the first 1 to 2 weeks of life and manifested by prolongation of both PT and aPTT. Symptoms include ecchymosis, gastrointestinal bleeding and intracranial hemorrhage. Late VKDB occurs from 2 weeks to as late as 6 months. Intramuscular vitamin K prophylaxis is protective against VKDB; orally administered vitamin K is protective against early VKDB, but not for late VKDB. Risk factors include exclusively breast fed infants who have received inadequate vitamin K prophylaxis. Another risk factor for VKDB is fat malabsorption. Administration of vitamin K intravenously carries a small risk of anaphylaxis, but can restore activity of vitamin K-dependent coagulation factors (by gamma-carboxylation) in 4 to 6 hours. Thus, vitamin K deficiency with mild bleeding symptoms may be managed

with vitamin K administration alone. However, with life-threatening bleeding, both FFP and vitamin K are indicated. FFP alone without vitamin K will only be of transient benefit. Cryoprecipitate is enriched for fibrinogen, vWF, FVIII, and FXIII; all of these factors are not vitamin K dependent, and thus their activity is not expected to be deficient in this patient. rFVIIa is FDA approved for treatment of inhibitors in patients with hemophilia and in patients with congenital FVII deficiency; although it has been used for the treatment of other bleeding disorders, it would not be the appropriate initial choice for treatment in this case.

6) A 15 month old boy on the general pediatric service is being treated with IV antibiotics for osteomyelitis. He is noted to have mild bruising over the lower extremities. Family history is notable for mild FVIII deficiency in a paternal uncle. Laboratory evaluation from a peripheral venepuncture shows a platelet count of 353,000 per cu mm and a PT of 11.5 seconds and an aPTT of 52 seconds. The most appropriate recommendation for the initial work up in this patient?

- a. von Willebrand screen
- b. Thrombin time
- c. FVIII activity
- d. DIC screen
- *e. aPTT Mixing study

Explanation: This child has minimal bleeding symptoms with an isolated prolongation of the aPTT. The differential diagnosis includes a coagulation factor deficiency of the intrinsic pathway (FVIII, FIX, FXI, FXII), a circulating inhibitor (lupus anticoagulant) or heparin contamination. An appropriate first screen is an aPTT mixing study. Correction of the aPTT with normal plasma suggests a coagulation factor deficiency and further investigation of specific factors would then be warranted. Failure to correct the aPTT would be consistent with a lupus anticoagulant or heparin. In the majority of children, lupus anticoagulants are benign and transient, but they can be associated with thromboembolic disease. Bleeding can also rarely be associated with lupus anticoagulants, but in those cases, the PT and aPTT are often prolonged due to depletion of prothrombin. Thrombin time is a useful screen for prolongation of both PT and aPTT. It will be elevated with fibrinogen deficiency or dysfunction and DIC (due to inhibition of thrombin from fibrin split products). Thrombin time will also be prolonged with heparin. A reptilase time will be normal with heparin. DIC usually results in prolongation of the PT initially, followed by prolongation of the aPTT. Some individuals with vWD will have isolated prolongation of the aPTT, but the prolongation tends to be mild. The family history of FVIII deficiency in the paternal uncle does not increase the risk of FVIII deficiency in this patient. Platelet aggregations may reveal a platelet dysfunction, but will not provide an explanation for the prolonged aPTT.

7) A 17 year old girl was diagnosed with a DVT at an outside hospital and was initially treated with heparin, then transitioned to warfarin. She and her family come to your clinic now a month later for a second opinion about thrombophilic risk factors. Which of these thrombophilic tests will be affected by warfarin?

- a. Prothrombin 20210 mutation
- b. Protein C antigen
- *c. Protein S activity
- d. Antithrombin activity
- e. Anti-cardiolipin antibody test

Explanation: Protein S and Protein C are vitamin K dependent factors, as well as the serine proteases, FII, FVII, FIX and FX. Thus protein C and S activity will be depressed with warfarin due to reduced gamma carboxylation of the proteins. However, the protein C and S antigen (total amount of protein, active and inactive) should not be significantly affected by warfarin. The prothrombin mutational analysis is

performed on genomic DNA; it is therefore not affected by warfarin. Antithrombin is produced in the liver, but is not vitamin K dependent, and the activity should not be affected by warfarin. Anticardiolipin antibody testing is ELISA based and is also not affected by warfarin. Of note is that tests for lupus anticoagulants, such as the DRVVT, are aPTT based, and is often prolonged on warfarin due to depletion of vitamin K dependent procoagulant factors.

8) You diagnose an 18 month old boy with acute megakaryocytic leukemia. The white count is 18,000 per cu mm with 23% circulating blasts. The hemoglobin is 10 gm/dl and the platelet count is 190,000 per cu mm. He develops significant oozing and a large hematoma around a recent central line placement. He also has persistent epistaxis and increased bruising. You obtain further laboratory testing which shows aPTT of 28 seconds, PT of 11.8 seconds, fibrinogen of 285 mg/dl and D-dimers are elevated at 2.3 mg/L (0.17-0.88). You note that in addition to the blasts on the peripheral blood smear, many of the platelets are unusually shaped and appear hypogranulated. Based on the evaluation, the most effective treatment for the bleeding symptoms is:

- a. FFP
- b. Cryoprecipitate
- c. rFVIIa
- *d. platelet transfusion

Explanation: The abnormal appearing platelets are actually cytoplasmic fragments from the leukemia megakaryoblasts. These will be enumerated as platelets and is the reason for the normal platelet count reported on the CBC; however, these platelets are dysfunctional. While DIC should be considered in a newly diagnosed patient with acute leukemia and bleeding, the normal PT, aPTT, and fibrinogen do not support the diagnosis of DIC. The D-dimer elevation is non-specific. Thus, replacement products with FFP or cryoprecipitate are not likely to be effective treatment for bleeding symptoms. rFVIIa is FDA approved for the treatment of hemophilia with inhibitors and congenital FVII deficiency; it has also been used for bleeding associated with other etiologies, such as DIC, trauma, platelet dysfunction, thrombocytopenia and liver disease. However, because of the risk of thrombosis and promoting DIC, rFVII should be used with caution. Platelet transfusions are effective for the treatment bleeding symptoms from platelet dysfunction and would be an appropriate initial treatment for this patient. Other therapies for platelet dysfunction include DDAVP and antifibrinolytic (ie amicar).

9) A 4 month old boy with an expanding violaceous chest wall mass is seen in the emergency room. A PT and aPTT are >100 seconds and >200 seconds respectively. The fibrinogen is 50 mg/dl, the platelets are 20,000 per cu mm and the D-dimers are elevated at >50 mg/L. Which of the following is expected to be elevated in this condition?

- a. Antithrombin
- b. ADAMTS-13 activity
- c. Protein C
- d. FVIII
- *e. PAI-1

Explanation: This case illustrates a patient with DIC associated with a hemangioendothelioma, termed Kasabach-Merritt syndrome. The cardinal feature of DIC is activation of systemic coagulation resulting in microvascular fibrin deposition. Consumption of procoagulants factors and platelets result in bleeding risk. In addition, the activity of natural anticoagulant proteins, such as antithrombin, protein C and protein S, are decreased. Deficiency of ADAMTS-13 is a cause of congenital TTP, which is characterized by a microangiopathic hemolytic anemia. It is not expected to be elevated with DIC. Increased PAI-1 (an inhibitor of plasmin generation) expression from vascular endothelial cells is thought to be the major mechanism of impaired fibrinolysis in DIC.

10) A 5 year old girl with relapsed ALL is undergoing evaluation for bone marrow transplant. She developed a catheter-associated thrombosis during chemotherapy and had undergone a thrombophilic work up. Which of the following thrombophilic conditions would be potentially corrected with bone marrow transplantation from an unaffected donor?

- *a. Antiphospholipid antibody syndrome
- b. Prothrombin 20210 mutation
- c. Antithrombin deficiency
- d. Protein S deficiency
- e. FV Leiden

Explanation: Factor V, Factor II, antithrombin and protein S are primarily produced in the liver. The prothrombin G20210A describes is a single nucleotide change (G to A) in the 3' untranslated region (nucleotide 20210) of the prothrombin (Factor II) gene. FV Leiden is a point mutation in the Factor V gene that results in resistance to cleavage by activated protein C. While the majority of Factor V is produced in the liver, it is notable that a fraction of FV (~20%) is expressed from platelets. Antiphospholipid antibody syndrome arises from dysregulation of the immune system with production of abnormal antiphospholipid-dependent antibodies from lymphocytes. When these antibodies interfere with aPTT based tests (resulting in prolongation) they are termed lupus anticoagulants. Antibody specificity may also be demonstrated against cardiolipin (anti-cardiolipin antibodies, ACA) or beta 2 glycoprotein I (B2GPI). How these antibodies predispose to thrombosis is not entirely clear, but may involve platelet activation with microparticle formation or endothelial dysfunction. Bone marrow transplantation would be expected to ablate the recipient's immune system and reconstitute with donor immune system.

11) A 2 week old girl with congenital heart disease is admitted the PICU with a newly diagnosed atrial thrombus. She is treated with systemic thrombolysis with tPA, but there is no evidence of clot lysis. A possible etiology is:

- * a. Plasminogen deficiency
- b. PAI-1 deficiency
- c. Antithrombin deficiency
- d. FV Leiden homozygote
- e. Antiphospholipid antibodies

Explanation: The inactive proenzyme, plasminogen, is converted to the active serine protease, plasmin, by t-PA or u-PA. Plasmin degrades fibrin clot into fibrin split products and D-Dimers. Plasminogen in neonates is lower than in adults, and rare patients have been identified with plasminogen deficiency. Low plasminogen activity may result in impaired fibrinolysis with t-PA. PAI-1 inhibits plasmin activation by inhibiting t-PA; thus, elevated PAI-1 may inhibit fibrinolysis, but PAI-1 deficiency would result in increased fibrinolysis and bleeding. Antithrombin deficiency, FV Leiden and antiphospholipid antibodies are all prothrombotic risk factors, but do not significantly impair fibrinolysis.

12) A 14 year old girl with SLE is admitted with a swollen left leg and chest pain. She is diagnosed with a lower extremity DVT and pulmonary emboli. She is also noted to have generalized edema and 4+ protein in the urine. She is started on an UFH drip, but requires very high doses to maintain a therapeutic aPTT. You suggest a possible reason for this:

- *a. Antithrombin deficiency

- b. Renal insufficiency
- c. Protein C deficiency
- d. FV Leiden homozygote
- e. antiphospholipid antibodies

Explanation: UFH is monitored by prolongation of the aPTT, but the pharmacokinetics can be affected by many factors. The anticoagulant effect of heparin is mediated by antithrombin. Thus, antithrombin deficiency is a potential etiology for heparin resistance. Deficiency of antithrombin can be either congenital or acquired. Acquired antithrombin deficiency can be seen in conditions such as nephrotic syndrome due to urinary loss of antithrombin, which was the case in this patient. Asparaginase therapy and liver disease are also associated with acquired antithrombin deficiency. Congenital antithrombin deficiency is seen in about 2 to 4 individuals in 100,000 in the general population. Another etiology for heparin resistance is elevated FVIII secondary to inflammation. UFH is cleared primarily by the reticuloendothelial system, and not renally; thus renal insufficiency would not be expected to affect heparin metabolism significantly. This is in contrast to LMWH (low molecular weight heparin), which is cleared renally and should be used with caution in renal insufficiency. Antiphospholipid antibodies are a risk factor for thrombosis, and can be seen in patients with SLE. However, these antibodies would be expected to prolong the aPTT. Protein C deficiency, FV Leiden and the prothrombin mutation would not be expected to alter heparin metabolism.

13) 5 year old boy undergoes a preoperative evaluation for elective tonsillectomy and adenoidectomy. There is no family history of bleeding. The aPTT is elevated at 48 seconds and the PT normal at 10.5 seconds. He is referred to you clinic for further work up. You order the following studies:

	Patient	normal
aPTT	48 seconds	(23-34)
1:1 mix	42.5 seconds	(23-34)
DRVVT	68 seconds	(27-45)
1:1 mix	55 seconds	(27-45)
DRVVT after neutralization with phospholipid	38 seconds	(27-45)

What is the most appropriate management plan?

- a. FFP prior to surgery
- b. Start aspirin therapy
- *c. Postpone elective surgery and recheck aPTT in 2 to 3 months
- d. Refer to rheumatology for work up of lupus

Explanation: The mixing studies indicate that the etiology of the aPTT prolongation is due to an inhibitor rather than factor deficiency. The correction of the DRVVT after neutralization with phospholipid demonstrates that the antibodies are phospholipid dependent. Antibodies that inhibit aPTT based tests (such as the DRVVT), and are phospholipid dependent, are called lupus anticoagulants (LA). In the majority of children, these antiphospholipid antibodies are benign and transient. In some cases, however, they may be a risk factor for thrombosis, particularly if they are identified in association with an autoimmune disease such as lupus. In the absence of clinical findings suggestive of an underlying autoimmune disease, an extensive workup or anticoagulation is not indicated. Significant bleeding does not appear to be a common association, except in the instances when both PT and aPTT are prolonged. In these cases, the antibody appears to target and deplete prothrombin. In this healthy child, the LA is likely to be benign and transient, but the risks of bleeding with surgical challenges have not been extensively

assessed. If the surgery is elective, a reasonable approach would be to postpone the surgery and determine if the LA resolves over several months. If the patient is to proceed with surgery, then administration of FFP or platelets only as needed for bleeding would be appropriate (rather than prophylactic given), as FFP would not be expected to correct the aPTT, and the added bleeding risk posed by the LA is likely minimal to none.

14) 7 year old boy undergoes a preoperative evaluation for elective tonsillectomy and adenoidectomy. There is no family history of bleeding. The aPTT is elevated at 48 seconds and the PT normal at 10.5 seconds. He is referred to you clinic for further work up. You order the following studies:

	<u>Patient</u>	<u>normal</u>
aPTT	48 seconds	(23-34)
1:1 mix	33 seconds	(23-34)
DRVVT	52 seconds	(27-45)
1:1 mix	40 seconds	(27-45)

You obtain specific coagulation factor activities:

FVIII	83%
FIX	110%
FXI	72%
FXII	31%
ristoCoF	69%
vWF ag	89%

What is the most appropriate management plan?

- FFP prior to surgery
- perioperative amicar therapy
- Postpone elective surgery and recheck aPTT in 2 to 3 months
- * Proceed with elective surgery without additional bleeding prophylaxis

Explanation: The workup demonstrates that the etiology of the aPTT prolongation is due to FXII deficiency rather than an inhibitor or deficiency of other coagulation factors that prolong the aPTT in isolation. The correction of the aPTT and the DRVVT after mixing with normal plasma is consistent with a deficiency of a coagulation factor. For an isolated aPTT prolongation, these include FVIII, FIX, FXI, FXII, high molecular weight kininogen (HMWK) and prekallekrien (PK). A minority of patients with vWD will also have an isolated prolongation of the aPTT. Of these factors, only deficiencies of FVIII, FIX and FXI would be expected to contribute a significant bleeding risk. The contact activation factors included FXII, FXI, HMWK and PK. These factors appear to participate in complement activation and kinin regulation. A deficiency of these contact factors will result in an isolated prolongation of the aPTT; however, deficiencies of these factors--with the exception of FXI--do not confer an increased bleeding risk. The FXII gene is an autosomal, and the activity levels in this patient (31%) may arise from either a heterozygous mutation or compound heterozygous mutations (2 alleles affected); the levels would not be expected to change significantly with time. Thus, in this patient with FXII deficiency, no additional prophylactic measures such as FFP or amicar are warranted.

15) You are consulted for a 15 year old girl with a preoperative PT and aPTT of 17 sec and 52 sec prior to scoliosis surgery. The CBC is normal with a platelet count of 275,000 per cu mm. The fibrinogen activity is low at 82 mg/dl. The D-dimer is not elevated. Liver function tests and albumin are normal. A thrombin time is elevated at 65 seconds. She reports easy bruising and heavy menses, but no other symptoms of excessive bleeding. There is no family history of bleeding, but father reports a history of DVT at age 25 years. The appropriate next step for this patient:

- a. CT of abdomen and pelvis for occult vascular lesion causing Kasabach-Merritt syndrome
- *b. obtain a fibrinogen antigen
- c. refer to GI for evaluation of liver failure
- d. heparinase of plasma for evaluation of heparin contamination
- e. 5 mg of vitamin K by mouth for 3 days then repeat the PT and aPTT

Explanation: The low fibrinogen activity will result in prolongations of the PT and aPTT. Fibrinogen is not a vitamin K dependent factor, so vitamin K deficiency is not the etiology of this picture. DIC will result in consumption of the fibrinogen, but the D-dimer is not elevated and the platelet count is normal, making the diagnosis of DIC (associated with Kasabach-Merritt syndrome) unlikely. Fibrinogen is produced by the liver, and can be decreased in liver disease; however, this patient has normal liver functions tests and albumin. The thrombin time is elevated with decreased fibrinogen activity. Other reasons for elevations in thrombin time include heparin and fibrin split products (with DIC). Heparin however does not cause a decrease in fibrinogen activity. Deficiency of ADAMTS-13 is a cause of congenital TTP, which is characterized by a microangiopathic hemolytic anemia, but does not cause depression of fibrinogen.

The fibrinogen antigen in this patient was 246 mg/dl, which was discordant with the activity of 82 mg/dl. This finding indicates the diagnosis of dysfibrinogenemia. Fibrinogen is composed of 3 protein chains that are encoded by separate genes; primary disorders of fibrinogen arise from mutations in these genes. Dysfibrinogenemia can result in either bleeding symptoms, or thrombotic symptoms. The father in this case also had the diagnosis of dysfibrinogenemia. Other clinical phenotypes associated with fibrinogen chain mutations include afibrinogenemia (absence of fibrinogen antigen) and hypofibrinogenemia (low fibrinogen activity and antigen). Bleeding symptoms can be managed with cryoprecipitate.

16) You are asked by the NICU about a newborn boy with a maternal uncle who has the diagnosis of mild FIX deficiency. The infant is well without any bleeding. The cord blood PT is 12.8 seconds and aPTT is 42 seconds (normal for age). The FIX activity from cord blood is 39%. You recommend:

- a. begin FIX prophylaxis beginning between 1 to 2 years of age
- * b. recheck the levels at 6 months to 12 months
- c. clinic visit asap to discuss the new diagnosis of mild FIX deficiency
- d. a dose of recombinant FIX for prophylaxis around birth

Explanation: FIX, like other vitamin K dependent factors, is lower than adult levels at birth. Thus, a FIX activity of 39% obtained at birth likely normal, and is not diagnostic of mild FIX deficiency; it should be repeated at a least after 6 to 12 months of age to more confidently exclude FIX deficiency. Primary FIX prophylaxis is considered for individuals with severe FIX deficiency in the 1 to 5 year range, but rarely for mild FIX deficiency. There is no consensus for prophylactic FIX replacement around birth, even with the diagnosis of severe FIX deficiency.

2013 ASPHO Board Review Questions

Blood Coagulation Overview and Acquired Hemorrhagic Disorders

Question 1:

A 7 year old girl requiring a tonsillectomy and adenoidectomy undergoes pre-operative laboratory testing by her surgeon revealing a prolonged activated partial thromboplastin time (PTT) of 150 seconds (normal range 22-36 seconds). Her prothrombin time (PT) is normal. She had previously had 2 dental extractions that were uneventful. She otherwise has no personal or family history of bleeding. Which of the following is most likely:

- A. Factor VIII activity of 2%
- B. Factor IX activity of 2%
- C. Factor VII activity of 2%
- D. Factor XI activity of 2%
- E. Factor XII activity of 2% (*)

Explanation: A prolonged PTT and normal PT means that there is either a deficiency of an intrinsic factor or the presence of a lupus anticoagulant. None of the choices offer the possibility of a lupus anticoagulant. With respect to the choices, clearly C cannot be correct because FVII deficiency would affect the PT and not the PTT. With respect to choices A and B, since deficiencies of factors VIII and IX are inherited in an X-linked recessive fashion, it would be highly unusual for a girl to have such low levels although extreme Lyonization of the X chromosome can occur. More importantly, this child has no personal history of bleeding even in spite of a previous hemostatic challenge making such deficiencies highly unlikely. While FXI deficiency does occur in females and bleeding symptoms are milder than for deficiencies of factors VIII and IX, it is still likely that with dental extractions, excessive bleeding would occur. Deficiency of FXII especially to this level would substantially prolong the PTT yet it is not associated with any bleeding symptoms making it the correct answer.

Question 2:

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

- Factor VIII—8%
- Factor IX—12%
- Factor XI—15%
- Factor XII—6%

The most likely diagnosis is:

- A. Factor VIII deficiency (*)
- B. Factor IX deficiency
- C. Factor XI deficiency
- D. Factor XII deficiency
- E. All the factor levels are normal for age

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

Question 3:

You are asked to consult on a newborn female with purpura fulminans. Upon taking the medical history, you learn that this child had a male sibling who died in the neonatal period after presenting with purpura fulminans. She has 3 other siblings who are healthy and did not have purpura fulminans. This child's underlying condition leads to which physiologic consequence:

- A. Excess von Willebrand factor high molecular weight multimers
- B. Decreased fibrinogen

- C. Inability to inactivate factor VIII (*)
- D. Decreased production of plasminogen
- E. Thrombocytopenia

Explanation: The differential diagnosis of neonatal purpura fulminans includes disseminated intravascular coagulation as well as deficiencies of proteins C and less likely, protein S. In this vignette, the child had an older sibling who presented in the same manner, and while DIC can occur to any newborn, this scenario suggests the presence of an autosomal recessive disorder. As such, the most likely diagnosis is protein C (or S) deficiency. The protein C/S complex is responsible for inactivating factors V and VIII thus the correct answer is C.

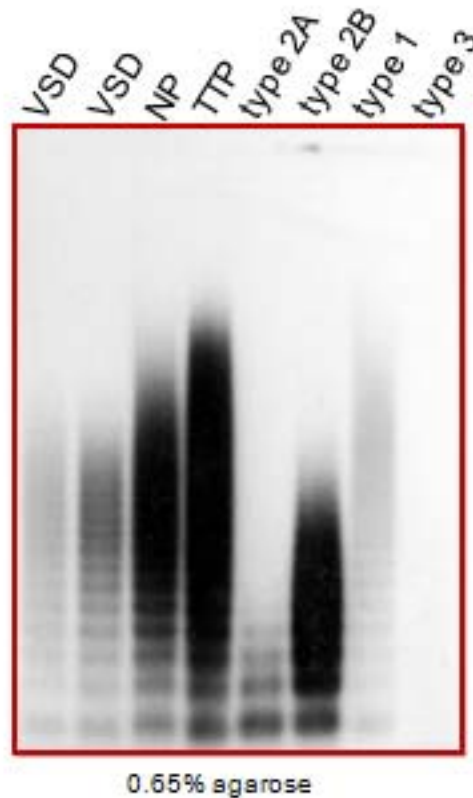
Question 4:

You are evaluating a 12 year girl who was admitted to the hospital for anemia (hemoglobin concentration of 85 gm/L) who has had significant vaginal bleeding with the onset of menarche 3 weeks ago. Her family history includes several females who were diagnosed with von Willebrand disease (VWD). Which of the following tests are necessary to detect the presence of type 2A VWD?

- A. Von Willebrand factor (VWF) antigen concentration
- B. Ristocetin cofactor activity
- C. Factor VIII activity
- D. VWF multimer analysis (*)
- E. Ristocetin-induced platelet aggregation with low dose ristocetin

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

Plasma VWF Multimers



Question 5:

A 12 year old child with a deep vein thrombosis received a loading dose of warfarin of 0.2 mg/kg (8 mg) and then started on a dose of 0.1 mg/kg (4 mg) with a target INR of 2-3. The INR the next day was 2.1. When the patient returns to see you after 10 days, the INR is 1.4. This effect can be best explained by which of the following:

- A. The child had a change in a medication that affects warfarin metabolism 3 days after starting warfarin.
- B. The different half-lives of factors II, VII and X. (*)
- C. The child has a mutation in VKORC1 making them more sensitive to the effects of warfarin.
- D. The child ate a meal with a high content of vitamin K.
- E. The child was on the generic version of warfarin rather than Coumadin.

Explanation: Warfarin is a vitamin K antagonist which interferes with gamma-carboxylation of the vitamin K-dependent proteins (factors II, VII, IX, and X and proteins C and S). In order to understand how to properly treat a child with warfarin, one must know the half-lives of the affected proteins. The half-life of factor VII is short (~5 hours or less in younger children) while that of the other 3 factors range from 12-24 hours. Following a warfarin loading dose (which incidentally is not recommended), the factor VII level can drop precipitously leading to a rapid rise in the INR. The INR in this vignette measured the day after the dose of warfarin reflects only the effect on factor VII. Once the maintenance dose is started, it takes 5-7 days to reach the steady state (and lower) level of factors with the longest half-life (factors II and X). Thus, the high early INR only reflects the loading dose's effect on factor VIII while the subtherapeutic INR at day 10 reflects the balanced reduction of all the vitamin K-dependent clotting factor. Therefore, the correct answer is B. The vignette did not mention any other medications the child was taking. The presence of a VKORC1 mutation increasing the sensitivity to warfarin would not lead to a subtherapeutic INR at day 10

though it could lead to a supratherapeutic INR. A single meal with a high vitamin K content would not have a prolonged effect on the INR. In fact, it takes very large quantities of ingested vitamin K to impact the INR, and with the exception of a vegan diet is unlikely to influence the dose of warfarin. The generic form of warfarin is as effective as the branded variety so even a change from Coumadin to warfarin wouldn't result in such a change.

Question 6:

A 1 year old male presents to the emergency room with irritability and vomiting, and a CT scan demonstrates a large intracranial parenchymal hemorrhage. The mother reports that his only other bleeding symptom was prolonged bleeding from the umbilical stump. The patient comes from a large pedigree with numerous male and female first and second degree relatives, however there is no history of excessive bleeding in any of them. Which of the laboratory test patterns are most consistent with this history?

- A. Normal PT and PTT. (*)
- B. Prolonged PT, normal PTT.
- C. Normal PT, prolonged PTT.
- D. Prolonged PT, prolonged PTT.

Explanation: This presentation is most consistent with factor XIII deficiency. The family history suggests a disorder inherited in an autosomal recessive pattern. The location of the 2 hemorrhages (intracranial and umbilical stump) are classic for factor XIII deficiency. As factor XIII is not required to form the initial fibrin clot which is what the endpoint of the PT and PTT assay are, both tests are normal in the presence of even severe factor XIII deficiency. Factor XIII activation results in the cross-linking of fibrin monomers which can be assessed qualitatively in a clot solubility assay using either urea or acetic acid. Thus the correct answer is A.

Question 7:

A 2 year old female develops a femoral artery thrombus following cardiac catheterization and is noted to have pallor of the lower half of the leg which is cool to the touch. Her pulses in her foot are present but diminished. Her physician decides to treat the thrombus with tissue plasminogen activator (TPA). Her laboratory test prior to initiation of TPA demonstrate a PT of 10.2 seconds (normal 9.7-11.2 seconds) and a PTT of 31.3 seconds (normal 22-36 seconds), a fibrinogen of 2.75 g/L (normal 2-4 g/L) and a D-dimer of 2,450 ng/mL (normal <500 ng/mL). After 6 hours of TPA, there is no improvement of the symptoms related to the thrombus. The laboratory tests are unchanged. Her dose is increased to what is considered to be the maximum dose of 0.5 mg/kg/hour. Again 6 hours later, there is no clinical improvement and the laboratory tests are unchanged. What is the most reasonable next step in her management?

- A. Change the TPA infusion to urokinase.
- B. Change from TPA to unfractionated heparin.
- C. Give 10 cc/kg of fresh frozen plasma. (*)
- D. Start aspirin.
- E. Perform a surgical thrombectomy.

Explanation: This child has an arterial thrombus of the leg following cardiac catheterization and the decision is made to treat the thrombus with TPA. It is important to understand that TPA is an enzyme which cleaves plasminogen to plasmin and that plasmin is the effector protein which lyses the fibrin clot. In the absence of plasminogen, TPA has no effect. Following administration of TPA, one should look for a lytic effect as evidenced by a decrease (often substantial) of the fibrinogen level along with a rise in the D-dimer. Absence of this effect on these laboratory tests should raise the concern that the patient does not have a sufficient amount of circulating plasminogen and fresh frozen plasma should be administered. In this vignette, it would have been appropriate to do this even after the first set of laboratory tests showed no effect. Therefore the correct answer is C. Merely changing from one fibrinolytic drug to another is not going to be effective. While changing to heparin is not unreasonable, given this child's symptoms, and the initial decision to treat with TPA, switching to heparin would be less appropriate than giving fresh frozen plasma. Starting aspirin is not indicated as it will not help in dissolving the clot and is more effective at

preventing arterial thrombosis than treating it. Surgical thrombectomy would be a very radical approach in this scenario and in a child so young.

Question 8:

You are seeing a 12 year boy old with easy bruising and recurrent epistaxis as a second opinion. He is active in a variety of sports, however his mother feels that his bruising is excessive. His pediatrician sent the following laboratory tests all of which are normal: WBC, Hemoglobin, platelet count, PT, PTT. Another hematologist ordered the following all of which were normal: VWF Ag, ristocetin cofactor activity, factor VIII activity, factor XIII activity, and platelet aggregation studies. Which of the following physical exam findings would be most informative:

- A. Petechiae where the blood pressure cuff was placed.
- B. Hypermobility of the finger joints.(*)
- C. Palpable bruises over the tibial surface.
- D. A conjunctival hemorrhage
- E. Albinism.

Explanation: It is not unusual for a hematologist to be referred a patient with bleeding symptoms that are sufficient enough to warrant concern yet for a detailed laboratory evaluation to be completely negative. While some of the laboratory testing often warrants repeating (particularly ristocetin cofactor levels), another consideration for such patients is the presence of a connective tissue disorder. This scenario suggests the possibility of a patient with Ehlers-Danlos syndrome, a primary collagen disorder in which patients have joint hypermobility, hyperelastic skin, and mucocutaneous bleeding symptoms. Thus, the answer to this question is B. Answers A, C, and D suggest the possibility of a bleeding disorder but would not be informative to the diagnosis. Answer E suggests the possibility of Hermansky-Pudlak syndrome, a disorder characterized by albinism and platelet dysfunction, however in that disorder, platelet aggregation studies are abnormal.

Question 9:

A 10 day old male is being seen in the emergency room due lethargy and poor feeding. Her anterior fontanel is full. A CT scan demonstrates an intraparenchymal hemorrhage. Coagulation tests are ordered with the following results: PT—37 seconds (normal 9.7-11.2 seconds) and a PTT of 66 seconds (normal 22-36 seconds). This child may have which of the following factor deficiencies:

- A. Factor VII.
- B. Factor VIII.
- C. Factor IX.
- D. Factor X.(*)
- E. Factor XI.

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

Question 10:

A 14 year old female with osteomyelitis is receiving antibiotics at home via a percutaneously inserted central catheter (PICC line). She has developed an abscess despite antibiotic therapy and requires incision and drainage. The orthopedic surgeon orders a PT and PTT. The patient has never had any bleeding symptoms. She had 2 teeth extracted when she was 3 years old and a tonsillectomy and adenoidectomy at the age of 7 years neither of which resulted in excessive bleeding. The PT is 16.2 seconds (normal 9.7-11.2 seconds) and a PTT of 61.3 seconds (normal 22-36 seconds). The most appropriate next step is:

- A. Order a fibrinogen level.
- B. Order levels of factors II, V and X.
- C. Repeat the PT and PTT.
- D. Determine the details regarding sample procurement.(*)
- E. Proceed with the procedure without further testing.

Explanation: This question raises two critical points. First, is the need for pre-operative laboratory testing and second is understanding the pitfalls of coagulation testing. With regards to the first point, one could conceivably conclude that this child doesn't have a bleeding disorder based on her negative history for bleeding which in particular includes two significant hemostatic challenges. As such, it would be reasonable to proceed with this relatively minor procedure without any testing and one would be tempted to answer E, however given that the tests were already performed and it is also possible for children with bleeding disorders to not bleed excessively with dental extractions and even tonsillectomy and adenoidectomy, it would not be prudent to ignore the test results. Since she has a PICC line, it is possible if not likely that the lab tests were drawn from it, and results of coagulation testing from heparinized lines be they central or peripheral are not reliable. Therefore the next most appropriate step is to determine if the laboratory tests were drawn from the PICC line and thus the correct answer is D. Ordering factor levels or a fibrinogen level is premature considering that the abnormalities may be artifactual. Repeating the PT and PTT seems reasonable, however without knowing where the labs were drawn from, if they were drawn from the PICC line the first time and then repeated from the same place, the results could be the same which could "strengthen" the argument that she has a bleeding disorder and lead to unnecessary tests or even potentially harmful treatment.

Question 11:

A 4 year old male is in the intensive care unit intubated and sedated. You are asked to consult due to the presence of numerous generalized petechiae and some large ecchymosis on the abdomen and trunk. Laboratory evaluation demonstrates a platelet count of $45 \times 10^9/L$, a PT 15.4 seconds (normal 9.7-11.2 seconds), a PTT of 48 seconds (normal 22-36 seconds), and a fibrinogen level of 0.87 g/L (normal 2-4 g/L). Which of the following most likely led to these clinical findings:

- A. Immune thrombocytopenic purpura (ITP).
- B. Systemic lupus erythematosus (SLE).
- C. Congenital hypofibrinogenemia.
- D. Acute promyelocytic leukemia.(*)
- E. Vitamin K deficiency.

Explanation: Although the data provided in this vignette is limited, it is clear that this is a very sick child and a very sick child with the laboratory profile provided is strongly suggestive of the presence of disseminated intravascular coagulation (DIC). It is important to know the underlying causes of DIC in children and from the answer choices provided, the most likely answer is D. Acute promyelocytic leukemia is notorious for causing DIC. Children with ITP are generally well-appearing and furthermore would not have abnormalities in coagulation testing unless they had a massive hemorrhage. As that information is not provided, one must assume the answer refers to uncomplicated ITP. The same can be said for SLE, and of note, a 4 year old male is not the typical demographic for SLE. Congenital hypofibrinogenemia should not cause a child to be this sick nor should it lead to thrombocytopenia. Lastly, this is not the typical age for a child with vitamin K deficiency and in that disorder, the platelet count is normal.

Question 12:

For the child in the above scenario, the most effective therapy to control his DIC is which of the following:

- A. Treatment of the acute promyelocytic leukemia.
- B. Fresh frozen plasma.
- C. Cryoprecipitate.
- D. Platelet transfusion.
- E. Exchange transfusion.

Explanation: The most important aspect of the management of DIC is treatment of the underlying disorder and thus the answer is A. While supportive care in the form of blood products may be indicated in certain situations (severe bleeding, thrombotic complications), none of these will “control” the DIC. Exchange transfusion will reverse the laboratory findings and perhaps help with bleeding or clotting symptoms, it will not control the DIC either. Treatment of DIC requires treatment of the condition which led to the DIC in the first place.

Question 13:

A 3 day old infant is brought to the ER due to a seizure. A CT scan demonstrates massive intracranial hemorrhage. On your examination, the child has numerous bruises on the abdomen and trunk. Which of the below scenarios is most likely:

- A. The baby was born to an infant of a diabetic mother.
- B. The baby was born at home. (*)
- C. The baby is exclusively breastfed.
- D. The baby has craniosynostosis.
- E. The baby had no prenatal care.

Explanation: This is a classic presentation for vitamin K deficiency bleeding. The so-called “classical” presentation occurs between 2-7 days of age and babies not infrequently present with intracranial hemorrhage. From the above choices, only B suggests that this is the diagnosis. Infants born at home are at highest risk for not receiving prophylactic vitamin K at birth. Infants of diabetic mothers are not at risk for bleeding complications nor are children with craniosynostosis. Exclusively breastfed infants are at risk for late vitamin K deficiency bleeding which generally occurs from 4-12 weeks of age, however they are not at risk for bleeding at this age. A baby with no prenatal care is not necessarily at higher risk for vitamin K deficiency than other babies.

Question 14:

A 15 year old female with cystic fibrosis is going to undergo a partial pneumonectomy due to severe bronchiectasis. The surgeon orders pre-operative coagulation testing which demonstrates a PT of 17.2 seconds (normal 9.7-11.2 seconds) and a PTT of 36 seconds (normal 22-36 seconds). Due to the abnormality she is given supplemental oral vitamin K of 5 mg once a day for 3 days over and above the ADEK vitamin she has already been taking. After the third dose, repeat testing demonstrates a PT of 16.9 seconds (normal 9.7-11.2 seconds) and a PTT of 37 seconds (normal 22-36 seconds). You are asked to consult. What is the most appropriate next step:

- A. Increase the oral vitamin K dose and repeat the testing.
- B. Perform a mixing study on the PT.
- C. Give a parenteral dose of vitamin K and repeat the testing. (*)
- D. Proceed with surgery with a pre-operative dose of recombinant factor VIIa.
- E. Proceed with surgery with a pre-operative dose of a prothrombin complex concentrate.

Explanation: It is important to understand the vitamin K is a fat-soluble vitamin which can be malabsorbed in patients with fat-malabsorption disorders. In cystic fibrosis, pancreatic dysfunction leads to malabsorption of fat-soluble vitamins and such patients received ADEK (an oral fat-soluble supplement with vitamins A, D, E, and K). Despite this, however, patients with cystic fibrosis are at risk for vitamin K deficiency. In this scenario, the patient received a trial of oral vitamin K supplementation with no benefit. The dose this patient received was adequate and increasing the dose is unlikely to have an effect. A mixing study is not likely to yield useful information since only the PT is prolonged. Lupus anticoagulants affect the PTT much more commonly than the PT and this clinical scenario is not suggestive for the presence of a lupus anticoagulant, regardless. Giving recombinant factor VIIa or prothrombin complex concentrate while likely to correct the abnormality are very expensive medications which carry with them the risk for thrombosis and giving them in the absence of a diagnosis is not appropriate. Repeating the vitamin K challenge with a parenteral dose of vitamin K could be both diagnostic and therapeutic. If the repeat testing is normal, then the diagnosis of vitamin K deficiency is confirmed and in fact the patient has been treated. If the repeat testing is abnormal, then more tests would be indicated. Of note, if such a patient were not to

proceed immediately to surgery, e.g. if it were to be weeks later, then repeating the PT and PTT would be important as an additional dose of parenteral vitamin K might be needed.

Question 15:

A 5 year old male presents with fulminant acute hepatic failure. He is noted to be bleeding from his gums, nose and has hematochezia. This patient's bleeding is most likely due to which of the following combinations:

- A. Deficiency of fibrinogen, factor VII and factor II.(*)
- B. Thrombocytopenia and factor XI deficiency.
- C. Factor VIII, IX and XI deficiency.
- D. Factor V and VIII deficiency.
- E. Low levels of von Willebrand factor and factor VIII.

Explanation: Liver failure results in severe derangements in the coagulation system and while most of the clotting factors are synthesized in the liver, a number of clotting factors have extrahepatic synthesis either wholly or at least in part. Fibrinogen and factors VII and II are exclusively made in the liver and thus A is the correct answer. Although low platelets are not unusual in patients with liver failure, it is also possible for the platelets to be normal or even elevated as an acute phase reactant. Although factor XI is made in the liver, a combination of thrombocytopenia and FXI deficiency is not as likely in this scenario as choice A. Although FVIII is also made in the liver, it is also synthesized in extrahepatic sites, and importantly and probably due to being an acute phase reactant, FVIII levels are often elevated in acute hepatic failure, sometimes significantly. This makes choices C, D and E incorrect. Regarding choice D, factor V is also synthesized in megakaryocytes and is delivered to the site of bleeding by platelets. Regarding choice E, von Willebrand factor is synthesized in endothelial cells and megakaryocytes and its production is unaffected by liver disease. As it is also an acute phase reactant, its levels are often elevated in acute hepatitis and this is also a reason for an elevated factor VIII in liver disease.

Question 16:

An 8 year old female with recurrent tonsillitis is referred for a tonsillectomy. Her surgeon orders pre-operative laboratory tests and the results demonstrate a PT of 10.2 seconds (normal 9.7-11.2 seconds) and a PTT of 58 seconds (normal 22-36 seconds). The most appropriate next test to order is:

- A. Factor VIII activity.
- B. Factor IX activity.
- C. Factor XI activity.
- D. Factor XII activity.
- E. A mixing study.(*)

Explanation: This is a typical scenario for the presence of lupus anticoagulant in a child and therefore ordering a mixing study is the most appropriate next test to order. With no further history, ordering just one of the factors of the intrinsic system would not be informative and therefore not appropriate.

Question 17:

In the scenario above, the mixing study demonstrates no correction of the prolonged PTT and a lupus anticoagulant assay demonstrates the presence of a lupus anticoagulant. You are asked to consult regarding the surgery the child has been recommended to undergo. What is the most appropriate recommendation:

- A. Cancel the surgery as tonsillectomy is not indicated in this child.
- B. The surgery can go forward so long as fresh frozen plasma and cryoprecipitate are given pre-operatively.
- C. Postpone the surgery until the PTT is normal.(*)
- D. The surgeon may proceed with the surgery as the child is not at risk for bleeding.
- E. Evaluate the patient for systemic lupus erythematosus.

Explanation: This again is a typical scenario seen in the hematology clinic. This patient has a lupus anticoagulant and you must decide what to recommend. Cancelling the surgery is not appropriate as you are the hematology consultant and while you are also trained as a pediatrician, it is not your role to determine whether this child should have surgery or not. Furthermore, there is insufficient information in the vignette to adjudicate if the tonsillectomy is indicated or not even if it would be appropriate to provide that input. Most patients with a lupus anticoagulant in this scenario don't have a bleeding diathesis and thus attempted correction with blood products is not indicated. Choices C and D are the most reasonable and represent somewhat of a dilemma, however, since one cannot be sure that this patient's lupus anticoagulant won't cause bleeding, the most prudent and appropriate course and thus the right answer is to postpone the surgery until the PTT is normal which generally occurs over 4-6 weeks. Of note, one syndrome associated with a lupus anticoagulant and bleeding is the lupus anticoagulant-hypoprothrombinemia syndrome. Such patients will have a prolonged PT and PTT as a result of the low prothrombin level. Lastly, an evaluation for lupus is not indicated in this otherwise healthy child. Most patients with a lupus anticoagulant don't have lupus and most patients with lupus don't have a lupus anticoagulant. This is an unfortunate misnomer that we are stuck with.

