**Thrombotic Disorders**

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1. A 3,500-g infant girl has neonatal purpura fulminans. Which of the following is the most likely explanation for this condition?

A. Heterozygous protein C deficiency

B. Heterozygous antithrombin deficiency

C. Heterozygous factor V Leiden

D. Homozygous protein C deficiency

E. Homozygous antithrombin deficiency

**Explanation**

A severe inherited prothrombotic state must be considered for any infant presenting with neonatal purpura fulminans. Of the choices, the most likely diagnosis is homozygous protein C deficiency. Heterozygous protein C deficiency, heterozygous antithrombin deficiency, and heterozygous factor V Leiden are all inherited prothrombotic states but are not severe enough to result in neonatal purpura fulminans. Homozygous antithrombin deficiency is not compatible with life.

2. A 10-day-old infant presents with a left-sided abdominal mass and hematuria. A diagnosis of renal vein thrombosis is established. You are consulted and asked whether anticoagulation should be initiated with unfractionated heparin or low-molecular-weight heparin.

Which of the following is an advantage of low-molecular-weight heparin compared with unfractionated heparin in this clinical scenario?

A. Low-molecular-weight heparin is completely reversible with protamine.

B. Low-molecular-weight heparin is renally cleared.

C. Low-molecular-weight heparin is associated with a lower risk for heparin-induced thrombocytopenia.

D. Low-molecular-weight heparin’s mechanism of action is independent of antithrombin.

E. Low-molecular-weight heparin does not require monitoring.

**Explanation**

Heparin-induced thrombocytopenia is an uncommon adverse event associated with anticoagulation in children. The risk is higher for unfractionated heparin compared with low-molecular-weight heparin.

Low-molecular-weight heparin is less effectively reversed by protamine than unfractionated heparin. Low-molecular-weight heparin is renally cleared, but this is a disadvantage in children with renal insufficiency.

Both low-molecular-weight heparin and unfractionated heparin exert anticoagulant effects through antithrombin, and both anticoagulants require monitoring.

3. A 15-year-old girl would like to start oral contraceptives. She is referred to the hematology clinic because of a family history of venous thrombosis and thrombophilia. Her father reports that he developed a pulmonary embolism at age 45 years after reconstructive knee surgery. He reports a diagnosis of protein C and protein S deficiency but no longer takes an anticoagulant.

What is the most appropriate counseling to provide to the family?

A. The father probably has multiple inherited thrombophilias; test the child for protein C and protein S deficiency and do not prescribe oral contraceptives if she is positive for protein C or S deficiency.

B. The father probably has multiple inherited thrombophilias; test the child for protein C and protein S deficiency; initiate anticoagulation and do not prescribe oral contraceptives if she has protein C or S deficiency.

C. The father’s testing was probably influenced by anticoagulation therapy; recommend retesting the father for protein C and protein S deficiency before testing the child.

D. No testing is necessary; the child definitely has at least one inherited thrombophilia, and oral contraceptives should be avoided.

**Explanation**

Interpretation of thrombophilia testing can be confounded by anticoagulation. Warfarin decreases all vitamin K–dependent factors, including proteins C and S. It would be extremely unlikely to co-inherit protein C and protein S deficiency. Acute thrombosis also can cause a transient decrease in natural anticoagulant levels. Therefore, if possible, the father should be retested now that he has stopped anticoagulation. The new test results can guide further discussion of thrombophilia testing with the family. If not possible to retest the father, you could then check Protein C and S in your patient. Even in the setting of a severe inherited protein C or protein S deficiency, anticoagulation would not be initiated for an asymptomatic patient. However, oral contraceptives are contraindicated for patients with known inherited thrombophilia, regardless of whether they have themselves experienced thrombosis.

4. A healthy 17-year-old African American male presents with a right subclavian vein thrombosis. His past medical history is remarkable only for sickle cell trait. The history is negative for recent risk factors for thrombosis (illness, surgery, immobility). He is a pitcher for his high school baseball team.

Which of the following is the most likely risk factor contributing to his thrombosis?

A. Anabolic steroid use

B. Anatomic abnormality

C. Heterozygosity for Factor V Leiden

D. Sickle cell trait

**Explanation**

This adolescent likely has thoracic outlet syndrome. Thoracic outlet syndrome involves compression of the subclavian vein by the cervical rib. Activities such as pitching cause repeated trauma to the vein, resulting in thrombosis. Anabolic steroid use has not been linked to risk of venous thrombosis. Factor V Leiden is rare in African Americans, and heterozygous FVL is very unlikely to present as an unprovoked thrombosis in an otherwise unhealthy patient. The risk of venous thromboembolism with sickle cell trait is elevated about two times over the general population, but the absolute risk is still small and would be unlikely in this clinical scenario of extremity overuse.

5. A 14-year-old boy presents with occlusive deep vein thrombosis from the popliteal veins up through the inferior vena cava to the level of the renal veins. A recommendation is made to initiate thrombolytic therapy with tissue plasminogen activator (t-PA). t-PA is initiated at a dosage of 0.03 mg/kg/hour via a peripheral IV. Unfractionated heparin is administered at 10 U/kg/hour via a separate peripheral IV. The baseline platelet count is 200 × 109/L (normal is 150-450 109/L). After 4 hours, oozing is noted at the peripheral IV sites. Repeat laboratory studies and imaging are performed every 6 hours.

Which of the following complications indicates that thrombolysis should be discontinued?

A. Blood oozing from the line site

B. Fibrinogen less than 100 mg/dL

C. Platelets less than 50,000/mm3

D. Decline in Hb greater than 2 g/dL

E. Elevation of D-dimers

**Explanation**

Patients receiving thrombolysis must be monitored very closely. Oozing from line sites and elevation of D-dimers indicate that thrombolysis is occurring, and the bleeding can be managed with local pressure. Reduced fibrinogen and platelet counts are expected and can be replaced easily. A drop of hemoglobin greater than 2 g/dL in a 24-hour period indicates excessive bleeding, so thrombolysis should be discontinued to assess and correct the bleeding.

6. You are managing a teenage girl on chronic warfarin therapy. Her international normalized ratio (INR) has been stable for the past 6 months but is now 1.4. She denies missing any doses except for the day before her routine lab test, and a pill count suggests that no other doses have been missed.

What is the most likely reason for the drop in INR?

A. She has started to drink alcohol on the weekends.

B. She was prescribed an antibiotic for a sinus infection the week before.

C. She has a gene polymorphism making her resistant to warfarin.

D. She started a new diet this month consisting mostly of fruits and vegetables.

E. She missed the dose the day before the test.

**Explanation**

Because she had never had a problem achieving therapeutic INR in the past, a genetic polymorphism for warfarin resistance is unlikely. This should be considered for children very difficult to anticoagulate initially with anything other than very high dosages of warfarin. Alcohol use and the use of most antibiotics usually increase the INR. Missing one dose of warfarin does not typically decrease an INR between 2 and 3 down to 1.4. Discontinuing warfarin will usually drop the INR to less than 1.5 in 3 to 5 days. Therefore, the most likely reason for this new warfarin resistance is the increase in vitamin K–containing foods in her diet.

7. For which patient is the finding of a low protein S most indicative of an inherited risk factor for thrombosis?

A. A newborn with suspected sepsis

B. An adolesecent female with history of unprovoked deep vein thrombosis who presents for follow-up after completing her course of anticoagulation

C. An adolescent male who was tested while taking warfarin for his recent deep vein thrombosis

D. A patient in the emergency room whose radiologic testing has just revealed a massive pulmonary embolism

E. A pregnant adolescent undergoing thrombophilia evaluation because of a family history of thrombosis

**Explanation**

Newborns have naturally low levels of protein S. Warfarin also lowers protein C and protein S activity. Pregnancy causes low protein S levels. Acute thrombosis also lowers the levels of all natural anticoagulants. Therefore, a finding of low protein C or protein S in any of these settings would need to be repeated (eg, at an older age, after pregnancy) to confirm the diagnosis. The adolescent female who is off therapy at the time of testing likely does have Protein S deficiency, especially given the history of unprovoked thrombosis.

8. A 5-year-old girl is referred to hematology before a tonsillectomy and adenoidectomy. Preoperative testing by her ENT surgeon revealed a prolonged partial thromboplastin time (PTT). Although the patient’s mother has a history of postpartum thrombosis, there is no personal or family history of easy bruising or bleeding. You suspect a lupus anticoagulant (LA) as the cause of the prolonged PTT.

Which of the following is a true statement about LAs?

A. The prolonged PTT will correct after the addition of factor VIII.

B. The prolonged PTT will correct with 1:1 mixing with normal plasma.

C. Most patients with an LA have systemic lupus erythematosus.

D. The PTT will correct if excess phospholipid is added to the plasma before the clotting time test is performed.

E. Lupus anticoagulant is an inherited thrombophilia.

**Explanation**

The LA is characterized by a prolonged PTT that does not correct on 1:1 mixing with normal plasma. The LA is caused by an antiphospholipid antibody that binds the phospholipid in the PTT. Excess phospholipid neutralizes the antibody and allows the reaction to proceed. The LA can occur in otherwise well children after a viral illness. LA is an example of an acquired thrombophilia, not an inherited thrombophilia.

9. A 17-year-old boy with newly diagnosed T-cell acute lymphoblastic leukemia (ALL) has been admitted for induction chemotherapy. You are considering whether to initiate thromboprophylaxis during the hospitalization.

Which of the following statements is true about the risk of thrombosis in ALL?

A. T-cell ALL has a lower risk of thrombosis than B-cell ALL.

B. Adolescent patients have a higher risk of thrombosis than younger patients with ALL.

C. The risk of thrombosis will be stable throughout the planned course of therapy.

D. Placing a peripherally inserted catheter (PICC) line in lieu of a central indwelling catheter will minimize the risk of thrombosis.

E. The risk will be increased during times of asparaginase administration because of transient increases in protein S activity.

**Explanation**

T-cell ALL has a higher risk of thrombosis than B-cell ALL. Among pediatric patients with ALL, adolescent patients have the highest risk of thrombosis compared with other age groups. The risk of thrombosis is increased during induction because of active cancer and the use of steroids and asparaginase. Some studies suggest the risk of thrombosis increases with PICC lines. Asparaginase increases the risk of thrombosis because of transient decreases in antithrombin III.

10. A 2-year-old boy with congenital heart disease is admitted for cardiac catheterization and subsequent cardiac surgery. The day after surgery, his course is complicated by a right femoral line–related deep vein thrombosis. Unfractionated heparin is chosen for his anticoagulant therapy because of his recent major surgery, and partial thromboplastin time tests (PTTs) have been in the therapeutic range. Six days later, the right thigh has increased swelling, and repeat ultrasound shows extension of the femoral thrombosis into the iliac vein. Platelet count is noted to be 48,000/µL; before surgery the platelet count was 275,000 IU/mL. He is otherwise stable and afebrile.

What is the most appropriate recommendation?

A. Increase the dosage of unfractionated heparin.

B. Check anti-Xa level to ensure that the unfractionated heparin dosage is therapeutic.

C. Evaluate for disseminated intravascular coagulation.

D. Initiate systemic thrombolytic therapy.

E. Discontinue unfractionated heparin and initiate bivalirudin.

**Explanation**

This patient has suspected heparin-induced thrombocytopenia (HIT). Answers A and B are incorrect because unfractionated heparin should be discontinued in the setting of suspected HIT, although anti-Xa is a more accurate method of measuring the effects of heparin. The patient is afebrile and otherwise stable, so disseminated intravascular coagulation is unlikely. Thrombolysis is contraindicated given the recent major surgery.

11. An obese 16-year-old girl presents to the emergency room with chest pain and shortness of breath. A CT scan of the chest reveals a pulmonary embolism. Upon taking additional history, the physician learns that the patient has irregular, heavy menstrual periods and was started on estrogen-containing oral contraceptive pills (OCPs) approximately 2 months ago. Low-molecular-weight heparin is initiated, and the patient is admitted to the hospital.

Which of the following statements is true regarding the association between thrombosis and use of estrogen-containing OCPs?

A. The OCPs are unlikely to be related to her thrombosis, because she just started this medication.

B. The risk of venous thromboembolism (VTE) due to OCPs is similar to that seen during pregnancy.

C. OCPs increase the risk of thrombosis due to an increase in protein S activity.

D. All hormonal contraceptive agents are now contraindicated for this patient.

E. Obesity is an independent risk factor for thrombosis in women using estrogen-containing hormonal contraception.

**Explanation**

OCPs increase the risk of VTE, stroke, and acute myocardial infarction. OCPs shift the balance of the hemostatic system toward a procoagulant state by several mechanisms, including a decrease in protein S activity and an increase in activated protein C resistance. OCPs increase the risk of VTE about fivefold, but this risk is still smaller than the risk with pregnancy. Most OCP-related VTE occurs in the first year of use, particularly in the first 3 months of use. Most teens who develop OCP-related thrombosis have additional risk factors such as obesity or family history of thrombosis. Even in adults, smoking, age, and obesity are independent risk factors for VTE in women who use OCPs. Although estrogen-containing contraceptives would now be contraindicated in this patient, there are many progestin-only alternatives that she can safely use.

12. A 17-year-old girl is referred to the hematology clinic for education and counseling regarding Factor V Leiden (FVL). She was tested by her gynecologist before initiating hormonal contraception for heavy menstrual bleeding and was found to be heterozygous for FVL. There is no family history of thrombosis in first-degree relatives.

Which of the following are true regarding the diagnosis of heterozygous Factor V Leiden?

A. FVL is a mutant form of coagulation factor V, which renders factor V insensitive to actions of protein S, a natural anticoagulant.

B. Approximately 5% of patients with heterozygous FVL will develop venous thromboembolism (VTE) in their lifetime.

C. The risk of arterial thrombosis is greater than the risk of venous thrombosis in patients with FVL.

D. Women should be counseled that they will need to receive prophylactic anticoagulationin the event of pregnancy.

E. Because of the negative family history of thrombosis, there is no contraindication to estrogen-containing contraceptives.

**Explanation**

FVL is the most common inherited thrombophilia, occurring in 5% of Caucasians and 1% to 2% of other ethnic groups. FVL is a mutant form of coagulation factor V, which renders factor V insensitive to actions of protein C, a natural anticoagulant. Heterozygous FVL increases the risk of VTE approximately fourfold. However, the risk of arterial thrombosis is much lower. It is a mild thrombophilia, and 95% of patients with heterozygous FVL never develop VTE. Guidelines do not recommend anticoagulation during pregnancy or post-partum for asymptomatic women with heterozygous FVL. However, current guidelines still recommend that progestin-only contraceptives be used as first-line therapy for such patients, with estrogen-only considered in special circumstances or when progestin-only contraceptives are not efficacious.

13. A healthy 16-year old boy presents to the emergency room with 2 days of swelling and pain of his left lower extremity. An ultrasound of the left lower extremity reveals an ileofemoral venous thrombosis, and he is admitted to the hospital. Medical history reveals no chronic health conditions and no recent risk factors for thrombosis such as surgery, injury, or immobility. There is no maternal family history of thrombosis, but paternal history is unknown.

Which of the following statements is true regarding the recommended evaluation and management of this patient?

A. Local thrombolysis is the first-line therapy because of the extensive nature of this venous thrombosis.

B. Systemic thrombolysis is the first-line therapy because of the extensive nature of this venous thrombosis.

C. Compression stockings should be prescribed to minimize the risk of post-thrombotic syndrome in this high-risk patient.

D. This patient should undergo additional radiologic imaging to evaluate for an anatomic abnormality.

E. An evaluation for protein C and protein S should be performed during this admission for this patient with an idiopathic thrombosis and limited family history.

**Explanation**

The relative risk/benefit ratio of thrombolysis in the management of deep vein thrombosis (DVT) remains unclear, and traditional anticoagulation is still recommended as first-line therapy, although thrombolysis can be considered on an individual-patient level based on the size and clinical impact of the DVT. Compression stockings are used to treat symptoms of DVT and post-thrombotic syndrome but have not been shown to reduce the risk of developing post-thrombotic syndrome. Anatomic abnormalities such as May-Thurner syndrome (narrowed left iliac vein) and ileofemoral venous thrombosis atresia and abnormalities must be considered for a patient with this presentation and lack of other obvious risk factors. An inherited thrombophilia (probably a major one such as protein C or protein S deficiency) should also be considered for this patient but should be performed at a later time. Protein C and Protein S are likely to be decreased due to consumption at the time of presentation because of the extensive nature of this patient’s thrombosis.

14. A 6-year-old boy with newly diagnosed acute lymphoblastic leukemia is in the intensive care unit because of severe tumor lysis syndrome. He develops discomfort and swelling in the extremity in which his central venous line was placed. Ultrasound confirms an acute thrombosis of the right subclavian vein. You are weighing the advantages and disadvantages of using unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for this critically ill patient.

Which of the following statements is true?

A. LMWH has a shorter half-life than UFH.

B. LMWH is preferred because of this patient’s increased risk of renal dysfunction.

C. LMWH cannot be reversed with protamine.

D. The PTT can be used to monitor LMWH more closely in a critical care setting.

E. The risk of heparin-induced thrombocytopenia would be higher if LMWH is used.

**Explanation**

LMWH has a longer half-life than UFH. It must be used with caution for patients with renal dysfunction because of the risk of bioaccumulation. It can be partially reversed with protamine. LMWH can be monitored only by anti-Xa levels. Although the evidence is of poor quality, it seems that the risk of heparin-induced thrombocytopenia is lower for patients receiving LMWH as compared with UFH.

15. You receive a phone call that a 3-year-old patient on long-term warfarin therapy for congenital heart disease has an international normalized ratio (INR) of 5.8. On further history, you learn the patient and several family members have had recent gastrointestinal illnesses, but the patient is recovering. His mother reports he is not experiencing bleeding symptoms.

Which of the following interventions would be most reasonable in this clinical scenario?

A. Hold 1 to 2 doses of warfarin and recheck INR

B. Administer oral vitamin K therapy

C. Administer fresh frozen plasma (FFP)

D. Administer recombinant factor VIIa

E. Administer prothrombin complex concentrates (PCCs)

**Explanation**

Holding warfarin is a reasonable approach for this patient who is not bleeding, is at low risk of subsequent bleeding, and is recovering from his gastrointestinal illness. Vitamin K reverses the action of warfarin but can lead to over-correction. Fresh frozen plasma (FFP) and prothrombin complex concentrates (PCCs) contain vitamin K–dependent proteins but are only indicated in patients with active bleeding or when urgent reversal is required (eg, need for emergency surgery). Evidence does not indicate that recombinant factor VIIa is an effective antidote for warfarin, and this intervention is also associated with a high risk of thrombosis.

16. A healthy 17-year-old African American male presents with a thrombosis of the right upper extremity. His past medical history is remarkable only for sickle cell trait. The history is negative for recent risk factors for thrombosis (illness, surgery, immobility). He is the pitcher for his high school baseball team. Imaging confirms anatomical compression/narrowing of the right subclavian vein.

Which of the following interventions is most likely to decrease this patient’s long-term risk of recurrent thrombosis?

A. Systemic thrombolysis

B. Catheter-directed thrombolysis

C. Extended 12-month course of anticoagulation with low-molecular-weight heparin (LMWH)

D. Resection of right first rib

E. Use of compression sleeve during baseball practices and games

**Explanation**

Although thrombolysis may reduce the risk of post-thrombotic syndrome, there is not evidence that it decreases the risk of recurrent venous thromboembolism (VTE). Likewise, there is also not evidence that 12 versus 3 to 6 months of anticoagulation would reduce risk of long-term recurrence. This patient has an anatomic abnormality (thoracic outlet syndrome) and will continue to be at risk of VTE recurrence unless the abnormality is surgically corrected. Use of a compression sleeve can help alleviate symptoms of post-thrombotic syndrome and improve circulation during activity but will not reduce risk of VTE.

17. A 16-year-old female presents to the emergency room with a new complaint of chest pain. When performing a review of systems and physical examination, which of the following would substantially decrease your suspicion for a diagnosis of pulmonary embolism?

A. Cough

B. Fever

C. Rib tenderness

D. Shortness of breath

E. Normal pulse oximetry

**Explanation:**

Shortness of breath and chest pain are the most common symptoms of pulmonary embolism. Cough and/or fever would make you suspect infection more but are also seen in pulmonary embolism, so the diagnosis would still need to be considered in the differential. Hypoxia can be seen in patients with pulmonary embolism, but most patients will have normal oxygen saturations. Point tenderness of the costal cartilages is highly suggestive of costochondritis, which is one of the most common causes of chest pain in teenagers.

18. The pathophysiology of venous thrombosis is often explained by Virchow’s triad, which includes hypercoagulability, endothelial injury, and venous stasis. Based on Virchow’s triad and your knowledge of risk factors for thrombosis, which of the following pediatric patients has the greatest risk of hospital-acquired venous thromboembolism?

A. 3-day-old full-term infant admitted to hospital pediatrics for hyperbilirubinemia

B. 6-month-old male admitted to the infectious disease unit for respiratory syncytial virus

C. Ex-28 week premature infant, requiring NICU-level care for necrotizing enterocolitis

D. 7-year-old male with acute lymphoblastic leukemia receiving maintenance chemotherapy admitted to hematology/oncology unit for fever and neutropenia

E. 17-year-old male admitted to the ENT unit for postoperative bleeding and dehydration after recent tonsillectomy

**Explanation**

The correct answer is C. Premature infants have among the highest rates of venous thromboembolism (VTE). This patient requires intensive care and would have a central line in place as well as inflammation. The other patients do not requiring critical care, and the patients described in options A, B, and E would not have a central line in place, which is the most important risk factor for VTE in pediatrics. The patient described in option D does likely have a central line, but cancer would be in remission at this point, he is not critically ill, and he would not be receiving asparaginase while in maintenance phases of chemotherapy.