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Emergent Transfusion and Hemolytic Disease of the Fetus and Newborn Risk-Mitigation in Females of Childbearing Potential with Life-Threatening Bleeding: A Clinical Practice Guideline

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Short title: Transfusion in Females of Childbearing Potential

Background: Timely resuscitation of patients in hemorrhagic shock is lifesaving. Blood product composition for massive transfusion protocols varies (whole blood versus conventional component therapy). Current whole blood inventory is predominantly RhD-positive, raising questions regarding the transfusion approach for females of childbearing potential (FCP).

Study Design: Working groups were assembled that included experts in Trauma Surgery, Transfusion Medicine, Hematology, Maternal and Fetal Medicine, Emergency Medicine, Anesthesiology, Neonatology, and Pediatrics. Patient stakeholders and ethics representatives were included in each working group. An evidence review team at Johns Hopkins University performed systematic reviews and provided final reports. The Delphi method was used to refine recommendations and practice points for each key question that reflected consideration of the following factors: Balance of Benefits and Harms; Certainty of Evidence; Values and Preferences; Resource Use and Costs; Ethics, Equity; Feasibility.

Results: Key questions addressed were: 1) strategies to increase blood donation and availability of RhD-negative blood products; 2) optimal blood product for FCPs in hemorrhagic shock whose RhD type is not known and RhD-negative LTOWB is not available; 3) indications for Rh immune globulin (RhIg) for post-exposure D-alloimmunization prophylaxis in RhD-negative FCPs who received RhD-positive blood products; 4) timing and performance of antibody screening following RhD-positive blood transfusion in RhD-negative FCPs. Herein, we report the detailed literature review and analysis, including articles screened, retrieved, assessed and included, as well as the recommendations with their rationale. Consensus was achieved for all recommendations and practice points.

Conclusions: These recommendations provide guidance for the optimal resuscitation and post-resuscitation care of FCP with life-threatening bleeding.

Key Words: Hemolytic disease of the fetus and newborn, hemorrhage, transfusion, shock, female of childbearing potential

INTRODUCTION

The optimal transfusion strategy for resuscitating patients with life-threatening hemorrhage is an active area of investigation. Current evidence-based practice emphasizes balanced blood product resuscitation, provided either in a fixed ratio if using conventional component therapy (CT; red blood cells (RBCs), plasma, and platelets) or with low titer group O whole blood (LTOWB).[1] Timely hemostatic resuscitation is lifesaving; however, blood products are a scarce resource with potential adverse events. One such adverse event is D-alloimmunization, the production of an antibody against the RhD protein, which can occur if RhD-negative recipients are transfused with RhD-positive blood products.[2] If a female of childbearing potential (FCP) (age 0-55 years) becomes D-alloimmunized, she could experience hemolytic disease of the fetus and newborn (HDFN)[3] in a future pregnancy if several other events also occur.[2,4,5]

Traditional dogma has emphasized the use of Rh-negative blood products in FCP due to the potential risk of D-alloimmunization and possible subsequent HDFN. However, the rate of future HDFN following receipt of RhD-positive blood products during trauma resuscitation has been calculated to be between 0.04% to ~6% depending on the severity of the disease and the population of FCPs studied.[5-7] When HDFN does occur, it is a serious yet treatable disease with access to advanced antenatal healthcare [8]; however, diagnosis and management of HDFN can be complex, highly specialized, resource-intensive, invasive, and stressful. While the exclusive use of RhD-negative blood products in FCPs would avoid D-alloimmunization, it is unlikely given the distribution of blood types amongst the population that Rh-negative blood products will ever be available in sufficient quantities for pre-hospital use and emergent in-hospital resuscitation in military and civilian settings. [9] [10] Additionally, recent evidence has suggested that LTOWB has advantages over CT for the resuscitation of hemorrhagic shock [11,12] which has increased the

frequency of its use in US trauma systems[13,14] with the downstream consequence of increased exposure of RhD-negative FCPs to RhD-positive blood products. Therefore, updated clinical guidance is required.

The following are the recommendations of an expert panel regarding blood product availability and selection for resuscitating injured FCPs, and the management of RhD-negative FCPs who were exposed to RhD-positive blood products.

METHODS

The development of these guidelines was supported by the Department of Defense Combat Casualty Care Research Program, the Trauma, Hemostasis, and Oxygenation Research (THOR) Network Foundation, and the Allo Hope Foundation. These guidelines follow international standards for guideline development,[15]and have been reported in accordance with the AGREE II (Appraisal of Guidelines for Research and Evaluation II) reporting checklist (Supplemental Digital Content 1, Appendix A, http://links.lww.com/JACS/A586).[16] Detailed methods are provided in Supplemental Digital Content 1, Appendix B, http://links.lww.com/JACS/A586. Four working groups were formed to address major content areas of Trauma and Transfusion Medicine, Hematology, Maternal and Fetal Medicine, and Neonatology. In order to ensure diverse perspectives and balance priorities across multiple disciplines, the panel responsible for creating and voting on these guidelines comprised experts in the fields of trauma surgery, emergency medicine, anesthesiology, transfusion medicine, hematology, maternal and fetal medicine, neonatology and pediatrics. Each working group also included a bioethicist and patient advocates. The members of these working groups are listed in Supplemental Digital Content 1, Appendix C, http://links.lww.com/JACS/A586.

PICOT framework (Population, Intervention, Comparison, and Outcome, with Time) was used by the working groups to define clinical research questions (Table 1). A team at Johns Hopkins University was commissioned to conduct systematic reviews. Protocols were registered on PROSPERO for the 7 systematic reviews conducted for this guideline. Searches were conducted in February 2024 of PubMed and Embase and, for questions related to interventions, the Cochrane Central Register of Controlled Trials (CENTRAL). Trials and observational studies were considered. The certainty of the evidence for critical outcomes identified *a priori* was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation).[17] Details on systematic review methods, including the inclusion and exclusion criteria for each research question, are presented in Supplemental Digital Content 1, Appendices D-G, http://links.lww.com/JACS/A586.

All working groups presented draft recommendations at a public meeting on November 19, 2024. Revised recommendations were voted on by the multidisciplinary work group members in a closed guideline meeting on November 20, 2024; percentage agreement was calculated. Consensus was defined prior to voting as at least 75% agreement. Voting was conducted online using Poll Everywhere. Discussion and revision occurred between voting rounds. If a recommendation did not achieve consensus after 3 rounds of voting, then that recommendation was considered to have not reached consensus. The final recommendations and the rationale to support them were provided by the working groups for comment to key stakeholders including alloimmunized women who have experienced a pregnancy affected by HDFN, and medical associations and societies. Herein we report the guidelines from the Transfusion, Trauma, and Hematology working group; the guidelines for the Maternal and Fetal Medicine and Neonatology working groups will be reported separately.[18,19]

Role of the Funding Source

The funding sources had no role in selecting the questions for review or the conduct of the systematic reviews, including the search, determination of study eligibility, synthesis, grading, or preparation of the systematic review reports. The funding sources did not influence the content of these guidelines. Representatives from the funding agency and other supporting organizations participated as subject matter experts and stakeholder representatives during the Delphi process. Conflicts of interest were fully disclosed and managed on an individual basis (Supplemental Digital Content 1, Appendix C, http://links.lww.com/JACS/A586).

RESULTS

The full reports for the systematic reviews by question can be found in Supplemental Digital Content 1, Appendices D-G, http://links.lww.com/JACS/A586. All of the recommendations and practice points from the transfusion, trauma, and hematology working group achieved consensus approval in the Delphi process and are presented below.

Trauma and Transfusion Section

Trauma and Transfusion, Question 1:

What is the effectiveness of methods to increase the donation of RhD-negative blood products?

RECOMMENDATION 1:

We recommend that blood centers optimize methods to increase donation from RhD-negative donors through targeted and informative recruitment and retention methods.

(97.6% Agreement; certainty of evidence = very low)

Rationale: The certainty of evidence for methods to increase and sustain donations from RhD-negative donors is very low (Supplemental Digital Content 1, Appendix D, http://links.lww.com/JACS/A586).[20-22] Even in the absence of published data, there are

obvious benefits to increasing donation amongst group O and RhD-negative individuals and those with rare blood groups because these blood products are scarce and, in some cases, might be the only suitable product for some recipients. Practice points for Trauma and Transfusion Question 1 can be found in Table 2.

Trauma and Transfusion, Question 2:

What are the benefits and harms of LTOWB transfusion compared to transfusion of conventional component therapy for children and adults with life-threatening bleeding?

RECOMMENDATION 2A:

We recommend the use of RhD-positive blood products for the initial resuscitation of patients with life-threatening hemorrhage when RhD-negative blood products are not available, regardless of patient age or sex.

(97.6% Agreement; certainty of evidence = very low)

RECOMMENDATION 2B:

We suggest the use of RhD-negative LTOWB for the initial resuscitation of ABO-type unknown female patients with life-threatening hemorrhage. If unavailable or impractical, we suggest the use of RhD-positive LTOWB.

(80.5% Agreement; certainty of evidence = very low)

Rationale: There are practical and logistic benefits to using LTOWB. LTOWB provides all of the components of blood in a single bag, thereby ensuring that balanced resuscitation is provided immediately, which might not be the case when CT is used for the resuscitation.[23,24] The importance of time to transfusion in the setting of hemorrhagic shock has been well-described.[25] LTOWB is a more potent product with less additive solution, higher hemoglobin, clotting factor, and platelet concentrations per volume.[26]

Preclinical data show improved hemostasis with cold versus room temperature stored platelets,[27-29] and clinical trial data show no increased safety risk or mortality with use of cold platelet product in patients at risk of hemorrhagic shock.[30] The cold-stored platelets in LTOWB should confer a lower risk of bacterial contamination compared to room temperature platelets. An LTOWB unit has a longer storage duration compared to thawed plasma or room temperature platelets, thereby permitting provision of these products where they might not otherwise be available. Furthermore, in prehospital or austere environments when only a limited supply of blood product can be brought to the patient, LTOWB ensures compatibility and balanced resuscitation.

Regarding the outcomes of mortality and blood product use between recipients of LTOWB compared to CT alone, the systematic review showed substantial variability across studies in terms of results, methodology, and degree of bias (Supplemental Digital Content 1, Appendix E, http://links.lww.com/JACS/A586). While overall the certainty of evidence was very low, for 24-hour and 28-day or 30-day mortality there was not an increased risk of death in the LTOWB group compared to the CT group. In total, 10 observational studies reported the median number of units of total blood products transfused. Most studies did not report a significant difference in amount of blood products transfused, though this analysis was made challenging by the use of different units of measure across studies. For the safety outcomes such as ICU-free days, ventilator-free days, thrombosis, infection, and transfusion reactions, none of the studies found an increased risk of adverse outcomes amongst the LTOWB recipients compared to the CT group.

The growing use and availability of LTOWB in emergency settings invites ethical scrutiny about sex-based differences in trauma care. If RhD-positive LTOWB is increasingly used to resuscitate males, is it ethical to withhold the same potentially life-saving product from females of childbearing potential (FCPs) due to future reproductive risks? In cases where an RhD-type unknown or RhD-negative FCP presents in hemorrhagic shock, the immediate benefit of transfusion is survival, while the potential harm, i.e., future HDFN, is both low in likelihood[5-7,31] and medically manageable with appropriate antenatal care.[8] Framed ethically, this is not a choice between survival and harm but between known, urgent benefits and hypothetical, future risks.[32] When institutions use RhD-positive LTOWB in such scenarios, they incur corresponding duties: to offer post-resuscitation D-alloimmunization monitoring, to ensure longitudinal reproductive counseling for those who become D-alloimmunized, and to steward their inventory of RhD-negative blood products to ensure their availability when needed.[32]

The values and preferences of potential LTWOB recipients have been analyzed via surveys of community stakeholders. Survey respondents included FCPs, their partners, parents on behalf of their children, and alloimmunized mothers who have had a pregnancy impacted by HDFN. These individuals possess unique insight into the potential impact of an HDFN diagnosis. When presented with the theoretical future risk of HDFN and potential survival benefit of LTOWB use, all surveys found a general willingness (>80-90%) of the participants to accept the potential risk of future HDFN in favor of improved chances of survival from the early administration of blood products.[33-36]

In summary, the quality of the evidence that compares outcomes following resuscitation with LTOWB or CT alone is very low. LTOWB has known benefits over CT, including efficiency and ease of administration, without an increased risk of mortality or safety concerns. Use of LTOWB in FCPs is consistent with the values and preferences of the majority of this population surveyed. Lastly, using LTOWB in injured FCPs is an ethically sound practice so long as clinicians accept the ethical obligation to mitigate this risk when feasible, ensure informed counseling, and support future reproductive health.

Trauma and Transfusion, Question 3:

What are the benefits and harms of using RhD immune globulin compared to no intervention in RhD-negative FCP who have received at least one dose of RhD-positive RBCs or LTOWB?

RECOMMENDATION 3A:

We recommend against the use of Rh immune globulin (RhIg) in RhD-negative females of childbearing potential (FCP) with life-threatening hemorrhage who have received more than a small quantity of RhD-positive RBC/LTOWB during their resuscitation.

(97.4% Agreement; certainty of evidence = very low)

RECOMMENDATION 3B:

We recommend against the use of RhIg for RhD-negative males or women who are no longer of childbearing potential regardless of the quantity of RhD-positive RBC/LTOWB transfused.

(97.4% Agreement; certainty of evidence = very low)

Rationale: RhIg is a biologic treatment that helps to prevent D-alloimmunization in RhD-negative individuals who were exposed to RhD-positive RBCs. The literature to inform this recommendation was sparse and the certainty of evidence was very low

(Supplemental Digital Content 1, Appendix F, http://links.lww.com/JACS/A586). [37]

There were not any recent studies in RhD-negative females who received RhD-positive RBCs or LTOWB that reported the rate of anti-D production after RhIg administration, nor any studies evaluating the benefits and harms of RhIg.

The risk of hemolysis following the use of RhIg likely increases with the volume of RhD-positive RBC/LTOWB that was administered. The RhD-positive transfusion volume threshold for when RhIg can be safely administered has not been, and is not likely to be, determined. Large-volume treatment with RhIg is an accepted therapy for RhD-positive individuals with an intact spleen suffering from immune thrombocytopenia purpura (ITP) that often results in a 1-2 g/dl decrease in the patient's hemoglobin concentration, which is similar to the expected decrease in hemoglobin concentration following the hemolysis of 1-2 units of RBCs.[38] Implicit in this treatment is that the ITP patient has normal kidney and liver function and that the benefit outweighs the risk from the products of hemolysis, which can be rapidly neutralized and/or excreted with normal organ function. However, this assumption might not be true for patients with life-threatening hemorrhage, especially trauma patients with systemic injuries and organ failure. One editorial offered an opinion that it is unsafe to hemolyze more than two RBC (or LTOWB) units.[39] Thus, the term "small quantity" indicates that it is likely unsafe to attempt to hemolyze more than 1-2 units of RhD-positive RBCs with RhIg.

RhIg, a medication in chronic short supply, should be prioritized for RhD-negative FCP when its benefit will be maximized, that is when an FCP has received only a small quantity of RhD-positive RBCs. Each institution should define this quantity in its policy for managing RhD-negative FCPs who have received RhD-positive RBCs. Because RhD-

negative males and females who are not of childbearing potential are not at risk of future pregnancy, and because RhIg is in chronic shortage, the RhIg inventory should be preserved for HDFN mitigation amongst patients who will have the most benefit from the medication. Reserving RhIg for those with the greatest potential to benefit reflects a just allocation of a scarce biologic resource. Practice points for Trauma and Transfusion Question 3 can be found in Table 3.

Hematology Section

Hematology, Question 1:

Among RhD-negative FCP, should antibody testing for anti-D antibodies be performed after exposure to RhD-positive blood products or at the next transfusion or during the first trimester of pregnancy? Among RhD-negative females of any age, how many weeks or months after exposure to RhD-positive blood products should screening for anti-D antibodies be performed?

RECOMMENDATION 1:

We recommend antibody screening at a minimum of 14 weeks after exposure to RhD-positive blood products for any FCP. If antibody screening is performed earlier than 14 weeks from exposure for any reason, repeat antibody screening should be performed at a minimum of 14 weeks from exposure since antibody testing could be falsely negative.

(97.4% Agreement; certainty of evidence = very low)

Rationale: Identifying RBC antibodies prior to pregnancy allows for pre-pregnancy consultation and treatment planning, which can mitigate time-sensitive barriers such as Maternal Fetal Medicine physician referral, paternal zygosity testing, and initiation of IVIg therapy in the first trimester when warranted. Timing of antibody formation is variable and based on many factors, including the immunogenicity of the red blood cell

antigen as well as the immune system of the FCP. Considerations around the appropriate timing for antibody screening include the test sensitivity relative to the time of antibody formation and the risk of patient attrition, among others. Antibody screening could miss a low level of antibody causing a false negative result, especially if performed too early after exposure to RhD-positive blood products (i.e. at hospital discharge). [40] Testing at a minimum of 14 weeks and no later than 24 weeks (6 months)[40] after exposure balances these competing factors. Practice points for Hematology Question 1 can be found in Table 4.

DISCUSSION

Injury is the leading cause of death in children and adults in the United States[41] and hemorrhage represents the primary driver of preventable death in both civilian[42] and military[43] settings. Timely balanced blood product resuscitation can be a life-saving intervention to reduce preventable mortality after trauma.[25] For the treatment of combat causalities, the Joint Trauma System Clinical Practice Guideline recommends the use of LTOWB and Fresh Whole Blood over component therapy, and Rh-negative blood products for FCP if available, else Rh-D positive products should be transfused as the "treatment of exsanguination takes precedence over potential future pregnancy outcomes".[44] In civilian practice, the optimal hemostatic resuscitation for adult FCPs and children in the setting of increased LTOWB availability and use is not well-described, and therefore practice patterns vary widely. Current recommendations to guide clinicians in the care of these patients are limited. A practice management guideline from the Eastern Association of the Surgery of Trauma (2024) conditionally recommended using WB in adult civilian trauma patients receiving blood transfusions, although this recommendation notably excluded children and FCPs.[45] As 62% of the females in the USA in 2021 were between

0-49 years old,[5] the Trauma, Transfusion Medicine, and Hematology working groups of this initiative sought to address this knowledge gap through the development of four major questions (Table 1) and corresponding systematic reviews of the literature. These recommendations are critical at this time given the increasing likelihood that Rh-negative FCP will receive Rh-D positive emergency transfusions; updated clinical guidance for both transfusion practices and post-exposure surveillance of at-risk FCP is now required.

Six recommendations and twelve practice points were developed and approved through an extensive Delphi process that addressed the current RhD-negative blood product shortage, resuscitation practices in FCPs and children, use of RhIg after exposure to RhD-positive blood products, and timing of antibody screening for RhD-negative FCPs after exposure to RhD-positive blood products. Widespread implementation of these guidelines will require investment and input from various stakeholders, including blood suppliers, clinicians, medical societies, hospital systems and patients. The guidelines are intended to be broadly applicable in variably resourced environments including forward military locations, prehospital civilian and in-hospital settings. Implementation will require understanding of blood product inventory and massive transfusion logistics. Regardless of setting, post-exposure management for RhD-negative FCPs should follow standardized pathways that include documentation, counseling, and scheduled antibody screening (14 weeks–6 months) with results shared with outpatient clinicians to ensure continuity of care, informed decision making, and future reproductive health.

While these guidelines rely on multiple factors in addition to the existing literature, the strength of the recommendations is limited by the overall low quality of evidence. High quality research is needed to further inform evidence-based care and guide optimal resuscitation practice for all.

Future research priorities include: To assess the effectiveness of LTOWB to reduce mortality in the setting of life threatening bleeding; To determine the rate of D-alloimmunization in RhD-negative females of childbearing potential who are transfused with RhD-positive RBC/LTOWB during resuscitation from life threatening bleeding; and To better understand the LTOWB demand and practice patterns in order to optimize donor recruitment. These guidelines will be updated in 5 year intervals as new data become available, specifically the results of several ongoing randomized-controlled trials comparing LTOWB versus CT in various populations and settings (MATIC2, SWIFT, TOWAR, TROOP).

Limitations of the guideline development process include the lack of high-quality data in the literature, such that some recommendations are based on little or low-quality evidence. However, existing literature was only one criterion upon which to base the recommendations, and other important considerations were included, including balance of benefits and harms; certainty of evidence; values and preferences; resource use and costs; ethics, equity; and feasibility. Additionally, there was less than 100% agreement amongst experts (range 80-100%), though consensus ultimately was achieved for all recommendations and practice points with the majority having greater than 90% agreement.

CONCLUSION

These recommendations, developed by experts in multiple disciplines including transfusion, trauma, and hematology describe optimal resuscitation strategy and post-resuscitation care of FCPs. These guidelines have the potential to standardize and improve the care of FCPs with life-threatening hemorrhage. In doing so, they offer ethically grounded guidance for balancing individual patient rights, public health imperatives, and stewardship of scarce resources.

Appendix

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Legend:

Figure 1. RhD antibody screening algorithm for RhD-negative females of childbearing potential who receive RhD-positive low titer group O (whole blood) or RBCs (red blood cells).

Precis

This clinical practice guideline addresses key knowledge gaps regarding best practice for emergent transfusion and risk-mitigation of hemolytic disease of the fetus and newborn in females of childbearing potential (FCP) with life-threatening bleeding. These guidelines have the potential to standardize and improve the care of FCPs with life-threatening hemorrhage.

Table 1. Review Questions, using PICOT framework (Population, Comparison, Outcomes, Study Design, Timing and Setting)

Trauma and Transfusion Working Group
Question 1: What is the effectiveness of methods to increase the donation of RhD-negative blood products?
Population
Group O RhD-negative donors who are eligible to donate LTOWB or RBCs
People with rare or uncommon blood types
Intervention
Incentives
Social media
Community-based competition for donation rates and dissemination of when the products were used in the community
Gift cards
Provision of information about how donation used
Any other incentives to increase the donation rate amongst people with rare or uncommon blood groups
Donor notification of blood use (where it was used)
Recipient option to notify donor
Comparison
Different methods
Current practice
Different values or levels of incentives
No incentives
No social media recruitment
Outcomes
Number of new donors*
Rate of repeat donations from group O or from rare blood types*
RhD-negative donors who are eligible to donate LTOWB or RBCs*
Study design
Trials
Observational studies
Excluded no original data and meeting abstracts
Timing and setting
Civilian blood collection centers (national, community/hospital or university-based)
Question 2: What are the benefits and harms of transfusion of LTOWB compared to transfusion of conventional component therapy for children and adults with life-threatening bleeding?
Population
Adults and children with life-threatening bleeding
Excluded patients who did not meet the definition of life-threatening bleeding
Intervention
Transfusion of LTOWB (with or without conventional components)
Excluded studies with warm fresh whole blood as the intervention or cold stored whole blood that was supplemented with conventional room temperature platelets

Comparison
Transfusion of conventional components exclusively (RBCs, plasma, platelets)
Outcomes*
Mortality
≤ 24 hours*
28/30-day*
In-hospital*
Total blood products up to 72 hours post-admission (in units or mL/kg)*
Adverse clinical outcomes
Renal failure
Acute respiratory distress syndrome
ICU free days
Mechanical ventilation free days
Myocardial infarction
Cerebrovascular accident
Arterial and venous thrombosis events (non-superficial vein)
Infection/sepsis
Transfusion reactions
Time to balanced resuscitation (time from start of massive bleeding to at least a 2:1 ratio of red cells to plasma or red cells to platelets). Use of whole blood is a balanced resuscitation
Number of donor exposures
Study Design
RCT
Prospective observational studies
Retrospective observational studies
Excluded studies with no original data, meeting abstracts, and case reports
Timing and Setting
All settings
Question 3: What are the benefits and harms of using RhD immune globulin compared to no intervention in RhD-negative FCP who have received at least one dose of RhD-positive RBCs or LTOWB?
Population
RhD-negative FCP who have received at least one dose (or weight appropriate volume) of RhD-positive RBCs or LTOWB
Intervention
Rh immune globulin (RhIg)
Comparison
No intervention
Outcomes
Rate of anti-D production after Rh immune globulin administration*
Adverse events
Hemolysis*
Renal insufficiency/failure*
Study design
RCT
Observational studies

Excluded studies with no original data and meeting abstracts
Timing and setting
All settings
Hematology Working Group
Question 1: Among RhD-negative FCP, should antibody testing for anti-D antibodies be performed after exposure to RhD-positive blood products or at the next transfusion or during the first trimester of pregnancy? Among RhD-negative females of any age, how many weeks or months after exposure to RhD-positive blood products should screening for anti-D antibodies be performed?
Population
RhD-negative females receiving:
RhD-positive RBC
RhD-positive LTOWB
RhD-positive platelets
Intervention
Antibody testing after known exposure
Comparison
Performing antibody testing:
At next transfusion
During first trimester of pregnancy (only among FCP)
Number of weeks after exposure
Outcomes
Anti-D antibody identified*
Time from exposure when anti-D antibodies were identified*
FCP seek early OB care (only among FCP)
FCP deciding against another pregnancy (only among FCP)
Poor pregnancy or fetal outcome(s), including HDFN, hydrops, heart failure, kernicterus, death, and any fetus/newborn requiring any therapy, including intrauterine transfusions, phototherapy for hyperbilirubinemia, RBC transfusion, or exchange transfusion (only among FCP)*
Study design
Prospective observational studies
Retrospective observational studies
Excluded studies with no original data and meeting abstracts
Timing and setting
All settings

*Outcomes indicate critical outcomes (ie those which were graded).

FCP, females of childbearing potential; HDFN, hemolytic disease of the fetus/newborn; ICU, intensive care unit; LTOWB, low titer group O whole blood; OB, obstetric; RBC, red blood cells; RCT, randomized controlled trial; Rh, rhesus

Table 2. Practice Points and Rationale for Trauma and Transfusion Question 1

Practice point	Text	Agreement, %
1.1	RhD-negative red blood cells (RBC)/ Low Titer Group O Whole Blood (LTOWB) do not pose a D-alloimmunization risk to an RhD-negative recipient thereby eliminating the possibility of these products causing anti-D alloimmunization and anti-D mediated hemolytic disease of the fetus and newborn (HDFN) in the future.	90
1.2	RhD-negative donor recruitment strategies should be targeted, personalized, non-coercive, and informative to increase the likelihood of donation. Strategies can include targeted letter campaigns, incentivizing donation with gift cards, texts indicating when their donation was used thereby linking donors with recipients, and competitions between regions for who can donate the most RhD-negative whole blood, and specifically LTOWB.	97.6
1.3	LTOWB units near expiration should be recycled into group O RBC or redistributed to larger volume centers to reduce waste.	100
1.4	Hospitals should: a. Implement a policy of switching group RhD-negative or RhD-status unknown patients to Rh-positive RBC wherever clinically appropriate. b. Issue ABO group-specific RBC as often as possible to non-group O recipients for non-urgent transfusions.	92.7
1.5	Nulliparous women or multiparous women who are not HLA-alloimmunized can donate LTOWB.	100

Rationale: Preventing HDFN in trauma patients requires a multifaceted approach that includes increasing the availability of RhD-negative RBCs or LTOWB and prioritizing these products for emergent transfusion to RhD-negative or RhD-type unknown FCPs. A two-pronged approach to this end is needed: 1) Enhancing RhD-negative donor recruitment; 2) Stewardship of the Rh-D negative blood supply, including minimizing inappropriate use and reducing waste of this precious resource.

Table 3. Practice Points and Rationale for Trauma and Transfusion Question 3

Practice point	Text	Agreement, %	Rationale
3.1	When determining eligibility for RhIg administration, clinicians should consider the patient's age, future childbearing potential, the quantity of RhD-positive RBCs transfused, the patient's ability to tolerate the effects of potential hemolysis within 72 hours of exposure to the RhD-positive transfusion, and ability to tolerate the RhIg infusion.	86.8	RhIg, a medication in chronic short supply, should be prioritized for patients when its benefit will be maximized and outweighs potential harm.
3.2	A consultation with hospital service(s) knowledgeable about the small risks of D-alloimmunization and the potential future risk of HDFN is advisable so that an eligible patient/her decision-makers can make an informed choice about RhIg administration and understand the rationale for, and potential future implications of, an Rh incompatible blood transfusion.	86.8	Shared decision-making between a knowledgeable clinician and patient should balance the multiple factors that contribute to the risk of future HDFN.
3.3	RBC exchange should not be utilized for D-alloimmunization prevention in any RhD-negative patient who received RhD-positive RBC/LTOWB during their resuscitation.	97.4	The 9th edition of the American Society For Apheresis (ASFA) guidelines state that performing RBC exchange for RhD-alloimmunization prophylaxis following transfusion is potentially ineffective or harmful and is therefore not recommended.[46]
3.4	RhD-negative patients with life-threatening hemorrhage who receive only RhD-positive platelets should not receive RhIg regardless of age or sex.	86.8	The risk of D-alloimmunization to the most commonly transfused platelet product in the US, apheresis platelets, has been reported to be 0.75%.[47]

Table 4. Practice Points and rationale for Hematology Question 1

Practice point	Text	Agreement, %
1.1	The transfusion service should notify the attending provider when a RhD-negative female receives RhD-positive blood. Antibody screening should be ordered by the provider who was caring for the patient at the time of RhD-positive blood product exposure, if possible. In a patient who received emergency, uncrossmatched blood products who may, for example, be discharged from the Trauma Surgery service to a patient's outpatient clinician for follow-up (who may be trained in Family Medicine, Internal Medicine, or Obstetrics/Gynecology), appropriate hand-off communication is critical such that the outpatient provider orders antibody screening at a minimum of 14 weeks after exposure. This algorithm is depicted in Figure 1.	100%
1.2	Alloimmunized women should be counseled by the provider at an institution with the most expertise in this area, which can vary by specialty or role. Some examples of physicians who may be well-versed in alloimmunization include Transfusion Medicine or Clinical Pathology Physicians, Obstetricians/Gynecologists, Maternal-Fetal-Medicine or High-Risk Obstetricians, Hematologists or Family Practice Physicians.	94.1%
1.3	Any female of childbearing potential (of any blood type) who has ever been transfused should have an antibody screen once pregnancy is confirmed as soon as possible to diagnose alloimmunization and manage potential HDFN.	95.1%

Rationale: People of any blood type can develop non-RhD RBC antibodies following transfusion. See Hematology Recommendation 1 regarding benefits of prompt diagnosis.

Figure