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TRANSFUSION

HOW DO I DO IT

Transfusion Complications

How I do it: An institutional protocol for the management of RhD negative women who receive RhD positive blood

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Abstract

Background: RhD alloimmunization can result from blood transfusion or fetomaternal hemorrhage (FMH). Preventing alloimmunization in childbearing-age women with FMH via utilization of RhD immunoglobulin (RhIG) is well known; however, there are no established protocols for RhD-mismatched transfusions in emergent or traumatic settings. Here, we describe our hospital protocol for managing RhD negative women who receive RhD positive transfusions.

Design: Pathology or Transfusion Medicine staff are notified of RhD-mismatched blood transfusions. Women with childbearing potential are evaluated by Obstetrics and Gynecology (ObGyn) to determine patients' childbearing desires and physical capabilities, as well as their ability to tolerate RhIG administration. Pathologists determine eligibility for therapy with RhIG: criteria include RhD negative females, ≤50 years old, without current or historical Anti-D, who have been transfused <20% of their total blood volume (TBV) with RhD positive blood.

Results: Management strategy depends on red blood cell volume (RBCv) transfused. Patients who receive an RBCv ≤20% of their TBV are eligible to receive RhIG, while an RBCv >20% makes individuals ineligible for prophylaxis with RhIG. Red cell exchange (RCX) is not offered at our institution, regardless of RBCv transfused. Women who receive RhIG should be screened for the development of antibodies using direct and indirect antiglobulin tests for 6–12 months posttransfusion. Future pregnancies of alloimmunized women should be carefully monitored.

Conclusion: Our therapeutic plan involves identifying eligible patients based on set criteria. This is the first published protocol to prevent RhD alloimmunization in females of childbearing age due to RhD-mismatched transfusions.

KEYWORDS

childbearing-age females, RhD alloimmunization, RhD mismatch, transfusion, whole blood

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1 | RhD AND THE CLINICAL SIGNIFICANCE OF ALLOIMMUNIZATION

Exposure of RhD negative individuals to the RhD antigen on red blood cells (RBCs) is highly immunogenic, meaning that this exposure can cause alloimmunization and future production of RhD antibodies (Anti-D).

Potential sensitizing events in RhD negative women can occur through transfusion of RhD positive blood or transplacental hemorrhage from an RhD positive fetus. Complications of RhD alloimmunization include delayed hemolytic transfusion reactions after future RhD positive transfusions or hemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies with RhD positive fetuses.[1] Alloimmunization can lead to significant perinatal morbidity and mortality if untreated, as well as the need for repeat invasive procedures, with intrauterine transfusions necessitating referral to high-risk centers.[2]

The probability of the development of anti-D antibodies in RhD negative patients who receive RhD positive blood products has been evaluated in multiple populations. The reported risk of alloimmunization ranges from 80% in healthy individuals to 15% in immunosuppressed transplant patients to 0% in those with Acquired Immunodeficiency Syndrome (AIDS).[3–5] Three retrospective studies have found that the average rate of RhD alloimmunization after receiving RhD positive packed red blood cells (pRBCs) is 20.5% (72/351, 95% confidence interval (CI) 16.6%–25.1%).[3,6,7] An additional study has reported an RhD alloimmunization rate of 1.4% following RhD positive platelet transfusions.[8]

Many groups have looked specifically at the risk of alloimmunization following transfusion for trauma. Rates vary widely in the literature, from as low as 8% to as high as 44%. When study results are combined, as they were by Ji et al., the rate of alloimmunization in trauma patients receiving RhD-mismatched transfusions is around 27%.[9,10] Importantly, this does not seem to be affected by the volume of transfused blood or type of transfusion, leukoreduced pRBCs versus Low-Titer O positive whole blood (LTO + WB).[6,11–13] Given the national burden of trauma and widespread use of O RhD positive, un-crossmatched blood in emergency settings, alloimmunization secondary to RhD mismatch has potentially significant ramifications.

Guidelines for the administration of RhIG during pregnancy and after delivery to reduce the risk of RhD alloimmunization are well described in the obstetric literature. A single 300-μg vial of RhIG will suppress alloimmunization by 30 mL of fetal whole blood or 15 mL of RhD positive fetal RBCs.[14] The risk of alloimmunization to the RhD antigen can be reduced from 16% to approximately 2% following postpartum RhIG administration and further reduced to around 0.28% with routine antenatal prophylaxis during the third trimester of pregnancy.[12,15–17]

There are, however, no clear recommendations to reduce the RhD alloimmunization rate following RhD-mismatched transfusions; that is, transfusions in RhD negative women of childbearing potential, including female children, who are transfused with RhD positive blood products. Massive transfusion makes decision-making regarding the use of post-transfusion RhIG even more difficult, as its administration could lead to massive hemolysis of transfused RBCs and subsequent hemodynamic collapse. Due to the inability to predict which patients will become alloimmunized, a management strategy for RhD negative women of childbearing potential who receive RhD-mismatched transfusions is needed to prevent potentially avoidable alloimmunization.

There are a limited number of case reports describing the management of RhD negative females who receive RhD positive RBCs.[17–19] In this report, we describe our hospital-based protocol for managing RhD negative women of childbearing age who receive RhD positive blood products, either pRBCs or LTO + WB.

2 | HOSPITAL-BASED GUIDELINES TO PREVENT RhD ALLOIMMUNIZATION IN CHILDBEARING-AGE FEMALES WHO RECEIVE RhD-MISMATCHED TRANSFUSIONS

Prior to 2018 at our institution, O RhD negative pRBCs were utilized for emergency-release transfusions in female patients ≤50 years old with unknown blood types. Rarely, due to various circumstances, some RhD negative individuals were exposed to RhD positive RBCs. In February 2018, our institution implemented an emergency-release protocol to transfuse LTO + WB to trauma patients, which was initially restricted to males ≥10 years old and females >50 years old, while males <10 and females ≤50 continued to receive O RhD negative RBCs with AB plasma. A population study at our institution demonstrated that more than 88% of our possible donors and potential recipients are RhD positive based on known differences in RhD prevalence within ethnic groups.[20–22] Due to the low prevalence of RhD negative individuals within our population and data, both internal and external, demonstrating a mortality benefit with utilization of LTO + WB, the emergency-release trauma protocol was modified in March 2019 to allow transfusion of LTO + WB in select trauma patients

≥10 years old, including females of childbearing age and children, both male and female.[23,24] While this protocol change did increase the probability of RhD-mismatched transfusions being administered to young, RhD negative females, data gathered at our center from 2019 to 2022 suggest that only 14.5% of trauma patients requiring massive transfusion on arrival were RhD negative women of childbearing age. Only 1 such RhD negative woman who received un-crossmatched LTO + WB survived to discharge over the 30-month retrospective study period. This, taken together with cited rates of RhD alloimmunization in trauma patients of 8%–44%, means that it would take approximately 250 years at the current rate to expose 100 RhD negative women to RhD positive whole blood. Without administration of RhIG, this would result in alloimmunization in between 8 and 44 women.[20] While the overall risk of the development of HDFN is low and certainly preferable to the risk of morbidity and mortality associated with delay to blood transfusion in a hemorrhaging woman, it is not zero. We have therefore established a guideline to reduce the risk of RhD alloimmunization in cooperation with multidisciplinary teams (Trauma, ObGyn, and Pathology/Transfusion Medicine).

A. How do I detect if a clinically significant RhD-mismatched transfusion has occurred?

The Blood bank staff or Trauma team immediately notifies the Pathologist/Transfusion Medicine specialist when an RhD-mismatched blood transfusion occurs. The patient will be considered for treatment with RhIG, and the ObGyn team will be consulted accordingly for any patient who meets all of the following criteria:

1. RhD negative.
2. Childbearing-age woman (≤50).
3. Negative for historical presence of Anti-D.
4. Current antibody detection screen (indirect antiglobulin test, or IAT) is negative for Anti-D.
5. Confirmed to have received LTO + WB or RhD positive pRBC.
6. The ability to tolerate therapy (RhIG) within the next 72 h is based on the patient's current comorbidities and severity of injuries.
7. The availability of adequate RhIG within the institution (and supply chain) should prioritize allocation for women of childbearing age for obstetric indications during pregnancy and the postpartum period.

B. How do I manage future transfusions once an RhD mismatch has been identified?

Once an RhD mismatch has been identified, the priority should be to limit exposure to additional RhD positive red cells and administer RhD negative, crossmatched blood products when possible. However, as long as the patient remains in extremis with continued significant blood loss, she should continue to receive RhD positive blood products.

Considerations to switch to RhD negative red cells after RhD mismatched transfusion include 1) inactivation of massive transfusion protocol, massive transfusion event, or emergency-release event, 2) improvement in control of hemostasis with decreasing quantities of blood being utilized or ordered (i.e. subsequent orders received are limited to 1–2 units of additional red cell containing products), 3) consultation with the clinical team reveals improved hemostasis and decreased continued expected blood loss, and 4) evaluation of the available inventory of RhD negative red cells.

There is literature to suggest that risk of alloimmunization does not depend on number of RhD positive units transfused.[9,13] We prefer to switch to crossmatched, RhD negative blood products according to the criteria above, as it is unknown at what point during a patient's hospitalization that her immune system will recover and mount a response to RhD positive RBCs, leading to alloimmunization.

C. How do I determine if a patient is eligible for prophylactic therapy?

Once the patient fulfills the above criteria, a Pathology/Transfusion Medicine consult will be initiated. Subsequently, the patient/legal guardian will be interviewed by the ObGyn team to determine her prior obstetric medical history and desire, as well as the physical capability to have future pregnancies. The patient's current medical injuries and ability to tolerate possible therapeutic interventions will also be evaluated.

Therapy with RhIG to reduce the risk of alloimmunization should not be pursued if the patient does not desire future pregnancies, is unable to have future pregnancies (i.e. hysterectomy or permanent nonreversible contraception method), or is not medically stable enough to tolerate prophylactic therapy within 72 h.

Treatment with RhIG will be offered to the patient/legal guardian, and the risks and benefits of the treatment will be explained. In addition, the discussion will include potential risks should she choose not to receive any treatment. The patient will be informed of the likelihood of future pregnancies being affected by RhD alloimmunization to include the rate of alloimmunization without prophylaxis (27%), the probability of becoming pregnant, the probability of having an RhD positive fetus in future pregnancies (60%), and the probability of having morbidity/mortality in pregnancies with RhD positive fetuses (4%).[3,11,12,21,23,24] The overall

risk of alloimmunization and fetal death due to RhD positive blood transfusion in trauma patients has been estimated to be 0.3%, which is extremely low when compared with the immediate survival benefit associated with resuscitation efforts with RhD positive RBCs.[23] Once consent is obtained for treatment, the Pathologist/Transfusion Medicine specialist will write a detailed consult note describing the appropriate therapy plan.

D. What are the side effects and risks of treatment associated with RhIG?
   1. Administration of large volumes of RhIG in a short period of time could cause rapid destruction of the RhD positive RBCs, leading to a moderate to severe hemolytic episode. This risk of moderate to severe hemolytic reactions increases proportionally to the volume of transfused RhD positive RBCs.[17]
   2. When intramuscular (IM) administration is utilized, large doses of RhIG requiring multiple injections can lead to injection-site reactions. We utilize intravenous (IV) preparations when more than 3 IM injections would be required.
   3. RhIG is derived from human blood and may contain infectious agents (viruses and prions) or globulins (including IgA) that are capable of inducing anaphylactic reactions.
   4. Special precautions and close monitoring need to be considered before administering RhIG to neonates or elderly patients, as well as to those with renal dysfunction, preexisting hemolysis, hepatitis, or infection.[18]

Historically, red cell exchange (RCX) with RhD negative RBCs has been offered prior to RhIG administration to decrease the proportion of circulating RhD positive RBCs to less than 20% and reduce the risk of severe hemolysis.[18] However, performing RCX requires additional exposure to more donor red cells, which could lead to alloimmunization to antigens other than RhD. Considerations would need to then be taken to perform an extended phenotype match to include Rh (C, c, E, e) and Kell blood group systems to prevent alloimmunization to highly immunogenic RBC antigens. Recently, the American Society for Apheresis now considers RCX for RhD prophylaxis after transfusion to be contraindicated (Category IV indication) since the risk of sensitizing individuals to additional RBC antigens likely outweighs the potential benefit of avoiding alloimmunization to RhD.[22] With these data in mind, we do not offer RCX to patients following RhD-mismatched transfusions.

E. How do I choose the appropriate therapy plan: RhIG alone versus no intervention?

Selecting the appropriate treatment strategy, RhIG versus no treatment, depends on the volume of the RhD positive RBCs transfused. Initial RhIG administration is contraindicated if the RhD positive RBC volume transfused is >20% of the patient's total blood volume (TBV) due to the potential for marked red cell splenic sequestration and hemolysis.

Individuals with greater than 20% of their TBV replaced are not eligible for RhIG administration to prevent isoimmunization due to the risk of hemolysis and increased likelihood of additional required transfusions with potential sensitization to other RBC antigens.

Some institutions may consider a practical cutoff such as a maximum number of units transfused (i.e. 2 units of pRBCs or whole blood with 500 mL total of RBC content) for a female with an estimated average TBV (i.e. 3500–5000 mL), rather than 20% TBV replaced. However, we believe that utilizing a blood volume calculation is more precise in determining total volume transfused to adequately assess the risk of potential hemolysis in individuals with lower-than-average TBV, to include female children.

F. How do I estimate the volume of RhD positive RBCs transfused?

It should be noted that the traditional methods to determine the quantity of RBCs within circulation during fetomaternal hemorrhage (FMH) are not appropriate for the evaluation of RhD-mismatched transfusions. The Rosette test is a qualitative screening test that is designed to detect >15 mL RhD positive RBCs or >30 mL RhD positive whole blood (15 mL RBCs in 15 mL plasma) and is not required in RhD-mismatched transfusions since this volume will be exceeded during all transfusion events. It is important to note the significance of 15 mL, as it is the threshold for RhD positive RBC neutralization from 1 vial (300 μg) of RhIG. If this test is negative in a patient who is known to have received an RhD-mismatched transfusion – meaning <15 mL of RhD positive RBCs remain in circulation – she may be effectively treated with 1 vial of RhIG.

Tests utilized for quantification of FMH to assist in RhIG dosing such as Kleihauer-Betke and the most widely available flow cytometry assays utilize methodologies to detect the presence of fetal hemoglobin rather than quantifying RhD positive RBCs. Therefore, unless a flow cytometry methodology that detects and quantifies RhD positive red cells is available, the volume of transfused RhD positive RBCs must be estimated based on the RBC content of the transfused blood component.

1. Calculate the volume of the RhD positive RBCs transfused to the patient, and estimate the volume and red-cell content within blood products.
   a. In order to simplify calculations, both LTO + WB and RBCs contain approximately 250 mL of RBCs. The RBC content of LTO + WB varies slightly but is between 200 and 250 mL. To avoid underdosing RhIG and to maximize safety, we will estimate this volume to be 250 mL.
      i. Each unit of LTO + WB is approximately 500 mL and is composed of 250 mL of RBC content. The remainder of the unit's volume comes from plasma and citrate-based anticoagulants.[25]
      ii. Each unit of RBCs collected in AS-1 (Adsol preservative) contains an average of 250 mL of RBCs along with similar anticoagulants.[26]

2. Calculate the patient's TBV[27].
   a. Commonly used approximation of TBV: TBV = Patient's weight (kg) × 70 mL/kg.
   b. Or, Nadler's equation: Women TBV = (0.3561 × H^3) + (0.03308 × W) + 0.1833. H is defined as patient's height in centimeters, and W is defined as the patient's weight in kilograms.
3. Determine the percentage of transfused RhD positive RBCs (Figure 1).
   a. (Volume of RBCs transfused/patient TBV) × 100 = Percentage of RBC content transfused.
   b. Example: 50 kg woman who received 1 unit LTO + WB (250 mL RBC volume):
      i. TBV = 50 kg × 70 mL/kg = 3500 mL.
      ii. (250 mL RBCs transfused/3500 mL TBV) x 100 = 7.1%. This is the percentage of transfused RhD positive RBCs.

G. How do I dose and administer RhIG?

There are five commercial formulations of RhIG available in the United States, which include HyperRho S/d Full Dose, MICRhoGAM Ultra-Filtered PLUS, RhoGAM Ultra-Filtered PLUS, Rhophylac, and WinRho SDF.[27] IV RhIG administration improves delivery, safety, and levels of antibody immediately present in circulation, which is advantageous over IM delivery.[27] In the United States, Rhophylac and WinRho are available for IV administration.[28]

In an emergent situation, if RhIG is not administered shortly after an RhD-mismatched transfusion and sensitization along with the formation of anti-D occurs, the patient is no longer eligible for any future RhIG administration. Thus, RhIG should be administered as soon as possible with the complete dose administered or at least initiated within the first 72 h of the patient's exposure to RhD positive RBCs in order to achieve maximal efficacy. Prior to offering or initiating treatment, the availability of RhIG within the treating institution and supply chain should be evaluated to ensure that limited resources are devoted primarily to women of childbearing age with obstetric indications during pregnancy and the postpartum period.

At our institution, we utilize IV Rhophylac®. With this formulation, each 20 μg (100 IU) of RhIG is sufficient

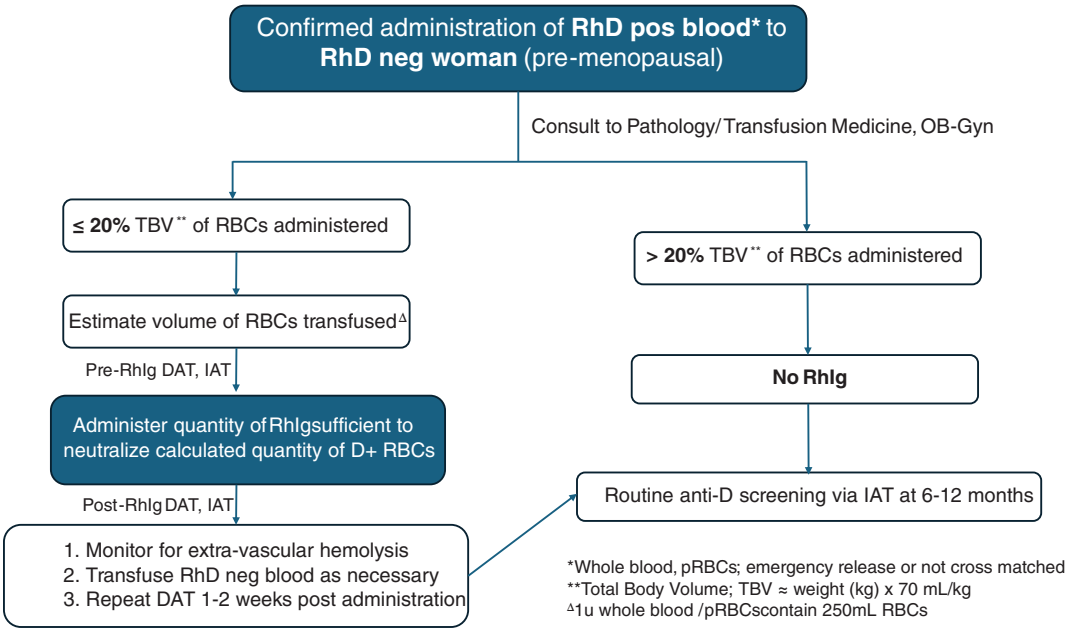

FIGURE 1 Protocol for management of RhD negative adult women ≤50 years old following RhD-mismatched transfusions.

TABLE 1 RhIG formulations and administration guidelines.

RhIG brand product	Route	Dose		Administration[a]
		Per total transfused RhD+ whole blood	Per total transfused RhD+ pRBCs[b]	
Rhophylac®,[18,30]	IM, IV	20 mcg per 2 mL	20 mcg per mL	IV: Administer 600 mcg/min every 8 h until total dose administered IM: Administer up to 1200 mcg every 12 h. Administer into deltoid or anterolateral upper thigh
WinRho SDF®,[31]	IM, IV	IM: 12 mcg per mL IV: 9 mcg per mL	IM: 24 mcg per mL IV: 18 mcg/mL	
RhoGAM-UHP®,[32]	IM		20 mcg per mL	
HyperRho-SD®,[33]	IM		20 mcg per mL	

[a]Administer doses as soon as possible; total dose must be in process within 72 h of incompatible transfusion.
[b]See Figure 1, "quantity of RhIG sufficient to neutralize calculated quantity of D+ RBCs".

to neutralize 1 mL of RhD positive RBCs.[18,29] Our recommendation would be to prioritize Rhophylac® or WinRho® for transfusion mismatch. These products have approval for IV administration, increasing both administration efficiency and patient comfort. See Table 1 for RhIG formulations available in the United States and their dosing.[38–40]

1. Example calculation for a 50-kg woman transfused 1 unit of LTO + WB with planned administration of IV Rhophylac.
   a. 1 unit of LTO + WB contains approximately 250 mL of RBCs.
   b. 250 mL of RhD positive RBCs × 20 μg (100 IU) per mL = 5000 μg (25,000 IU)
   c. 5000 μg RhIG/(300 μg RhIG per vial) ≈17 vials of RhIG,

H. What should be monitored during and after RhIG administration?

Administration of large amounts of RhIG over several days will likely necessitate monitoring in an inpatient setting versus serial/daily admissions to an outpatient infusion clinic until completion of the total dose. The patient should be observed during administration and for at least 20 min following the administration of IV RhIG for evidence of adverse reactions.

Successful removal of the RhD positive RBCs via extravascular hemolysis induced by RhIG should be followed by monitoring the patient. Patients at risk for clinically significant hemolysis due to the volume of RBCs transfused should be monitored for the rapidity and severity of extravascular hemolysis by trending hemoglobin, hematocrit, haptoglobin, bilirubin (direct & total), and absolute reticulocyte count prior to, upon completion of RhIG therapy, and at follow-up visits (approximately 1–2 weeks after treatment). Rarely, RhIG administration has been associated with intravascular hemolysis. If there is clinical concern for intravascular hemolysis, additional laboratory markers of hemolysis should be obtained, including lactate dehydrogenase (LDH) and a urinalysis to assess for hemoglobinuria. Additional labs to consider for patients with suspected intravascular hemolysis include renal function tests (creatinine) and tests to identify disseminated intravascular coagulopathy (platelet count, fibrinogen, prothrombin time [PT], activated partial thromboplastin [aPTT]). Extravascular hemolysis will result in a decrease in the patient's hemoglobin and hematocrit to pretransfusion levels, which may necessitate transfusion with RhD negative RBCs for signs or symptoms of acute anemia. A follow-up visit at least 1–2 weeks after administration is advised to evaluate for symptomatic anemia or other complications. Signs and symptoms of severe anemia, as well as when to return for medical care after discharge, should be discussed with the patient.

Additional laboratory testing should be performed to determine the efficacy of the therapy.

1. Direct antiglobulin test (DAT). DAT should be performed prior to, immediately after, and 1–2 weeks after RhIG administration.
   a. The pre-RhIG DAT may be positive or negative, but the eluate should not demonstrate anti-D.
   b. The DAT will be positive with IgG immediately after RhIG dosing is completed due to the coating of the RhD positive RBCs. An eluate will demonstrate anti-D specificity of the coating immunoglobulin.
   c. The DAT will be negative 1–2 weeks after RhIG administration, demonstrating that all RhD positive RBCs have been successfully removed from circulation.

2. Indirect antiglobulin test (IAT). IAT should be performed prior to, immediately after, and 6–12 months after RhIG administration.
   a. The pre-RhIG sample should be negative for Anti-D.
   b. The IAT will be positive for passive anti-D after administration of RhIG. The half-life of a standard dose of RhIG varies from 21 to 30 days, which would result in positive IAT up to 6 months after treatment[35].
   c. The IAT should be repeated between 6 and 12 months after RhIG administration to demonstrate the disappearance of passive RhIG and to evaluate the efficacy of the treatment[36]. If anti-D is detected between 6 and 12 months after the last RhIG administration, it likely indicates the formation of an alloantibody to the D antigen and therefore unsuccessful therapy.
   d. If anti-D is detected 6–12 months after the last RhIG administration and future pregnancies are desired, the patient should be referred to ObGyn for preconception counseling.
      i. Maternal anti-D antibody levels should be obtained at the patient's first prenatal visit. RhD genotyping of the father can also be considered.
      ii. Frequent measurements of maternal antibodies are of important predictive value in the first sensitive pregnancy. Peak systolic velocities in the fetal middle cerebral artery are of significant value in predicting the development of anemia in all future pregnancies.[34]
      iii. Referral to local and national support forums, like the Allo Hope Foundation, to empower patients with alloimmunization to advocate for optimization of prenatal care should be considered.[35]

I. How should we monitor women who do not receive RhIG and desire future pregnancies?

An IAT should be repeated 6–12 months after the RhD-mismatched transfusion event. Detection of anti-D indicates the formation of an alloantibody to the D antigen. If anti-D is detected at this time and future pregnancies are desired, the patient should be referred to ObGyn for preconception counseling with considerations outlined previously.

3 | CONCLUSION

It is a challenge to maintain and provide type O RhD negative blood products to females of childbearing age with unknown blood types during emergency or prolonged resuscitation. In addition, utilization of LTO + WB is increasing in the prehospital and hospital settings and is often offered exclusively as an RhD positive product. Due to these inventory challenges, the frequency of RhD-mismatched transfusions in females with childbearing potential may increase.

Prevention of alloimmunization after RhD-mismatched transfusions has not been widely studied. We have described our institutional protocol to prevent RhD alloimmunization in females of childbearing age who receive RhD-mismatched transfusions. To our knowledge, this is the first guideline to be published directing the management of such cases.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

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