**Congenital and Acquired Hemolytic Anemia**

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1. A previously healthy 15-year-old girl presents with 3-day history of fever, abdominal pain, fatigue, and pallor and 1 day of severe headache. She is a vegetarian and has had no diarrhea. Family history is negative. Lab studies reveal Hb 7.1 g/dL, reticulocytes 14%, platelets 60,000/mm3, and normal WBC count and differential. The PT and PTT are normal. The peripheral smear features numerous schistocytes. Other labs include indirect bilirubin 1.9 mg/dL, LDH 1,400 U/L, and creatinine 1.1 mg/dL; urine pregnancy test is negative.

Which of the following would be the best management choice for this patient?

A. Send and wait for ADAMTS13 enzyme and inhibitor studies. This could be thrombotic thrombocytopenic purpura (TTP), and the etiology should be proven before initiation of therapy.

B. Microangiopathy and thrombocytopenia suggest disseminated intravascular coagulation (DIC); therefore, admit the patient to the ICU for supportive care and launch a search for etiology (eg, infection or malignancy).

C. Initiate treatment for TTP immediately with plasmapheresis (with or without concomitant steroids) because the diagnosis of TTP is clinical, and the disorder can be life threatening. Do not wait for ADAMTS13 results to start treatment.

D. Follow renal function and provide supportive care for hemolytic-uremic syndrome (HUS), which is more common than TTP in pediatric patients, and initiate a search for *E. coli* O157:H7 strains, which produce HUS-inducing toxins.

E. Transfuse for symptomatic anemia but only after saving blood for enzymatic studies because congenital hemolytic anemia is likely.

**Explanation**

Answer C is correct. This scenario is typical for TTP, which can be life threatening. In this case, primary antibody-mediated TTP is likely because there is no history of drugs, pregnancy, or congenital causes.

Answer A is incorrect because the screening tests for the antibody to the von Willebrand cleaving protease, ADAMTS13, and the functional consequences of the antibody (low levels) are not available rapidly enough to be used for real-time diagnosis.

Answer B is incorrect because the normal PT and PTT rule out DIC, although the peripheral smear cannot necessarily be differentiated.

Answer D is incorrect as a management strategy, although it is true overall in pediatrics that HUS is more common than TTP. In postpubertal patients with no clinical exposures to suggest HUS, it is prudent to consider TTP immediately, and in variant cases to pursue supportive studies even as pheresis and steroids are begun.

Answer E is incorrect because the clinical scenario does not suggest a chronic hemolytic disorder.

2. A 17-year-old girl with no significant past medical history presents after her pediatrician notes that her lips are blue at an annual checkup. Oximetry readings are 84% saturated in room air. A quick emergency room visit leads to the following data: Hb 15.3 g/dL, reticulocyte count 2.1%, and Pao2 98 mm Hg by blood gas machine. The lab tech reports her blood is chocolate-brown in color, and methemoglobin by co-oximetry is 12% (normal is less than 1%). The peripheral smear reveals normal morphology. She works at an ice cream parlor.

Which of the following statements is true about this scenario?

A. The markedly elevated methemoglobin could be due to either a congenital deficiency of cytochrome b5 reductase or surreptitious use of nitrous oxide or other nitrates, to which she may have access at her job.

B. The role of the cytochrome reductase is to keep hemoglobin in its oxidized (Fe3+) state.

C. Hemoglobin M rarely presents as cyanosis.

D. High-affinity hemoglobins must be kept in the differential diagnosis of methemoglobin.

E. Low-affinity hemoglobins cause not only cyanosis but also poor tissue oxygenation.

**Explanation**

Answer A is correct. The differential diagnosis for methemoglobinemia includes drugs, defects in the system that keeps hemoglobin reduced (not oxidized), and abnormal hemoglobins that oxidize spontaneously. Whipped cream pressurized canisters at ice cream stores are propelled by nitrous oxide cartridges (“whippets”), which can be abused as a recreational drug.

Answer B is incorrect because the reductase helps keep hemoglobin in its reduced, Fe2+ state. Answer C is incorrect because hemoglobin M often causes cyanosis (although it is a rare disease). Answer D is incorrect because high-affinity hemoglobins cause poor tissue oxygen delivery, but the blood is very red and cyanosis is not seen. Answer E is only half right. Cyanosis may be found with some low-affinity hemoglobins, but tissue oxygen delivery is generally adequate at the capillary-tissue boundary because of low affinity.

3. A 3-year-old girl has had transfusion-dependent anemia since age 6 months. She is found to have an unstable hemoglobin by sequence analysis (Hb Hammersmith). She has obvious bony deformity from extramedullary hematopoiesis and marked splenomegaly. Her hemoglobin is 7 g/dL 4 weeks after a transfusion, and her reticulocyte count is 18%.

Which of the following statements is correct?

A. As in hereditary spherocytosis, anemia will be entirely ameliorated by splenectomy, and her gallstone risk will be reduced.

B. After splenectomy, she will no longer be at risk for gallstones.

C. This diagnosis could have been made by newborn screening (by electrophoresis, isoelectric focusing, or high-performance liquid chromatography), just as can be done with sickle trait, C trait, and other beta-hemoglobinopathies.

D. A decision about splenectomy should take into account growth status, transfusion requirements, interval change in spleen size, and potential long-term risks of infection and thrombosis.

E. Heinz bodies are nuclear remnants that increase in all hemolytic anemias.

**Explanation**

Answer D is correct because an unstable hemoglobin will result in both intravascular and extravascular hemolysis. Splenectomy will decrease extravascular hemolysis but not intravascular hemolysis.

Answer A is incorrect for unstable hemoglobins and for most hemolytic states except hereditary spherocytosis. However, transfusion requirements and growth problems may be partially ameliorated by splenectomy. Answer B is incorrect because splenectomy will only partially ameliorate the hemolysis, and so she will remain at risk for gallstones, although this risk will probably be lowered by splenectomy. Answer C is incorrect on two fronts. First, the amino acid substitution Hb Hammersmith is isoelectric (no change in charge), so it may not be distinguishable by some newborn screening methods. In addition, very unstable hemoglobins are hard to detect in the periphery, particularly when beta-globin is at a lower quantity in the newborn period. Answer E is incorrect. Howell-Jolly bodies are nuclear remnants. Heinz bodies are precipitated hemoglobin, seen only with supravital stains.

4. A previously healthy 5-year-old boy has sudden onset of dark urine, pallor, and tachycardia a week after a respiratory illness with pronounced cough and low-grade fever, treated with azithromycin. On presentation, his hemoglobin is 5.5 g/dL, reticulocytes 12%, bilirubin 5.2 mg/dL, with direct fraction 0.3 mg/dL. His direct antiglobulin test (DAT) is positive for complement C3 and negative for IgG. You suspect either cold agglutinin disease or a Donath-Landsteiner antibody (paroxysmal cold hemoglobinuria [PCH]). The blood bank receives a warm blood sample to evaluate, in which they find a “cold-reacting IgG of high thermal amplitude,” which fixes complement upon warming.

Which of the following statements is correct about this case?

A. Because this is not a cold agglutinin, there is no need to use a blood warmer, and cold will not be a factor for the patient upon discharge.

B. Donath-Landsteiner antibodies are readily removed by plasmapheresis.

C. The DAT (Coombs) reagent must be defective if the IgG cannot be detected on the cells, because the blood bank found it there on the specific testing.

D. PCH in children nearly always resolves spontaneously and may not respond well to steroids.

E. Extravascular hemolysis is the rule in PCH and leads to impressive splenomegaly in some cases.

**Explanation**

Answer D is correct because the patient has PCH due to the presence of a Donath-Landsteiner antibody. PCH is an autoimmune hemolytic anemia causing complement-mediated intravascular hemolysis. PCH is usually transient and self-limited.

Answer A is incorrect because cold-reacting IgGs do bind better in the cold and will fix complement when they get warm centrally. Fastidious attention to warming the extremities and the blood will help. Answer B is incorrect because IgGs distribute in extravascular space as well as intravascular. Thus, IgM is easy to remove by pheresis, but IgG is much less so. Answer C is incorrect because this lab scenario defines the Donath-Landsteiner antibody. DAT reagents are used at room temperature, and if all the coated cells have lysed from complement, the cells will not agglutinate with the Coombs reagent. Answer E is incorrect because the hemolysis in this circumstance (in contrast to most IgGs, which do not fix complement well) is often entirely intravascular, and the spleen may not be involved or enlarged.

5. A 2-year-old boy is evaluated for apparent ongoing hemolysis. His hemoglobin is 9.5 g/dL, with 7% reticulocytes and MCV 87 fL. Platelets and leukocytes are normal. His direct antiglobulin test (DAT) is negative. No cold agglutinin is detectable. His family history is negative for blood disorders. Peripheral smear reveals numerous stomatocytes and mild polychromasia.

Given these findings, which of the following blood group disorders should be evaluated in this patient?

A. Rh D negative but C positive

B. Duffy A negative

C. Rh null

D. Lewis X positive

E. Blood group “I” reactive

**Explanation**

Answer C is correct. Rare patients do not express any Rh proteins and type as Rh negative. The lack of the Rh antigens altogether changes the red cell shape, causing characteristic DAT-negative hemolysis and stomatocytes on the smear. This is a recessive disorder. The other surface antigens in answer options A, B, and D are not related to DAT-negative hemolytic anemia. The I blood group is a target of cold agglutinins, not present here, so E is incorrect.

6. A 2-week-old boy is so pale that his pediatrician orders a CBC, which reveals Hb 6 g/dL, reticulocyte count of 2%, and MCV 99 fL. The mean corpuscular hemoglobin concentration (MCHC) is mildly elevated at 37 g/dL. The smear has a few spherocytes, moderate anisocytosis, and some poikilocytosis. He was mildly jaundiced as a newborn, with maximum bilirubin 12 mg/dL, and no blood type mismatch setup was noted (mother and patient O negative). The bilirubin is now normal, as are the WBC, differential, and platelet counts. The child otherwise seems to be thriving. Family history is negative.

Which of the following statements about this scenario is correct?

A. This cannot be hereditary spherocytosis (HS) because the reticulocyte count is too low to support a diagnosis of hemolysis.

B. This cannot be HS because the jaundice history is much too mild.

C. This has a good chance of representing HS during the neonatal “physiologic nadir” period, when reticulocyte production is decreased.

D. He should undergo a nonincubated osmotic fragility test right away, before getting a transfusion.

E. Testing the parents should confirm or rule out HS in this case.

**Explanation**

Answer C is correct. Pronounced anemia a couple of weeks after birth is very common in HS for reasons that are not entirely clear. The mutation need not be severe to cause this effect.

Answer A is incorrect because the nadir renders reticulocyte counts useless for several weeks, dropping to near zero. Answer B is incorrect because the kinetics of newborn jaundice vary from individual to individual. Answer D is incorrect because the incubated test is much more sensitive, and the test has poor predictive characteristics in the newborn period compared with a few months later. Answer E also is incorrect. About one-third of patients with HS have “new mutations,” so testing the family may not suffice.

7. A 12-year-old boy with a history of idiopathic thrombocytopenic purpura (ITP) 3 years ago presents with 2-week history of fatigue and pallor and is found to have tachycardia and splenomegaly. He otherwise has been well with a normal diet. His labs include a hemoglobin of 6 g/dL, MCV 97 fL, platelets 68,000/mm3, LDH 1,100 U/L, uric acid normal, and minimally elevated indirect bilirubin 2 mg/dL. The reticulocyte count is 15%. The smear shows polychromasia but no schistocytes, teardrops, or blasts and no hypersegmented polys. Some giant platelets are seen. His direct antiglobulin test (DAT) is positive for IgG. His ITP responded promptly to 5 days of prednisone.

Which of the following statements is most likely to be true about this patient?

A. He should have a bone marrow test to rule out leukemia, at least before he receives steroids.

B. The macrocytosis suggests a primary nutritional or bowel absorption problem.

C. His apparent autoimmune hemolytic anemia (AIHA) is likely to respond to prednisone, but the kinetics of response may be different for red cells and platelets, and higher dosages and longer coursees of treatment are indicated for the AIHA than when he had isolated ITP in the past.

D. This cannot be due to a mutation in the Fas system (ie, autoimmune lymphoproliferative syndrome [ALPS]) because he has no massive adenopathy.

E. The AIHA is likely to be short-lived and self-resolving, and no therapy is necessary.

**Explanation**

Answer C is correct. This is a case of Evans syndrome marked by AIHA and autoimmune platelet destruction. Both forms of autoimmune destruction may respond to steroids; however, short courses (eg, 5-7 days) of steroids are used in ITP, whereas long steroid tapers (eg, 3-6 months) are necessary in AIHA.

Answer A is incorrect. Most hematologists would take a positive DAT and reassuring peripheral blood film as evidence against leukemia in this clinical setting. Answer B is incorrect because, although folate and B12 deficiency are theoretically possible, the history and smear findings do not support these as likely primary problems. Answer D is based on the clinical versus mutation analyses of patients with ALPS. Fas pathway mutations are common in Evans syndrome, even when overt adenopathy or other problems of ALPS are not present. Most patients with Evans syndrome have an underlying immunodeficiency. Answer E is incorrect because, in contrast to paroxysmal cold hemoglobinuria, warm AIHA associated with Evans syndrome is often protracted and warrants immunosuppression for months or longer.

8. The second child of a woman whose first infant was jaundiced at birth has evidence of hydrops in utero at 35 weeks. The child is delivered urgently and found to have ascites and severe anemia, with hemoglobin of 6 g/dL and 100 NRBCs/100 WBCs. Both child and mother are typed as “O positive,” but the mother has a circulating anti-e antibody, and genotyping reveals that mother is E/E and the infant is E/e. The child is transfused slowly with crossmatch-compatible O negative blood (e/e).

Which of the following is true about this scenario?

A. Prophylactic anti-D globulin (Rhogam or WinRho) during pregnancy could have prevented this hemolytic disease of the newborn.

B. The anemia and transfusion requirements could continue for 9 months or longer.

C. There is a 25% chance of chronic anemia.

D. Almost invariably, the anemia will be resolved by a few months of age.

E. The child has a 50% chance of having the same problem when she has children.

**Explanation**

Answer D is correct. Maternal antibodies acquired passively across the placenta are nearly always gone or clinically insignificant by age 3 months because they are being constantly cleared on the infant’s red cells.

Answer A is incorrect. Anti-D does not protect against variants in Rh, Ee, or Cc systems, and anti-D is not indicated in RhD+ mothers. Answer B is incorrect because antibody-mediated hemolysis in this scenario lasting 9 months is extremely unlikely. Answer C is incorrect because hemolytic disease of the newborn does not lead to chronic anemia in and of itself. Answer E is incorrect. The child is heterozygous, so the E/e system will not be a problem for her children.

9. A 13-year-old boy with pyruvate kinase deficiency had symptomatic anemia with a hemoglobin of 7 g/dL and progressive splenomegaly over a few years. He received transfusions periodically with infectious illnesses. Splenectomy was then performed at age 10 years. Now his lab studies reveal Hb 8.7 g/dL, reticulocytes 32%, and LDH 246 U/L. His energy has improved, and he has not been transfused since splenectomy.

Which of the following is true about pyruvate kinase deficiency?

A. Marked reticulocytosis is rare because splenectomy completely corrects hemolysis.

B. The biochemical lesion in the glycolytic pathway decreases 2,3-bisphosphoglycerate (2,3-DPG), which increases oxygen affinity and decreases tissue oxygenation.

C. Infection risk is lower in pyruvate kinase deficiency after splenectomy than in patients splenectomized for other reasons because of the biochemical lesion.

D. Splenectomy alleviates the risk of parvovirus aplastic crisis.

E. Monitoring for iron overload is necessary even in the absence of transfusions.

**Explanation**

Answer E is correct. Patients with congenital hemolytic anemias, including pyruvate kinase deficiency, are at risk for iron loading even in the absence of transfusions. Therefore, regular monitoring with ferritin levels or MRI studies is needed.

Answer A is incorrect because marked reticulocytosis is common, especially after splenectomy in this disorder. Answer B is incorrect because the biochemical lesions causes an increase in 2,3-DPG, which decreases oxygen affinity and increases tissue oxygenation. Answer C is incorrect because he infection risk is not lower in this disorder after splenectomy. Answer D also is incorrect. Unlike spherocytosis, hemolysis remains significant after splenectomy, although anemia is ameliorated. Parvovirus infection can still cause aplastic crisis.

10. A 2-year-old boy has had pallor since birth. Spasticity was first noted upon physical examination at 2 months of age, and hemolysis was first noted at 6 months of age, along with Hb 8.9 g/dL; reticulocyte count 7%; negative direct antiglobulin test; and numerous dense, speculated cells noted on peripheral smear. The pregnancy was uncomplicated, and the parents were unrelated and from a geographically isolated region of Spain. Progressive neuromuscular decline has been the patient’s main clinical problem, with intermittent infections, including pyelonephritis and pneumonia.

Which of the following enzyme disorders is the most likely candidate for the patient’s disease?

A. Triose phosphate isomerase (TPI) deficiency

B. Pyruvate kinase (PK) deficiency

C. Glucose-6-phosphate dehydrogenase deficiency

D. Pyrimidine 5′-nucleotidase deficiency

E. Hexokinase deficiency

**Explanation**

Answer A is correct. TPI is an enzyme in the Embden-Meyerhof pathway, catalyzing the interconversion of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. Deficiency of TPI is a rare autosomal disorder, characterized by hemolytic anemia, neonatal hyperbilirubinemia, progressive neuromuscular dysfunction, increased susceptibility to infection, and cardiomyopathy. The other forms of hemolytic anemia listed (answer options B, C, D, and E) are not associated with neurologic features or increased risk of infection in the absence of splenectomy. PK converts phosphoenolpyruvate to pyruvate in the glycolytic pathway. PK deficiency (answer option B) is the most common cause of hemolytic anemia due to defective glycolysis and is inherited as an autosomal recessive disorder without neuromuscular disease. Glucose-6-phosphate dehydrogenase deficiency (option C) is inherited as an X-linked disorder and is necessary for the production of nicotinamide adenine dinucleotide phosphate (NADPH) in the hexose monophosphate shunt. NADPH is used for production of glutathione, which helps prevent oxidative damage to erythrocytes. Pyrimidine-5′-nucleotidase participates in RNA degradation in reticulocytes. Deficiency of pyrimidine-5′-nucleotidase (option D) is inherited in an autosomal recessive manner and is associated with the presence of basophilic stippling in the erythrocytes. Lead is also a powerful inhibitor of pyrimidine-5′-nucleotidase and also is associated with basophilic stippling on the peripheral smear. Hexokinase deficiency (option E) is a rare autosomal recessive disorder associated with variable degrees of hemolysis.

11. An 18-year-old exchange student from Hong Kong develops sudden onset of icterus and pallor after eating dinner at a falafel food truck. He reports dark urine and fatigue. In the emergency department, he is noted to be anemic and has a high reticulocyte count. The resident in the emergency department sends a screening test for G6PD deficiency, and it is reported as normal.

Which of the following statements is correct?

A. A slide of his peripheral blood probably shows blister cells and spherocytes.

B. He probably has pyruvate kinase (PK) deficiency, in which red cells are susceptible to oxidative stress.

C. The oldest red cells have the highest G6PD activity, and therefore, in an acute hemolytic setting, a G6PD screen may be normal.

D. The patient could not have G6PD deficiency because he would have had symptoms previously.

E. If the G6PD screening test had been sent closer to the acute episode, it would have been more likely to show G6PD deficiency.

**Explanation**

Answer A is correct. This patient is experiencing an acute hemolytic episode due to exposure to fava beans in the setting of a class II or III G6PD deficiency. In the presence of oxidative stress, G6PD deficiency is associated with a fall in nicotinamide adenine dinucleotide phosphate, a cofactor in glutathione metabolism. During an acute hemolytic episode, patients with G6PD deficiency will classically have abnormal red cell morphology, including blister cells and spherocytes.

Answer B is incorrect because food triggers such as fava beans do not cause increased hemolysis in PK deficiency. Answers C and E also are incorrect. When G6PD enzyme activity is measured, the testing may lead to falsely normal levels if performed at the time of hemolysis because reticulocytes and young red cells have the highest G6PD activity levels. Except in class I deficiency (associated with a chronic congenital hemolytic anemia), hemolysis in G6PD deficiency is episodic, with no evidence of hemolysis between episodes. Answer D is wrong because some people are unaware of this diagnosis until an acute exposure and may present later in life. PK deficiency causes a congenital chronic hemolytic anemia, although infections can cause acute episodes of hyperhemolysis.

12. A 14-year-old healthy girl presents with isolated splenomegaly and mild scleral icterus. She reports worsening scleral icterus with exercise. Her labs reveal a hemoglobin of 14 g/dL, MCV 97 fL, reticulocyte count 12%, and an elevated indirect bilirubin of 2.4 mg/dL with otherwise normal CBC and LFTs. Her blood smear shows stomatocytes and target cells. Her incubated osmotic fragility test is consistent with decreased fragility.

Which of the following statements is correct?

A. These labs are most consistent with a diagnosis of hereditary spherocytosis due to an ankyrin mutation.

B. Her high/normal hemoglobin likely is related to increased 2,3-bisphosphoglycerate (2,3-DPG) levels with increased oxygen offloading into the tissues.

C. She should avoid fava beans because of the risk of hemolysis from oxidative stress.

D. She likely has hereditary xerocytosis due to a PIEZO1 or KCNN4 mutation.

E. Splenectomy should be considered to improve her anemia and exercise tolerance.

**Explanation**

Answer D is correct. This patient has a hemolytic process associated with a normal/high hemoglobin, decreased osmotic fragility, and stomatocytes. These findings are most consistent with a stomatocytosis syndrome, such as hereditary xerocytosis (HX). HX is associated with macrocytosis and an increased mean corpuscular hemoglobin concentration (MCHC). Decreased osmotic fragility is caused by a defect in cation permeability. HX is most commonly caused by mutations in the PIEZO1 gene (cation channel) or KCNN4 gene (Gardos channel), leading to intracellular potassium and water loss and dehydrated red cells.

Answer A is incorrect because her morphology and incubated osmotic fragility test findings are not consistent with hereditary spherocytosis, in which one would expect spherocytes and increased osmotic fragility. Answers B is incorrect. The high/normal hemoglobin seen in many of these patients is thought to be caused by decreased 2,3-DPG associated with decreased oxygen offloading in the tissues. Answer C is incorrect because HX red cells are not sensitive to fava beans, as is seen in G6PD deficiency. Answer E is incorrect because splenectomy is relatively contraindicated in HX because of the high risk of thrombosis after splenectomy.

13. A 29-week premature infant in the NICU develops worsening respiratory distress, hypotension, and abdominal distension 1 week after birth. He had a normal hemoglobin and platelet count at birth, but you are consulted for new onset anemia, with hemoglobin of 7.3 g/dL and hemoglobinuria. White count is elevated. The platelet count is 90 × 109/L. PT and PTT are both elevated for age. The peripheral smear reveals numerous spherocytes, left-shifted neutrophils, and large platelets. Schistocytes and teardrop cells are absent. The patient is ill-appearing and febrile to 39 ºC, and there is a concern about necrotizing enterocolitis.

Which of the following is true regarding this patient’s anemia?

A. Clostridial sepsis must be considered.

B. The anemia is most likely caused by disseminated intravascular coagulation (DIC).

C. The urinary and lab findings suggest congenital thrombotic thrombocytopenic purpura (TTP).

D. The scenario is typical of drug-induced anemia due to G6PD deficiency.

E. He likely has a congenital hemolytic anemia.

**Explanation**

Answer A is correct. Ischemic tissue in the GI tract is a possible site of clostridium infection, and the peripheral smear and hemoglobinuria are consistent with clostridium toxin–mediated hemolysis in this ill patient, even though there are signs of DIC as well.

Answers B and C are incorrect because schistocytes should be present if the main explanation for anemia is DIC or TTP. Answers D and E are incorrect because they do not fit the clinical scenario.

14. An 8-year-old boy with hereditary spherocytosis who had a splenectomy at age 5 years arrives in the emergency department with 1 day of fever to 104 ºF, rash, and lethargy. He is hypotensive and tachycardic. His labs reveal a WBC 30 × 109/L, Hb 9 g/dL, and platelets 55 × 109/L. His peripheral blood smear reveals spherocytes and schistocytes with large platelets. His PTT is 18 seconds and PTT 50 seconds with hypofibrinogenemia.

Which of the following statements is correct regarding this clinical scenario?

A. Splenectomized patients are at risk for serious bacterial infection from encapsulated organisms for only the first year after splenectomy.

B. His anemia and thrombocytopenia are most likely evidence of growth of a remaining splenule.

C. His fever and acidosis cause a right shift in the hemoglobin-oxygenation curve.

D. His fever, rash, and anemia are most likely caused by parvovirus infection.

E. Children with hereditary spherocytosis are at higher risk for sepsis even with intact spleens.

**Explanation**

Answer C is correct. This splenectomized child is presenting with sepsis complicated by disseminated intravascular coagulation. Fever, low pH, and increased 2,3-bisphosphoglycerate cause a right shift in the hemoglobin-oxygenation curve, which is associated with increased oxygen offloading into the tissues.

Answer A is incorrect. Splenectomized patients remain at risk for infection from encapsulated organisms for their lifetime. Answer B is incorrect. Although a growing splenule, which may be missed during splenectomy, can cause an increase in markers of hemolysis and has the potential to cause hypersplenism (which can be associated with mild neutropenia, anemia, and thrombocytopenia), it is unlikely that this is the explanation for this patient’s anemia at this time. Answer D is incorrect because this patient’s prolonged PT and PTT, hypofibrinogenemia, and schistocytes on peripheral blood smear are not consistent with parvovirus. Answer E is incorrect because patients with hereditary spherocytosis have a normal immune system unless they have had a partial or full splenectomy.

15. A 3-year-old boy with sickle cell disease presents to the emergency department with nasal congestion and fever to 102 ºF. He is well-appearing with normal vital signs except for the fever, for which he is given acetaminophen. A blood culture and labs are obtained, and then ceftriaxone is administered, which he has tolerated well in the past. He is observed, and 1 hour later he develops acute onset of back pain associated with dark urine and icterus. His repeat labs demonstrate a 4 g/dL decrease in his hemoglobin, an indirect bilirubin of 3 g/dL, and hemoglobinuria. His direct antiglobulin test (DAT) is positive for complement C3 and negative for IgG.

Which of the following statements about this patient’s clinical findings is correct?

A. This acute hemolytic episode most likely represents an infection with malaria or babesiosis.

B. The intravascular hemolysis and DAT are consistent with a drug-mediated immune hemolysis.

C. The presence of hemoglobinuria is most consistent with extravascular hemolysis.

D. This presentation is most consistent with a fever complicated by a vaso-occlusive episode.

E. This patient likely has G6PD deficiency with acute hemolysis triggered by acetaminophen or ceftriaxone.

**Explanation**

Answer B is correct. This child has developed acute intravascular hemolysis associated with immune complex type drug-induced hemolysis from ceftriaxone. These patients typically have tolerated the drug well in the past and then, within a few hours of receiving a dose, develop acute intravascular hemolysis, which has been associated with a high risk of mortality. Cephalosporins and penicillins are commonly implicated drugs.

Answer A is incorrect. Although malaria and babesiosis can cause acute intravascular hemolysis, the complement C3–positive DAT is not consistent with the lab findings with these infections. Answer C is incorrect because hemoglobinuria and a low haptoglobin are associated with intravascular hemolysis. Answer D is incorrect. Although fevers in patients with sickle cell disease can be complicated by vaso-occlusion and pain, this patient’s acute hemolysis is not consistent with this diagnosis. Answer E is incorrect because acute oxidative hemolysis from G6PD deficiency does not cause a positive DAT, and cephalosporins and acetaminophen are not oxidative triggers in patients with G6PD deficiency.