



Advancing Transfusion and
Cellular Therapies Worldwide

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To: AABB Members

From: Michael Murphy, MD, FRCP, FRCPath, FFPATH - President
Debra BenAvram - Chief Executive Officer

Re: Recommendations on the Use of Group O Red Blood Cells

Association Bulletins provide a mechanism for publication of documents that have been approved by the Board of Directors for distribution to individual and institutional members, such as:

- Standards that were adopted after publication of the most recent edition of *Standards*.
- Statements of AABB policy intended for distribution to members.
- Guidance, recommendations, and reports that have been developed by AABB Committees or National Office staff for distribution to members.

This Association Bulletin contains information and makes recommendations intended to decrease the over-reliance on group O Rh(D)-negative Red Blood Cells (RBCs). The recommendations provided are based on a review of current practice patterns, and the relative safety and feasibility of reducing group O Rh(D)-negative RBC use in specific patient populations. Hospitals and blood centers should work together to optimize the use of this precious resource; possible models for these collaborations are proposed. Although several important points are made in each section of this bulletin, the key recommendations are listed below.

Key Recommendations for Transfusion Services

1. Group O Rh(D)-negative RBCs should be reserved for three cohorts of females of childbearing potential: those who are group O Rh(D)-negative, those who are Rh(D)-negative requiring transfusion when type-specific blood is unavailable, and those of unknown blood type who require RBCs before the completion of pretransfusion testing.
2. Hospital transfusion services should closely monitor utilization of group O, Rh(D)-negative inventory, particularly during bleeding emergencies and during group O Rh(D)-negative shortages. Policies should be developed that describe when patients should be switched to Rh(D)-positive RBCs to avoid depletion of the group O Rh(D)-negative supply.
3. Hospitals should have protocols to expedite sample collection to quickly switch patients to type-specific blood upon completion of pretransfusion testing.



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4. Hospital transfusion services can have a policy for the use of Rh-positive-red-cell containing components in Rh-negative recipients including during times of critical inventory levels.

Key Recommendations for Blood Centers

1. Collection facilities should work with hospital clients to develop reasonable targets for group O usage.
2. Collection facilities can work with hospital clients to develop ways to encourage optimal use of group O Rh(D)-negative RBCs.
3. Collection facilities can create a policy to address product inventory shortages.¹⁷

Background on Use of Group O RBCs

Group O Rh(D)-negative RBCs may be safely transfused to recipients of any ABO Rh(D) type, which has led to a high demand for this limited resource. Utilization rates of group O Rh(D)-negative RBCs vary dramatically by practice setting. Factors that influence utilization rates include local availability of group O Rh(D)-negative units, available hospital and blood bank immunohematology testing services, and the variety and type of patient populations, among others.

Rural and/or smaller hospitals may stock only group A and O Rh(D)-negative RBCs to simplify inventory and decrease wastage, as these units are compatible with the majority of patient blood types.¹ This leads to a practice of transfusing more group O RBCs to non-group-O patients, as well as using group O Rh(D)-negative RBCs for non-group-O Rh(D)-negative patients.² Rural hospitals may also maintain proportionally larger group O Rh(D)-negative RBC inventories to avoid shortages during a bleeding emergency.^{1,3}

Large hospitals commonly located in urban areas often require sizable inventories of group O RBCs to accommodate complex patient populations, including: neonates; stem cell transplant recipients; and patients requiring antigen-negative blood (i.e., sickle cell anemia and other commonly alloimmunized populations). Urban hospitals also use a proportionately large number of group O RBCs to care for trauma patients requiring emergent transfusion prior to blood group determination. Finally, larger hospitals may use proportionally more group O RBCs if they accept short dated units to avoid wastage due to expiration.¹

In the United States approximately 6.9% of donors are group O Rh(D)-negative, yet the proportion of group O (Rh)D-negative RBCs transfused is higher, rising from 9.7% in 2013 to 10.8% in 2015.⁴ The Choosing Wisely campaign⁵ recommended that group O Rh(D)-negative RBCs should be reserved for group O Rh(D)-negative patients and females of childbearing potential. However, a recent study estimated that 44.5% of group O Rh(D)-negative RBC units used could have been replaced by group O Rh(D)-positive RBC units if age and gender factors were considered.⁶ This overuse of group O Rh(D)-negative could lead to critical shortages, limiting the supply for patients who need them most.



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Recommendations for Appropriate Group O Use

Recommendation 1: Group O Rh(D)-negative RBCs should be reserved for three cohorts of females of childbearing potential: those who are group O Rh(D)-negative, those who are Rh(D)-negative requiring transfusion when type-specific blood is unavailable, and those of unknown blood type who require RBCs before the completion of pretransfusion testing.⁵

Significant efforts should be made to avoid transfusion of Rh(D)-positive RBCs to females of childbearing potential (unless there is no alternative), as alloimmunization may cause hemolytic disease of the fetus/newborn during future pregnancies.

In emergencies, males and postmenopausal females should be given group O Rh(D)-positive RBCs,⁷ then switched to type-specific RBCs as soon as testing is completed. In addition, group O Rh(D)-positive RBCs should be given to group O Rh(D)-negative patients in cases of significant surgical or medical bleeding when group O Rh(D)-negative cells are not available or are in short supply.⁷ Under non-emergent conditions group O Rh(D)-negative males and females of no childbearing potential can also receive group O Rh(D)-positive RBCs when inventory conditions dictate, unless they are known to be alloimmunized to Rh(D).

Using Rh(D)-positive RBCs in Rh(D)-negative patients is generally a safe practice. The risk of alloimmunization is 21-26% for hospitalized Rh(D)-negative patients who have received at least one Rh(D)-positive RBC product in the setting of hemorrhage.⁷⁻¹¹ This risk decreases to less than 10% for marrow and solid-organ transplant patients on immunosuppressive regimens,¹²⁻¹⁴ and it is 3-6% for patients with an unknown blood type receiving Rh(D)-positive RBCs in the emergency room setting.⁷ The risk of an acute hemolytic transfusion reaction after receipt of an RhD-incompatible RBC unit is less than 1% in emergency settings,¹⁵ and it is usually mild. Unlike acute hemolytic transfusion reactions caused by isohemagglutinins, D antibodies cause extravascular hemolysis, which is usually not associated with severe complications. In addition, alloimmunization to Rh(D) will not be a clinical issue for the majority of patients who experience only a single lifetime transfusion episode.

Switching to Rh(D)-positive is discouraged for some Rh(D)-negative patient populations, as they are more heavily transfused. Patients who require chronic transfusion support, pediatric patients undergoing multiple surgical procedures, or patients destined for a stem cell transplant procedure should be maintained on Rh(D)-negative RBCs. Because most Rh(D)-negative patients in the United States are of the rr serotype (ce/ce), providing Rh(D)-negative RBCs will also mitigate the risk of alloimmunization to the C and E antigens, making it easier to find compatible units for future transfusions.

If a patient requires antigen-negative RBCs, the blood bank should try to provide ABO type-specific phenotyped RBCs. Even if group O antigen-negative RBCs are available, blood bank technologists should be trained to phenotype type-specific units instead. This may not always be



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practical, especially in emergent settings or in patients with multiple alloantibodies. However, ensuring that blood bank technologists are using type-specific RBCs when possible will help reduce overall group O usage.

Hospitals supporting sickle cell patients generally try to match Rh (D, C, and E) and Kell (K) antigens prophylactically to prevent alloimmunization.¹⁶ To avoid using Rh(D)-negative RBCs, hospitals should maintain an inventory of CEK-negative Rh(D)-positive RBCs for patients who require C-negative or E-negative RBCs. Approximately 17.6% of donors of European ancestry are Rh(D)-positive CEK-negative vs. 3% who are Rh(D)-negative CEK-negative, making this an obvious choice for inventory control.

Recommendation 2: Hospital transfusion services should closely monitor utilization of Rh(D)-negative inventory. Policies should be developed that describe when patients should be switched to Rh(D)-positive RBCs to avoid depletion of the group O Rh(D)-negative supply.

Benchmark data are not widely available to guide hospitals in what is appropriate group O Rh(D)-negative usage. Therefore, hospitals should conduct periodic audits of group O blood use to better understand their utilization patterns and develop policies for appropriate usage.

Recommendation 3: Hospitals should have protocols to expedite sample collection to quickly switch patients to type-specific blood upon completion of pretransfusion testing.²

Group O RBCs should be used for group O patients and for emergent/initial transfusion support in patients of unknown blood group. Other situations for which use of group O RBCs may be justified for non-group-O patients include neonatal transfusions, solid-organ transplant patients with passenger lymphocyte syndrome, and during stem cell transplantation, as discussed below.

Patients should be switched to type-specific RBCs as soon as pretransfusion testing is completed and compatible blood is available. Verification of the patient's ABO type requires either a second specimen drawn at the current visit or, if available, comparison of the current testing result with blood bank records. Alternatively, some institutions use electronic patient verification to eliminate the need to test a second separately drawn specimen to confirm the recipient blood type. This practice is permitted by AABB *Standards for Blood Banks and Transfusion Services*¹⁷ (Standard 5.16.2.2, ~~33rd ed~~ ^{31st ed.}) and described in guidance from the Food and Drug Administration.¹⁸

Because a group O RBC unit with additive solution (AS) contains approximately 10-15 mL of plasma,¹⁹ there is a small risk for hemolysis in non-group-O recipients due to the passive transfer of anti-A and anti-B isohemagglutinins. Although the plasma volume in a non-AS RBC unit (e.g., a CPDA unit) is greater than 10-15 mL, the risk of hemolysis remains small. Such plasma-



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related hemolysis has been reported, but it is exceedingly rare.²⁰ Innate protective mechanisms include A and/or B antigen expression on the vascular endothelium; and A and/or B substance found in the plasma of secretors.²¹ These additional antigens adsorb some of the isoagglutinins and thus prevent hemolysis. As a result, switching to type-specific units should be safe, even after a patient has been massively transfused with group O RBCs.

The importance of early sample collection must be clearly communicated to those responsible for patient care. Transfusion services should work with their hospital transfusion committees and clinical champions to make sure this message is relayed to care teams. In addition, transfusion service staff should be fully engaged in minimizing group O Rh(D)-negative usage, as this can significantly improve inventory management.

Group O Use: Specific Patient Populations

Trauma and Mass Casualties

For safety reasons, group O RBCs are appropriately administered during the initial resuscitation of massively hemorrhaging patients of unknown ABO type.²² Administering uncrossmatched RBCs in this setting is serologically safe, i.e., hemolysis is unlikely to occur even in recipients with RBC alloantibodies against antigens on the uncrossmatched RBCs.²³ As stated above, group O Rh(D)-positive should be given to males and females without childbearing potential in emergency settings. Switching to type-specific RBCs should be

accomplished once pretransfusion testing is complete; however, safety measures are essential when transfusing type-specific RBCs, especially in busy emergency departments with multiple trauma resuscitations.

The provision of uncrossmatched blood for transfusion in air and/or ground ambulances is an increasingly common aspect of planning for trauma care. The use of group O Rh(D)-positive RBCs should be considered for these settings as most patients in this setting are either males, or females of no childbearing potential.²⁴

With regard to mass casualty events (MCEs) and disaster preparedness, the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism recommends an estimate of 3 units of group O RBCs per admission for transfusion needs.²⁵ When faced with a large number of patients simultaneously, transfusion services should prioritize uncrossmatched group O Rh(D)-negative RBCs for females presumed to be of childbearing potential. Identification of such patients in the format of the hospital emergency medical record numbering system has been suggested to facilitate allocation of group O Rh(D)-negative RBCs.²⁶ Event demographics may accentuate this concern: in the 2017 Manchester concert bombing, 69% of the



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admissions were female and 39% were ≤ 21 years old.²⁷ As in other settings, rapid typing of MCE patients is very helpful, subject to check-typing requirements.

Neonatal and Pediatric Patients

Isohemagglutinins (anti-A, anti-B) present in neonates are passively acquired from the maternal circulation and usually disappear by two months of age,²⁸ therefore testing neonatal ABO forward type is all that is required. Further, these patients are thought to be at low risk of forming red cell alloantibodies. Therefore, type-specific RBCs may be issued but only after it is clearly shown that potential maternal isohemagglutinins will not be incompatible. According to AABB *Standards*, either the maternal ABO group must be compatible with the donor RBCs, or the neonatal serum or plasma must be tested for anti-A or anti-B at the antiglobulin phase to detect IgG isohemagglutinins.¹⁷ Because both tests present logistical challenges, it is often easier to issue group O RBCs to neonates. In addition, using small aliquots from a single group O RBC unit can efficiently provide compatible RBCs for multiple patients. As a result of these safety considerations, routinely switching neonates to type-specific RBCs is unlikely to occur, and the small quantities used are unlikely to have a material impact on group O Rh(D)-negative RBC inventory.

Stem Cell Transplantation

Major, minor, or bidirectional ABO incompatibility is present in a large number of stem cell transplants.²⁹ Due to the potential effect of isohemagglutinins on engraftment and hemolysis, transfusion strategies focus on minimizing the use of RBCs that are incompatible with donor, recipient, and passively transfused isoagglutinins.³⁰ As a result, group O RBC usage is considerable in the transplant setting.

Preengraftment

Published recommendations for transfusion strategies have separated the pretransplant (Phase I), immediately postinduction/transplant (Phase II), and postengraftment (Phase III) periods.³¹ Within this rubric, specific institutional transfusion recommendations may vary in practice. For example, transfused RBCs during Phase I may be compatible with both recipient and donor isohemagglutinins or simply compatible with the recipient.^{32,33} Importantly, each institution should establish clear guidelines defining the beginning and end of each phase.

Postengraftment

It is generally recognized that a transplant recipient with complete RBC engraftment can be transitioned to a donor type-specific transfusion strategy (Phase III), but the timing of this switch currently varies among institutions.²⁹ Most agree that a recipient's forward and reverse typing



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must show no evidence of recipient red cells or isohemagglutinins before switching to donor-compatible RBCs. Even in those cases, molecular chimerism assays may show evidence of incomplete marrow engraftment and the potential for graft failure.

Also, ongoing RBC transfusion requirements may be considered as evidence of potential graft failure in the future.³¹ Transfusion services should create guidelines specific to their workflows and the risk of graft failure in their particular transplant populations.

Recommendations for Blood Collectors to Reduce Overuse of Group O RBCs

Blood collection facilities can benefit from continuing to work with hospital transfusion services to limit unnecessary group O Rh(D)-negative use. Enhanced demand translates into increased collections, causing a never-ending cycle of recruitment and donation for group O Rh(D)-negative donors. The nearly incessant recruitment causes a generalized weariness in these donors, while frequent donation may increase the risk of iron depletion. Blood collection facilities should develop a plan to reduce group O Rh(D)-negative usage that includes education, targets based on benchmarks, and formal surveillance of group O usage. Implementation of this plan will require clear communication of (bilateral) expectations between blood center and hospital.

Collection facilities are an important source of information for community hospitals. Blood center representatives should provide guidance for improved group O Rh(D)-negative use in the form of live presentations, webinars and printed literature. Blood center representation on transfusion committees also helps with guidance and communication.

Reasonable targets for group O usage should be established. The inventory par levels for group O RBCs should be based on the best available evidence about the indications for their use and the specific circumstances of the hospital or system under consideration. Blood collection facilities and their customers should work together to define explicitly appropriate and inappropriate practices.

Blood centers can provide hospitals with information on the genotype or extended phenotype of RBC donors as part of an overall group O Rh(D)-negative reduction campaign. This will allow hospital blood banks to allocate type-specific RBCs quickly for alloimmunized patients, and also switch from Rh(D)-negative to Rh(D)-positive when it is feasible.

Collection facilities can also work with hospitals to establish surveillance programs to closely monitor and audit group O use. It may be useful to base any remediation program on such site-specific surveillance, and, in an iterative process, review the impacts of remedial interventions and modify them as needed over time. The consequences and “enforcement” procedures for nonadherence to predefined use guidelines will need to be determined prospectively, and bilaterally.



Education and surveillance are not likely to be adequate alone. Collection facilities can consider the use of both financial incentives and penalties to encourage optimal use of group O Rh(D)-negative RBCs to protect this critical clinical resource. Overuse should be defined and agreed upon. Many models may be acceptable including the following:

- Centers and hospitals should collaboratively establish inventory processes and procedures that reduce the risk that group O RBCs, near expiry, are transfused out-of-group solely to avoid outdate. This might, for example, involve structured stock rotation schedules to support optimal transfusion practices.
- Centers may wish to develop and implement financial strategies to help address group O RBC overuse. Issues to consider include the products' unique value, the need for conservation, and the marginal cost of finding, recruiting, and drawing the next group O donor.
- Clinically appropriate triage algorithms that assign specific decision-making responsibility and authority can be developed to control group O RBC use under both routine and shortage conditions (i.e., either short-term or extended shortfalls as might occur in the face of adverse local conditions, disasters or a pandemic, respectively).

General Recommendations from This Bulletin

A more extensive list of recommendations for transfusion services and blood centers is listed below.

Transfusion Services

- Patients should receive ABO type-specific blood for routine transfusion:
 - Switch patients receiving group O RBCs urgently to type-specific units as soon as possible, following completion of type and screen testing and verification of ABO group.
 - Implement an electronic patient verification system to eliminate the need for a second verification of the patient's blood type prior to providing type-specific blood (see Standard 5.16.2.2).¹⁷
- Group O Rh(D)-negative RBCs should be reserved for transfusion of group O Rh(D)-negative females of childbearing potential and in bleeding emergencies for females of childbearing potential with unknown blood group.
- A transfusion should never be withheld from a bleeding patient. If group O Rh(D)-negative units are not available for a female of childbearing potential then the benefit of an emergent Rh(D)-positive blood transfusion must be balanced against the risk of alloimmunization.
- Clinical conditions may dictate the need for a temporary switch to group O Rh(D)-negative RBCs for some patients. This remains within a medical director's purview.



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- Hospital transfusion services should have policies describing when patients should be switched to Rh(D)-positive RBCs to avoid depletion of the group O Rh(D)-negative supply.
 - Group O Rh(D)-positive RBCs may be given to group O Rh(D)-negative patients for significant surgical or medical bleeding.
 - Group O Rh(D)-negative critical care patients over age 50 can be switched to group O Rh(D)-positive RBCs as the situation and inventory indicates.
 - Hospitals should have protocols in place to expedite sample collection during bleeding emergencies so that patients can promptly be switched to type-specific blood upon completion of pretransfusion testing.
- Hospitals should closely monitor utilization of group O Rh(D)-negative inventory during bleeding emergencies and perform periodic audits of group O blood use to better understand utilization patterns.
- Hospitals should develop reasonable goals for group O Rh(D)-negative usage and work together with blood collection facilities to design feasible plans that meet specific hospital needs.
- Provision of group O Rh(D)-positive RBCs should be considered for air and/or ground ambulance and/or emergency department transfusions because most patients in this setting are either males or females of no childbearing potential.

Blood Collection Facilities

- Blood center representatives should provide guidance to their client hospitals for better group O Rh(D)-negative use in the form of live presentations, webinars, and printed literature. AABB plans to develop materials to help with this effort.
- Collection facilities should work with hospital clients to develop reasonable targets for group O Rh(D)-negative usage.
- Collection facilities should provide genotype or extended phenotype information for RBC units of all blood types to encourage type-specific usage.
- Collection facilities should work with hospitals to establish surveillance programs to closely monitor and audit group O use.
- Collection facilities can work with hospital clients to develop ways to encourage optimal use of group O Rh(D)-negative RBCs.

Conclusion

Blood collection facilities have dealt with an overall reduction in the demand for RBCs, but the pressure to maintain sufficient group O Rh(D)-negative inventory continues to grow. Group O Rh(D)-negative volunteers make up 6.9% of the donor base but their RBCs are often used for patients of other ABO types simply because it is safe and convenient. Taking steps to implement some of the recommended changes in practice can reduce the collective dependence on group O



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Rh(D)-negative use and avert potential shortages that could affect patient safety. Working together, collection facilities and hospital transfusion services can develop a mutually beneficial program that safely reduces group O usage.

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