For non-emergency transfusion, patient blood typing for ABO blood group and Rh(D) is performed prior to preparation of blood products. ABO-compatibility of red blood cells (RBCs) is essential since individuals naturally form antibodies to ABO blood group antigens not present on their own red cells. Transfusion of ABO-incompatible RBCs will likely result in an immediate, severe and potentially fatal intravascular hemolytic transfusion reaction.

Unlike ABO blood group antibodies, antibodies to the Rh(D) antigen are not naturally occurring. Formation of anti-D antibody requires exposure of an Rh(D) antigen negative individual to Rh(D) antigen positive blood through pregnancy or transfusion. To prevent alloimmunization (formation of anti-D antibody), Rh(D) negative patients should be transfused Rh(D) negative RBCs. However, in emergency situations when Rh(D) negative RBCs are in short supply, Rh(D) positive RBCs may be transfused to a patient with an unknown Rh(D) type who is not a female of childbearing potential.

The chance of anti-D development after exposure to Rh(D) positive RBCs varies from <10% in immunosuppressed patients to >80% in healthy volunteers. The incidence of anti-D formation in non-immunosuppressed patients is estimated to be 20-30%. If an individual develops an anti-D antibody, initial antibody production occurs days to weeks after exposure and non-severe and non-life-threatening extravascular hemolysis of remaining Rh(D) positive RBCs may occur. These patients will require Rh(D) negative units for all future RBC transfusions to avoid a hemolytic transfusion reaction.

Development of anti-D antibodies in females of childbearing potential must be avoided to prevent severe hemolytic disease of the fetus/newborn (HDFN) that may occur in future pregnancies. Once a female has made anti-D, Rh(D) Immunoglobulin (RhIg) will not prevent HDFN; all future Rh(D) positive offspring may be affected. Rh(D) negative RBCs should be transfused in females of childbearing potential and unknown blood type.

Platelets do not express Rh(D) antigen. However, platelet concentrate products for transfusion contain a very small amount of RBCs and RBC microparticles. Current blood product manufacturing practices yield a platelet concentrate product with only 0.036 mL RBCs per dose of pooled whole blood-derived platelet concentrate and 0.00043 mL RBCs per dose of apheresis platelet concentrate.
Although the amount of RBCs in platelet concentrate products is very low, there is still a small chance of alloimmunization if an Rh(D) positive platelet product is transfused to an Rh(D) negative recipient. The ADAPT study is the largest study to date designed to determine the frequency of Rh(D) alloimmunization following transfusion of Rh(D) positive platelets in Rh(D) negative recipients. This retrospective study found an alloimmunization frequency of 1.44%, with no statistically significant differences between transfusion of whole blood-derived or apheresis platelets. Two smaller studies (one retrospective and one prospective) examining only transfusions of apheresis platelets found the frequency of alloimmunization with transfusion of Rh(D) positive platelet products to Rh(D) negative recipients to be 0%.

Rh(D) negative patients should ideally receive Rh(D) negative platelet products. However, with the short shelf life of platelets and Rh(D) negative individuals comprising only 15% of the donor population, Rh(D) negative platelets are a limited resource. Due to inventory constraints, substitution of an Rh(D) positive platelet product may be necessary. When an Rh(D) negative patient is transfused with an Rh(D) positive platelet product, the clinician is faced with the decision of whether or not to treat the patient with RhIg to prevent formation of anti-D. A dose of RhIg administered within 72 hours of transfusion can neutralize the small amount of Rh(D) positive RBCs in the platelet product and minimize risk of formation of anti-D. Because of the serious consequences of hemolytic disease of the fetus/newborn, RhIg should be administered to females of childbearing potential following Rh(D)-incompatible platelet transfusion.

In patient populations other than females of childbearing potential, RhIg administration after Rh(D)-incompatible platelet transfusion is optional. The chance of anti-D formation with Rh(D)-incompatible platelet transfusion is very small, and should anti-D formation occur the main clinical consequence is that future RBC transfusions must be Rh(D)-negative. One factor to inform clinical decision-making is the anticipated transfusion needs of the patient. If a patient is expected to require significant transfusion support in the future, preventing anti-D formation allows for potential use of Rh(D) positive RBCs in the case of massive bleeding.

Key Points

• Rh(D) negative platelets should be preferentially given to RhD negative patients, particularly females with child bearing potential.

• Platelet products contain a very small number of RBCs. Although the chance is very low, it is possible to develop anti-D in response to transfusion of Rh(D) positive platelets to an Rh(D) negative patient.

• Rh(D) Immunoglobulin (RhIg) should be administered to prevent Rh(D) alloimmunization if Rh(D) positive platelets are used in Rh(D) negative females with childbearing potential.

• RhIg is an optional measure to prevent Rh(D) alloimmunization if Rh(D) positive platelets are used in Rh(D) negative patients other than females with childbearing potential.

References


A new challenge: How does Darzalex (Daratumumab) impact the blood bank?

Darzalex™ (Daratumumab) is a newly FDA approved oncology drug that binds to the CD-38 molecule, which is expressed on plasma cells. The drug, a monoclonal antibody is used to treat resistant multiple myeloma. However, CD-38 is also expressed on the surface of red blood cells (RBCs). When a patient is taking Daratumumab, false positive testing results may be found due to the in vitro interference of the drug on the patient RBCs and reagent RBCs. This creates a number of challenges for the blood bank.

Patients’ plasma with daratumumab interference can have variable serological reactivity in the indirect antiglobulin test (IAT). The reactivity ranges from no positive reactions, to positive reactions seen with a few reagent RBCs, to full interference when the plasma reacts with all tested RBCs and the autocontrol. Daratumumab interference can also cause a positive direct antiglobulin test (DAT). When there is interference, special lab procedures can be used to rule out underlying alloantibodies. The Immunohematology Reference Laboratory will use a reducing agent, dithiothreitol (DTT), which removes the cell surface CD38 molecule from the reagent RBCs. This allows the patient’s plasma reactivity due to daratumumab interference to be extinguished. This laboratory approach is useful to reduce the risk of hemolytic transfusion reactions; however, the DTT treatment also destroys the Kell, Dombrock, Lutheran and Cartwright blood group antigens. Thus, a negative IAT test result after DTT treatment does not provide evidence that the patient’s sample is free from antibodies to these blood group systems (Table 1).

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Due to the known weakness of the DTT approach, obtaining the patient’s extended RBC antigen phenotype to hold in their permanent blood bank record before commencement of daratumumab (or, before there is detectable daratumumab interference) can be helpful to guide future RBC transfusions. This allows for risk stratification so that the potential antigen specificities can be determined prior to transfusion. Although most antigens can be serologically determined, many of the antisera may not be available in every laboratory. RBC genotyping can provide the results for all of the antigens listed, except for Yt. For patients with chronic transfusion needs, or those with pre-existing RBC alloantibodies, knowledge of the extended RBC antigen type becomes more critical. Because DTT denatures the Kell antigens, prophylactic antigen matching for RBC transfusions by providing K antigen matched units has been proposed. This approach will ensure that K antigen negative patients do not form anti-K antibodies. RBC units that are K antigen negative are common in the donor population, so this approach may be feasible in many settings.

The daratumumab drug brings a number of new challenges to the blood bank; these will likely become familiar as the comfort and use of the drug expands. The company that manufactures daratumumab, Janssen, is working to help blood banks and providers learn about daratumumab (see link). It is estimated that one third of patients taking daratumumab may require transfusions. The drug takes about six months to be entirely metabolized and no longer detectable after therapy cessation. Because there is no serological finding that is specific for daratumumab, it is critical that the prescribing physician provides information to the blood bank that the patient is taking this drug. Further, blood bank medical directors must determine their approach and set policies for transfusion testing accordingly. For example:

- **A policy to guide the frequency that DTT treated antibody screening and identification testing is required;**
  - *In patients with no pre-existing alloantibodies, testing every 3 – 7 days since the last transfusion episode seems reasonable.*
  - *In patients with no pre-existing alloantibodies, K antigen typing (and matching)*
  - *In patients with pre-existing alloantibodies or chronic transfusions, extended antigen phenotype or genotyping, with K antigen matched RBC transfusions*

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**Resources**

   a. Note: All of the blood group antigens in the Kell, Lutheran, Dombrock blood group systems were not provided in the Table.


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Continued on page 4
The United States Food and Drug Administration (FDA) has approved on January 28, 2016 a biologics license application from Bloodworks for our Cord Blood Program. Bloodworks is only the sixth cord blood bank in the U.S to achieve official FDA licensure. The FDA license formally designates Bloodworks as an authorized national source for hematopoietic progenitor cell therapy—known as HPC Cord Blood.

Collection of cord blood from new moms is a voluntary and painless procedure that does not interfere with the birth, or with mother-and-child bonding after delivery. There is no risk to either mother or baby, and there is no cost associated with the donation.

In 1997, Bloodworks (then Puget Sound Blood Center) created the first public, non-profit umbilical cord blood program in the Northwest. Today the program has partnerships with 11 hospitals in Washington, one hospital in Oregon and six hospitals in the Hawaii Cord Blood Program. These expanding hospital partnerships create the opportunity to meet the needs of even more patients requiring stem cell transplants.

More information about the regulatory approval can be found in the FDA approval letter here.
The direct oral anticoagulants (DOAC) s, dabigatran, apixaban, edoxaban, and rivaroxaban were FDA approved for prevention and treatment of venous thrombosis and for prevention of embolic stroke in patients with atrial fibrillation, without the need to monitor drug activity levels. However, clinical circumstances exist where laboratory measures of drug activity may help guide clinical care. These settings may include life-threatening bleeding, need for emergency surgery, renal impairment, severe hepatic failure, extremes of body weight, or in patients with bleeding or thrombosis currently on therapy.

Screening laboratory tests, the prothrombin time (PT), aPTT and thrombin time, differ in their sensitivity to the drugs. The thrombin time is very sensitive to the drug dabigatran and a normal thrombin time can be used to exclude the presence of the drug. A modification of the thrombin time, a dilute thrombin time, can be used to quantify the amount of drug present. The aPTT is usually prolonged in patients who are taking dabigatran, but cannot be used to absolutely exclude drug or to determine the drug level. For rivaroxaban and edoxaban, the PT may be elevated but the sensitivity varies greatly by the reagent used and results cannot be interpreted unless the sensitivity of the assay to rivaroxaban is known. Both the PT and aPTT are usually insensitive to apixaban and may be normal in patients taking therapeutic doses. Anti-Xa assays calibrated to rivaroxaban and apixaban can be used to determine levels. The Bloodworks Hemostasis Laboratory has established the dilute thrombin time to measure dabigatran activity and the specific anti-Xa assay for rivaroxaban and apixaban. Trough drug levels correlate best with bleeding risk, although values measured in patients on the medications vary widely and there are few data to guide in dose adjustment.

Because of the relative short half-life of the DOACs, supportive measures for bleeding while the drug clears is usually all that is needed. Worsening renal function can be associated with drug accumulation, especially for dabigatran which is predominantly cleared renally. Prothrombin complex concentrates can be used as a pro-hemostatic in the setting of life-threatening bleeding associated with DOAC therapy, although this does not provide a specific reversal of the anticoagulation and laboratory testing will not be normalized. For reversal of dabigatran, idarucizumab, a humanized monoclonal antibody fragment that binds dabigatran, was approved by the FDA in October 2015 and is now commercially available and can be obtained through the Bloodworks pharmacy. It is administered in two 2.5-gram doses (total = 5 gm) intravenously, no more than 15 minutes apart. Several drugs to reverse the direct Xa inhibitors are under study and at least one is likely to get FDA approval soon. These act as a decoy factor X, interacting with the drug and preventing inhibition of coagulation.

The DOACs provide alternatives for outpatient anticoagulation. Bloodworks is ready to support physicians and hospitals in their use of these medications.
NORTHWEST
TRANSFUSION
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Hosted by
Bloodworks
Northwest

Join us for a day of interesting transfusion medicine topics, continuing education, and networking opportunities relevant to physicians, nurses, laboratorians, and blood bankers.

Save the Date
June 16, 2016

Contact us at
News@Bloodworksnw.org
More information coming soon!