**Blood Coagulation Overview and Acquired Hemorrhagic Disorders**

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1. Which of the following are the main elements involved in primary hemostasis?

A. Collagen, von Willebrand factor, and platelets

B. Factor XII, von Willebrand factor, and platelets

C. Factor XI, factor XII, and von Willebrand factor

D. Collagen, von Willebrand factor, and fibrinogen

E. Platelets, von Willebrand factor, and fibrinogen

**Explanation**

It is important to understand the various elements of primary hemostasis, which is the first phase of clot formation. When the endothelium breaks and the blood is exposed to the subendothelium, von Willebrand factor binds to the subendothelial collagen and has its platelet binding sites exposed, thus leading to platelet adherence. Thus, answer A is the correct answer. Factors and fibrinogen are part of secondary and not primary hemostasis.

2. Which of the following reasons explains why a patient with factor XII deficiency does not bleed?

A. Activation of factor XI is the key initiator of physiologic coagulation.

B. Factor XII first needs to be activated by pre-kallikrein.

C. Tissue factor and factor VII are the prime initiators of physiologic coagulation.

D. Factor XII does not bind to platelets.

E. Factor XII has no role in coagulation.

**Explanation**

Factor XII is one of the contact factors, and thus its role in initiating coagulation occurs when the blood is exposed to foreign substances such as extracorporeal circuits or central venous catheters, so answer E is incorrect. Factor XII has no role in physiologic coagulation.

In the absence of foreign surfaces, coagulation starts in the subendothelium with activation of tissue factor, which then activates factor VII to factor VIIa, which then activates factor IX and factor X, leading to thrombin generation, making answer C correct. Factor XII is activated in part by pre-kallikrein, but this is not the reason factor XII does not lead to bleeding. Factor XII does not bind to platelets, but this is not why it does not cause bleeding.

3. Patients with a deficiency of plasminogen activator inhibitor type 1 (PAI-1) may have bleeding symptoms for which of the following reasons?

A. They have diminished tissue plasminogen activator (t-PA), leading to bleeding.

B. They cannot form a proper fibrin clot.

C. They have decreased ability to activate fibrinogen.

D. They have unopposed effects of t-PA, leading to excess fibrinolysis.

E. The condition is associated with episodes of severe thrombocytopenia.

**Explanation**

The role of PAI-1, as its name implies, is to inactivate t-PA, and thus a deficiency leads to unopposed t-PA, causing fibrinolytic bleeding, making answer D correct. The other choices are all incorrect characterizations of PAI-1 functions.

4. You are seeing a 12-year-boy old with easy bruising and recurrent epistaxis for a second opinion. He is active in a variety of sports, but his mother thinks that his bruising is excessive. His pediatrician sent the following laboratory tests, all of which are normal: WBC, hemoglobin, platelet count, PT, and PTT. Another hematologist ordered the following, all of which were normal: von Willebrand factor 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 to warrant concern yet for a detailed laboratory evaluation to be completely negative. Although 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 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, but in that disorder platelet aggregation studies are abnormal.

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

This child may have which of the following factor deficiencies?

A. Factor VII

B. Factor VIII

C. Factor IX

D. Factor X

E. Factor XI

**Explanation**

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 when treatment is warranted as soon as possible. In this scenario, both 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 PTT, and deficiencies of factors VIII, IX, or XI would not prolong PT.

6. A 14-year-old girl with osteomyelitis is receiving antibiotics at home via a percutaneously inserted central catheter (PICC line). She has developed an abscess despite antibiotic therapy and needs 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 age 7 years, neither of which resulted in excessive bleeding. She has a PT of 16.2 seconds (normal 9.7 to 11.2 seconds) and a PTT of 61.3 seconds (normal 22 to 36 seconds).

What is the most appropriate next step?

A. Order a fibrinogen level.

B. Order levels of factors II, V, and X.

C. Repeat the PT and PTT.

D. Determine the details of sample procurement.

E. Proceed with the incision and drainage without further testing.

**Explanation**

This question raises two critical points. First is the need for preoperative laboratory testing, and second is understanding the pitfalls of coagulation testing. With regard to the first point, one could conclude that this child does not have a bleeding disorder based on her negative history for bleeding, which includes two significant hemostatic challenges. Therefore, it would be reasonable to perform this minor procedure without any testing, and one would be tempted to choose answer E; however, given that the tests were already performed, and it is 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. Because she has a PICC line, it is possible 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 whether 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.

7. A 3-day-old infant is brought to the emergency department after having a seizure. A CT scan demonstrates massive intracranial hemorrhage. On your examination, the child has numerous bruises on the abdomen and trunk. Which scenario is most likely?

A. The baby was born to 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 of vitamin K deficiency bleeding. The so-called classic presentation occurs between 2 and 7 days of age, and babies often present with intracranial hemorrhage. From the above choices, only answer 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 at 4 to 12 weeks of age, but 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.

8. A 15-year-old girl with cystic fibrosis is going to undergo a partial pneumonectomy due to severe bronchiectasis. The surgeon orders preoperative coagulation testing, which demonstrates a PT of 17.2 seconds (normal 9.7 to 11.2 seconds) and a PTT of 36 seconds (normal 22 to 36 seconds). Because of 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 to 11.2 seconds) and a PTT of 37 seconds (normal 22 to 36 seconds). You are asked to consult.

What is the most appropriate next step?

A. Increase the oral vitamin K dosage 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 preoperative dose of recombinant factor VIIa.

E. Proceed with surgery with a preoperative dose of a prothrombin complex concentrate.

**Explanation**

Vitamin K is a fat-soluble vitamin that can be poorly absorbed 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). 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 dosage this patient received was adequate, and increasing the dosage is unlikely to have an effect. A mixing study is not likely to yield useful information because only the PT is prolonged. Lupus anticoagulants affect PTT much more commonly than PT, and this clinical scenario is not suggestive for the presence of a lupus anticoagulant. Giving recombinant factor VIIa or prothrombin complex concentrate is likely to correct the abnormality, but they are very expensive medications that carry 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 (eg, if it were to be weeks later), then repeating the PT and PTT would be important because an additional dose of parenteral vitamin K might be needed.

9. A 5-year-old boy presents with fulminant acute hepatic failure. He is noted to be bleeding from his gums and nose and has hematochezia. This patient’s bleeding is probably caused by 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 although most 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 answer A is correct. 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 factor XI deficiency is not as likely in this scenario as answer A. Although factor VIII is made in the liver, it is also synthesized in extrahepatic sites, and importantly and probably due to being an acute phase reactant, factor VIII levels are often elevated in acute hepatic failure, sometimes significantly. This makes answers C, D, and E incorrect. Regarding answer D, factor V is also synthesized in megakaryocytes and is delivered to the site of bleeding by platelets. Regarding answer E, von Willebrand factor is synthesized in endothelial cells and megakaryocytes, and its production is unaffected by liver disease. Because 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.

10. A 2-year-old boy with congenital heart disease has a deep vein thrombosis and, after treatment with heparin, develops heparin-induced thrombocytopenia. He is placed on argatroban, a direct thrombin inhibitor. As a result of thrombin inhibition, which of the following effects is expected to occur?

A. Decreased activation of factors VII, IX, and X

B. Increased activation of factor XIII and thrombin-activatable fibrinolysis inhibitor

C. Increased conversion of fibrinogen to fibrin and factor V to factor Va

D. Decreased release of von Willebrand factor from Weibel-Palade bodies

E. Decreased activation of factors V and VIII

**Explanation**

To understand the physiology of the coagulation system, one must understand the function of thrombin. In essence, thrombin’s effects on the coagulation system are all prohemostatic. Specifically, it activates procoagulant factors (V, VIII, XI), activates antifibrinolytic factors (factor XIII, thrombin-activatable fibrinolysis inhibitor [TAFI]), activates platelets, and converts fibrinogen to fibrin. Thus, an inhibitor of thrombin would have the opposite effect, making answer E correct. Answer A is incorrect because thrombin does not activate factors VII, IX, or X, so there would be no effect on those clotting factors. Thrombin activates factor XIII and TAFI, so inhibition of thrombin would do the opposite, making answer B incorrect. Answer C is incorrect for the same reason as answer B, and answer D is incorrect because thrombin is not involved in the release of von Willebrand factor from Weibel-Palade bodies.

11. You are asked to consult on a 12-year-old patient with congenital heart disease and Eisenmenger phenomenon who needs to have a surgical procedure. The surgeon obtained the following pre-op laboratory tests:

 PT: 18 seconds (normal 10 to 13 seconds)

 PTT: 58 seconds (normal 23 to 36 seconds)

 WBC: 18.9 × 109/L

 Hgb: 22.3 g/dL

 Hct: 68%

 Platelet count: 126,000

You decide to order factor levels to determine what factor deficiency the patient may have, but the coagulation laboratory director refuses.

What is the correct next step?

A. Order a mixing study.

B. Repeat the PT and PTT.

C. Repeat the PT and PTT with modifications.

D. Order a thrombin time.

E. Order a heparin-neutralized PTT.

**Explanation**

All coagulation assays drawn into citrate tubes (blue tops) rely on a plasma:citrate ratio of 9:1, and any preanalytic conditions that significantly alter this ratio can affect the results. For example, an underfilled tube will result in a lower ratio of plasma or higher ratio of citrate, which will result in falsely elevated levels due to the citrate effect on the plasma. Similarly, a patient with a very high hematocrit will have, by definition, a lower concentration of plasma, and the effect is the same as that of an underfilled tube—too much citrate for the amount of plasma present, resulting in falsely abnormal results, in this case the PT and PTT. To correct for this, the PT and PTT can be done, but the laboratory must prepare a specialized citrate tube with less citrate so that the ratio of 9:1 plasma to citrate is maintained. Therefore, the correct answer is C.

12. You are asked to consult on a newborn girl 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 three other siblings who are healthy and did not have purpura fulminans.

Which physiologic consequence will result from this child’s underlying condition?

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 (DIC) and deficiencies of protein C and, less likely, protein S. In this vignette, the child had an older sibling who presented in the same manner, and although DIC can occur with any newborn, this scenario suggests the presence of an autosomal recessive disorder. Therefore, 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.

13. A 4-year-old boy is in the intensive care unit and has been intubated and sedated. You are asked to consult because of the presence of numerous generalized petechiae and some large ecchymosis on the abdomen and trunk. Laboratory evaluation demonstrates a platelet count of 45 × 109/L, a PT of 15.4 seconds (normal 9.7 to 11.2 seconds), a PTT of 48 seconds (normal 22 to 36 seconds), and a fibrinogen level of 0.87 g/L (normal 2 to 4 g/L).

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

14. A 4-year-old boy is in the intensive care unit and has been intubated and sedated. You are asked to consult because of the presence of numerous generalized petechiae and some large ecchymosis on the abdomen and trunk. Laboratory evaluation demonstrates a platelet count of 45 × 109/L, a PT of 15.4 seconds (normal 9.7 to 11.2 seconds), a PTT of 48 seconds (normal 22 to 36 seconds), and a fibrinogen level of 0.87 g/L (normal 2 to 4 g/L). You have determined this child is experiencing disseminated intravascular coagulation (DIC) caused by acute promyelocytic leukemia.

Which is the most effective therapy to control his DIC?

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; therefore, the correct answer is A. Although 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, but it will not control the DIC either. Treatment of DIC requires treatment of the condition that led to the DIC in the first place.

15. A 5-year-old boy contracts fulminant hepatitis A from contaminated vegetables. He is hospitalized in the intensive care unit with hepatic failure and hepatorenal syndrome necessitating dialysis. The intensive care physician is planning on placing a dialysis catheter and orders a PT and activated PTT (aPTT). The PT is 56 seconds (normal range 9 to 12 seconds), and the aPTT is 99 seconds (normal range 22 to 33 seconds).

Which combination of factor deficiencies is most likely in this scenario?

A. Factors II, V, VIII, and X

B. Factors II, VII, VIII, and IX

C. Factors II, VII, IX, and X

D. Factors VII, VIII, IX, and XI

E. Factors VII, VIII, IX, and von Willebrand factor

**Explanation**

It is important to know the sites of synthesis of all of the clotting factors, particularly in cases of organ failure, so that the correct tests and best therapy (if necessary) can be ordered. The majority of clotting factors are made exclusively in the liver; however, factor V also is made in megakaryocytes, and factor VIII and von Willebrand factor also are made in endothelial cells, making answers A, B, D, and E incorrect. In cases of liver failure, factors II, VII, IX, and X (along with fibrinogen) would be the most affected.

16. Which of the following is a key feature of Facto XIII?

1. Its half-life is about 10 days.
2. It is an important activator of thrombin.
3. Its levels are normal in newborns.
4. It is part of the contact activation system.
5. Low levels result in a prolonged PT and PTT.

Explanation

Factor XIII has some unique properties that differentiate it from the other clotting factors, and a key feature is its very long half-life, making A the correct answer. This is important when considering the management of Factor XIII deficiency. In addition, a deficiency of Factor XIII does not prolong the PT and PTT, making it the only factor deficiency that results in a normal PT and PTT, thus E is incorrect. It is not part of the contact activation system (Factor XI and Factor XII are), and it is activated by thrombin and not vice versa, making D and B incorrect. Lastly, similar to most of the clotting factors, its levels are low in the newborn period, making C incorrect as well.

17. Which of the following characteristics are similar with respect to Factor VIII and von Willebrand factor (vWF)?

1. Both are made in endothelial cells and megakaryocytes.
2. Both are activated by thrombin.
3. They are present in normal to high relative amounts in newborns.
4. They are stored in Weibel-Palade bodies in endothelial cells.
5. A deficiency of either one prolongs the PTT.

Explanation

Factor VIII and vWF circulate as a complex in the blood, and both are present in normal to high amounts in newborns, making C the correct answer. Option A is incorrect because Factor VIII is not made in megakaryocytes, and B is incorrect because vWF is not activated by thrombin. Thrombin cleaves Factor VIII from vWF and activates, but vWF circulates as an active protein, although it stays in a dormant form until it binds to subendothelial collagen. vWF is stored in Weibel-Palade bodies but not Factor VIII, so D is incorrect, and a deficiency of vWF without a concomitant reduction in Factor VIII does not prolong the PTT. A severe enough deficiency, however, will result in low circulating Factor VIII levels because Factor VIII is required to be bound to vWF, so a prolonged PTT can result from the low Factor VIII. The majority of patients with type 1 von Willebrand disease, however, can have a quite low vWF level but a normal Factor VIII level, and therefore their PTT is normal.

18. Which of the following alters the function of thrombin from a procoagulant protein to one that downregulates the formation of fibrinogen?

1. Protein C
2. Protein S
3. Antithrombin
4. Thrombomodulin (\*)
5. Factor V

Explanation

Thrombin is the key enzyme in the coagulation system. Its activation results in numerous prothrombotic steps (activation of Factor VIII to Factor VIIIa, cleaving fibrinogen to fibrin, activating Factor XIII and thrombin activatable fibrinolysis inhibitor); however, thrombin also plays a key role in limiting the coagulation reaction to the site of endothelial disruption. It does so by binding to thrombomodulin, which is a surface protein that is present on intact endothelial cells (ie, ones from whom bleeding is not occurring). This makes option D the correct answer. Although proteins C and S are key regulators of more thrombin generation, their activation is driven by the binding of thrombin to thrombomodulin—they do not in and of themselves alter the function of thrombin, although their activity ultimately does reduce further thrombin generation. Antithrombin does inhibit thrombin by directly binding to it and forming thrombin-antithrombin complexes, which nullify the activity of each, but antithrombin does not alter thrombin’s function, so option C is also incorrect. Factor V serves to activate thrombin and does the opposite of what the question is asking, making option E incorrect.