Lesson 272: PreAnesthetic Assessment of the Patient Who Has Had Multiple Blood Transfusions

PREANESTHETIC ASSESSMENT

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Pathophysiology

Sickle cell disease (SCD) is a chronic hemolytic condition. The prevalence of SCD in the United States is 1 in 325 births among African Americans, and 1 in 1,200 births among Hispanics. Of African Americans, 8% to 10% have the sickle cell trait and are clinically asymptomatic carriers of 1 allele of the sickle cell gene. Globally, the disease also affects Africans (of whom 15% to 25% are carriers), and to a lesser degree Arab, Indian, and Southeast Asian populations. With international population shifts, anesthesiologists in the United States and abroad will be faced with increasing numbers of patients with SCD.

Most patients with SCD have the hemoglobin SS (HbSS) variant; however, patients with HbSC, HbS-β-thalassemia, HbSO, and other, rarer HbS subtypes also exhibit the SCD phenotype. In those patients with HbSS, sickle cell hemoglobin (HbS) comprises 85% to 98% of the hemoglobin, and the remainder is fetal hemoglobin (HbF) and HbA0.

Very high levels of HbF are protective against severe forms of the disease. HbS is composed of 2 normal α chains and 2 abnormal β chains. The abnormal β chains result from the substitution of valine (as amino acid 6 on chromosome 11) for glutamic acid.

Complications of SCD are directly related to the deformation, adhesion, and hemolysis of red cells. The abnormal HbS, which does not respond well to repeated cycles of deoxygenation, polymerizes into rodlike structures that distort red cells into a sickle shape. Sickled red cells decrease the flow of blood and oxygen to tissues, leading to ischemia and chronic end-organ destruction. Sickled red cells (and leukocytes) adhere to vascular endothelium, causing chronic inflammation, abnormal vasomotor tone favoring vasoconstriction, and hypercoagulability. Acute chest syndrome, 1 of the many clinical complications, has a mortality rate of 1.1% in children and 4.8% in adults. Acute chest syndrome is defined as the development...
Many studies have suggested that low-risk perioperative transfusion practices are quite safe. However, the fact that preoperative transfusion (35% vs 0%) was found in patients with sickle cell disease (HbSS), who had undergone intra-abdominal procedures without preoperative transfusion (35% vs 0%).

On the other hand, at least 50% of the hemoglobin in patients with sickle cell trait (HbSA) is normal (HbA). Polymerization of red cells does not occur in these patients until the oxygen saturation is below 40%. Blood transfusions are usually not required in these patients.

**Sickle Cell Anemia, Anesthesia, and Transfusion**

Patients with SCD who undergo general anesthesia have an increased risk (intraoperative and postoperative) for a vaso-occlusive crisis—increasing acute chest syndrome. The risk for nonspecific complications, such as fever, bleeding, and pulmonary embolism, may also increase. In an observational study conducted over a 10-year period, a perioperative mortality rate of 1.1% was found among 717 patients with SCD who had undergone 1,079 procedures. Certain types of surgery, increased age, relatively frequent and severe crises, organ failure, and pulmonary disease are all risk factors for perioperative morbidity.

In patients with SCD, the hemoglobin—oxygen dissociation curve is shifted to the right. In addition, the sickling of red cells increases with a low pH, hypoxia, and a high temperature; it decreases with the presence of other, non-S hemoglobin. Historically, this pathophysiology has dictated the steps anesthesiologists take to manage patients with SCD—including the avoidance of hypovolemia, hypoxia, tourniquets, and hyperthermia, and preoperative transfusions of non-HbS blood. More recently, surgical stress and microvascular ischemia—reperfusion injury have also been identified as contributing to the endothelial damage of SCD.

The number of complications associated with blood transfusions in patients with SCD is greater than that in the general population. In addition to the usual complications of infection, increased blood viscosity, iron overload, and febrile reactions, the rates of alloimmunization and autoimmunization may increase.

Alloimmunization is a process in which antibodies to foreign antigens form after exposure to the antigens, as in allo-geneic blood transfusions. In autoimmunization, warm antibodies act at body temperature, form to the patient's own red cells. The incidence of autoimmunization appears to be increased in SCD, with antihemoglobin reportedly present in 8% to 10% of alloimmunized patients. Before undergoing anesthesia, many patients with SCD will have received red blood cell (RBC) transfusions intermittently (eg, for symptomatic anemia or aplastic crisis) or chronically (stroke prophylaxis). The transfusions can be simple or exchange transfusions. In exchange transfusions, higher volumes of RBCs are transfused while a volume of the patient's blood is simultaneously removed to prevent significant increases in blood volume and viscosity. The major goal of red cell transfusion is to increase the patient's oxygen-carrying capacity. In the blood with bringing a sickle cell crisis may be critical. Chronic transfusions decrease the incidence rates of both acute chest syndrome and pain crises in children—the most frequent causes of hospital admissions and stroke. Chronic transfusions also suppress the endogenous production of HbS by increasing tissue oxygenation.

Clinical transfusion practices, however, are disparate among medical centers. Two preoperative patients with SCD and similar clinical histories may have very different transfusion histories and consequently different titers of alloantibodies that interfere with the anesthesiologist's transfusion plan.

The American Society of Anesthesiologists has not yet established guidelines for perioperative blood transfusions in patients with SCD. Most health care centers encourage individual practitioners to review the current literature before deciding to transfuse blood to a patient. A 2001 Cochrane Review concluded that a conservative transfusion regimen is as effective as an aggressive regimen for preventing perioperative complications, and that further research is needed to examine the optimal regimen for different cases.

Many studies have suggested that low-risk procedures (e.g., herniorrhaphy, tympanostomy, dental and oral procedures) in adults and children can be safely performed without preoperative transfusion.

The current policy of the National Institutes of Health (based on a review of the literature) recommends transfusion of blood to patients for all but very low-risk procedures to achieve a hemoglobin level of 10 g/dL.

The study that has perhaps influenced contemporary perioperative transfusion practices the most was published in 1995 by the Preoperative Transfusion in Sickle Cell Disease Study Group. In this prospective study conducted in 36 centers, 604 surgical cases were randomized to receive either a simple, conservative transfusion to a hemoglobin level of 10 g/dL or exchange or serial transfusions to an HbS level of 30%. No significant benefit was found in the group randomized to the more aggressive transfusion regimen, and the incidence rate of SCD-related complications was similar (15%) in the 2 groups. Patients who were not given a transfusion were not included in the study.

In 1997, Haberkern et al were able to confirm these findings in a prospective study of patients undergoing cholecystectomy. In addition, they found an incidence of SCD-related events (including acute chest syndrome) in a group of patients not given transfusions that was twice that of comparison groups of patients who received simple or aggressive transfusions. However, the fact that the patients in the nonrandomized, transfused group were more likely to be older, female smokers may have introduced bias. Still, the study suggested no difference in outcomes between the conservative and aggressive transfusion regimens.

In a retrospective study lasting 10 years that was published in 2004, the population of 60 children had a lower incidence (6.6%) of acute chest syndrome than that reported in a number of other studies. The authors attributed the finding to the fact that blood had been transfused to 85% of the study patients to a hemoglobin level of 10 g/dL. Although definitive evidence of the benefits of prophylactic transfusions is lacking, transfusion is of course indicated to replace significant blood loss or correct severe anemia or hypoxia. Once the anesthesiologist decides to administer a transfusion, associated complications must be anticipated. Difficulties in crossmatching blood for patients who have SCD with alloantibodies can delay urgent, lifesaving blood transfusions.

**What Happens at the Blood Bank?**

When a blood specimen is received into a blood bank laboratory, a technician first checks the sample against the requisition slip. Whereas it may seem arbitrary that a blood bank would reject a sample for even the smallest discrepancy between the requisition slip and the blood sample, this practice is required for compliance with AABB (formerly known as American Association of Blood Banks) and national regulations, and with local policies. Even small errors in this first step are associated with an increased risk for transfusion reactions.

The type component of the type and screen testing, which determines the ABO and Rh status of the patient, takes approximately 15 minutes to complete. In this test, the recipient's red cells are incubated with commercial anti-A and anti-B antibodies to determine if the red cells have A or B antigens on the surface. For example, if agglutination occurs during mixing of the recipient's blood and the anti-A antibody, then the recipient's red cells have surface A antigens. Similarly, incubation with commercial anti-D antibodies determines the Rh-D status. There are approximately 50 Rh antigens; the D antigen is considered the most immunogenic and is the only Rh antigen for which blood is routinely tested. A second component of the type, called reverse typing, uses commercially available A and B reagent cells to determine if the donor's serum contains naturally preformed antibodies to these antigens.

The screen portion of the type and screen, which tests for non-A, non-B antibodies, takes at least 30 minutes to complete. Approximately 29 discrete blood group systems are currently identified, including ABO and Rh, that encompass more than 250 antigens coating the red cell surface. The FDA requires that approximately 18 antigens—those deemed most clinically significant—be present on reagent red cells used in the antibody screen. Between 3% and 10% of persons who have received multiple blood transfusions have antibodies to these "unexpected" antigens. Among pregnant women, it is estimated that 1 in 100 will have "unexpected" immunoglobulin G (IgG) antibodies not of AB or Rh-D specificity. A transfusion of unscreened red cells that are ABO- and Rh type-specific could be deleterious for such a patient.

The antibody screen significantly reduces the chance of incompatibility due to alloantibodies (Figure 1). The probability that the screening test will miss an antibody that is potentially dangerous in the general population has been estimated to be no more than 1 in 10,000. When Oberman et al studied 10,950 patients, they found 8 "clinically significant" antibodies after complete crossmatching that had not been detected during the screen. The antibody titer were too low to be detected by the antibody screen but might have been clinically significant in large numbers.

Screening is done by incubating the recipient's serum with commercially available type O reagent cells containing the approximately 18 most clinically significant antibodies causing hemolytic transfusion reactions. Agglutination or hemolysis of reagent cells simply means that unexpected antibodies are present. The blood bank technician identifies which of the 18 antibodies are expressed in the patient's serum and tries to locate donor blood that does not express those antigens. This exercise is called the crossmatch.

**What Takes So Long?**

When the results of an antibody screen are negative and the patient has no history of a positive result to antibody screening, the blood bank laboratory can perform an "immediate spin" crossmatch to issue blood. In this procedure to detect ABO incompatibility, the recipient's serum is added to ABO- Rh-compatible donor red cells at room temperature, centrifuged, and then graded for macroscopic agglutination. The process takes 1 to 5
minutes and reduces the risk for serious hemolytic reactions resulting from ABO mismatch. Unexpected antibodies in the MNS, P, and Lewis systems are also detected by this process.

If there are no unexpected antibodies on screening and no history of antibodies, another option for obtaining blood is with a computer crossmatch, which also takes 1 to 5 minutes. No mixing of blood occurs in a computer crossmatch. It uses laser wand and bar-code technology to electronically find a match based on the ABO and Rh status of the patient. The risk for a hemolytic reaction is less than 0.1%. A small number of centers may eliminate the antibody screen and proceed directly to a computer crossmatch if the patient’s risk for antibodies is low and the screen history is negative.

If clinically significant antibodies are present, antigen-negative units need to be located and a serologic crossmatch (including an antiglobulin test) performed. The negative frequencies of the antigens are multiplied to calculate the approximate number of units that need to be screened to find an antigen-negative donor. For example, 0.91 K antigen × 0.48 S antigen = 0.436 × 100 = 44%; in other words, approximately 1 in 3 units will lack the K and S antigens. The hospital inventory is checked for this antigen-negative blood. If it is not immediately available, the blood of phenotyped donors from limited donor programs, frozen inventories, and rare donor registries may be examined to find a match. The blood of the selected donor is then used for the serologic crossmatch.

In a serologic crossmatch, donor red cells and the recipient’s plasma are incubated and examined for agglutination/hemolysis at 37°C. Next, the indirect antiglobulin test is performed, followed by re-examination. This test uses anti-human IgG to detect antibody-antigen reactions not seen with 37°C incubation alone.

Some blood banks perform the serologic crossmatch even if no antibodies are detected on screening because the screen is imperfect. Not all clinically significant antigens are represented on the screening cells; RBCs used for antibody screening may weakly express the offending antigen if the patient is not homozygous for the antigen; weak antibodies may react with fresh donor units but not older screening cells; and antibodies can be missed if an error occurs in performing the technique or reading the screening test result. Most centers, however, do not perform the serologic crossmatch in nonalloimmunized patients with SCD. The serologic crossmatch can take up to 45 minutes to complete.

When a patient has no significant transfusion history, the chance of a compatible transfusion with ABO and Rh typing alone is 99.8%; an antibody screen increases the chance to 99.94%, and a serologic crossmatch increases it further to 99.95%. The odds of the screen missing a significant antibody is estimated to be 1 in 10,000.

Antibodies to the Rh antigens C and E, antigens of the Kell (K), Duffy (Fy), and Kidd (Jk) systems, and the S antigen (MNS system) are most likely to cause hemolysis. All alloantibodies that become serologically undetectable over time are implicated in delayed hemolytic transfusion reactions (HTRs) in patients with SCD. Thus, it is best to obtain a thorough transfusion history.

**Sickle Cell Antibodies**

Unexpected antibodies are more likely to develop in patients with SCD than in other patients chronically undergoing transfusion, such patients have an 8% to 40% rate of alloimmunization, and a disproportionately higher rate of alloimmunization with a higher number of transfusions. Vichinsky et al found a 30% incidence of alloimmunization in patients with SCD who had received multiple transfusions, compared with a 5% incidence in white patients with other types of anemia who had received multiple transfusions. Antigenic differences between patients with SCD and the blood donor pool (primarily white) may be 1 reason for increased alloimmunization. However, patients with SCD may also have a higher rate of autoantibody production.

The presence of antibodies in a patient with SCD not only delays the availability of blood for transfusion but also places the patient at risk for acute or delayed HTRs. The frequency of delayed HTRs in the SCD population is estimated to be 4% to 11%. Among the problems with detecting and identifying antibodies is that up to 30% of them may become undetectable over time, and no single procedure is currently able to detect all known antibodies.

A means to decrease the high frequency of alloimmunization in the SCD population given the current inadequacy of antibody detection in these patients is to phenotypically match for clinically significant antigens. Patients with SCD are most likely to form alloantibodies to the Rh (C and E), Kell (K), Duffy (Fy+), Kidd (Jk+), and MNS (M and S) antigens—all of which are associated with HTRs. In some centers, patients with SCD prophylactically receive blood that is negative for Rh and Kell antigens, and in addition they may receive blood negative for Duffy, Kidd, and MNS antigens. Others advocate phenotype-matched red cells only after the first antibody is detected. Matching for C, E, K, Fy, Jk, and S antigens in already alloimmunized recipients has been reported to decrease the rate of further alloimmunization to between 1% and 5%. Extensive antigen-matching programs are expensive and not widely available, however.
Knowledge about the detected antibodies and likelihood of a significant reaction can be helpful when the clinician managing a patient with SCD who has antibodies works with the blood bank (Figure 2). Knowledge about the most common presentations and the clinical course of transfusion reactions is also important.

Delayed HTRs develop within hours to several weeks after a transfusion. Symptoms range from pain crises to significant hemolysis and renal failure. A delayed reaction occurs when the antibody level is too low to be serologically detectable at the time of transfusion; antigen reexposure triggers an anamnestic response causing amplification of the antibody. The threshold should be very low for considering a delayed HTR in a postoperative patient with SCD who recently received a transfusion. Fortunately, most symptoms of delayed HTRs are treatable; patients require primarily supportive treatment.

Hyperhemolysis is a rare but severe and possibly fatal transfusion reaction that may occur in association with an allogeneic HTR. In this syndrome, the hemoglobin level falls below the pretransfusion value, and the patient may present with profound anemia, hemoglobinuria, and hyperbilirubinemia. In addition to the hemolysis of transfused red cells, hemolysis of autologous red cells or suppression of endogenous erythropoiesis is thought to occur. Hemolysis of autologous red cells may be the consequence of “bystander” hemolysis of autologous red cells, and not necessarily the production of autoantibodies. The results of direct antibody tests may be negative, and no new autoantibodies may be present. Successful treatment with corticosteroids and I.V. immunoglobulin or erythropoietin has been reported.34 The risk for febrile non-HTRs in patients with SCD—as in other patients—is directly related to the number of transfusions. Symptoms are similar to those of pain crises and infections, with fever and chills. Accordingly, patients with SCD should receive leukocyte-reduced blood in which the count of white blood cells is less than 5x10⁹/L to reduce the risk for human leukocyte antigen alloimmunization and cytokine release. Like other transfusion recipients, patients with SCD are treated for febrile non-HTRs with antipyretic medication.

Management of the Case Presented

At this writer’s institution, transfusion practices are not aggressive. Perioperative transfusions are not routinely done, especially in patients at low risk, children, patients with a stable cardiorespiratory status whose hemoglobin is near baseline, and patients undergoing elective and low-risk procedures. In the case presented, we believed that a simple transfusion was indicated given the patient’s age, her history of frequent episodes of acute chest syndrome, her low hemoglobin level, and the nature of the planned procedure. The blood bank estimated that it would take more than 1 hour from antibody identification to completion of the serologic crossmatch. We were concerned about the risks associated with transfusing non-crossmatched blood.

However, surgical expediency was a priority. Bacteremia from the acute cholecystitis would have placed the patient at even higher risk for a vaso-occlusive crisis and acute chest syndrome, with a possible hyperhemolytic crisis. The decision was made to proceed without transfusion and anticipate a postoperative transfusion. A laparoscopic surgical technique was planned because this approach is known to decrease hospital stay without increasing the complications of SCD.6

The patient was well hydrated preoperatively and given oral antipyretics. Her temperature and oxygenation were near baseline, and patients undergoing elective and urgent or massive transfusion.

References

8. Oberman HA, Barnes BA, Friedman BA. The risk of abbreviating the major crossmatch in urgent or massive transfusion. Transfusion. 1978;18(2):137-141.

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Post-test

1. The hemoglobin–oxygen dissociation curve in sickle cell anemia is:
   a. not shifted
   b. shifted to the left
   c. shifted to the right
   d. not applicable in this disorder

2. Which of the following is not a risk factor for perioperative morbidity in sickle cell anemia?
   a. Previous transfusions
   b. Pulmonary disease
   c. Frequent and severe pain crises
   d. Very young age

3. Which of the following is not associated with a protective clinical effect in sickle cell disease (SCD)?
   a. High concentration of fetal hemoglobin
   b. Temperature regulation
   c. Regional anesthesia
   d. High concentration of oxygen intraoperatively

4. The most common genotype of SCD is:
   a. hemoglobin SC
   b. hemoglobin SS
   c. hemoglobin S-β-thalassemia
   d. hemoglobin SA

5. The management of a patient with a delayed hemolytic transfusion reaction includes all the following except:
   a. transfusion of donor blood that is negative for previously identified antibodies
   b. steroids
   c. diphenhydramine
   d. I.V. immunoglobulin

6. Computerized crossmatching is appropriate for which of the following patients:
   a. no antibodies detected on the screen
   b. no antibodies detected on the screen and no history of antibodies
   c. a history of antibodies, but none currently detected on the screen
   d. inappropriate for any patient

7. Which of the following statements is true regarding testing for blood transfusion compatibility?
   a. The antibody screen is a test for non-A/non-B antibodies.
   b. Anti-D antibodies are found in the serum of patients with Rh-negative blood.
   c. The antibody screen eliminates the likelihood of a hemolytic transfusion reaction.
   d. A negative immediate spin means that no non-A/non-B antibodies are present.

8. Red cell sickling:
   a. decreases at pH 7.2
   b. may be triggered by hypoxia
   c. is increased by hypothermia
   d. is potentiated by non-S hemoglobin

9. Clinical transfusion practices in SCD:
   a. are standardized among medical centers
   b. are based on American Society of Anesthesiologists guidelines
   c. indicate that aggressive transfusion regimens are as effective as conservative ones
   d. suggest that a single transfusion should be administered whenever the hematocrit is below 30%.

10. Which of the following is a true statement about transfusions?
    a. Transfusions suppress the endogenous production of hemoglobin S.
    b. Transfusions decrease the incidence of vaso-occlusive disease.
    c. Transfusions are therapeutic in children experiencing pain crises.
    d. All of the above are true.