Pretransfusion Testing and Transfusion of Uncrossmatched Erythrocytes

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BLOOD transfusion is the most frequent procedure performed during hospital admissions[1] and many transfusions are administered in the perioperative period, often on a time-sensitive basis. In this clinical commentary, key points related to pretransfusion testing are reviewed with an emphasis on the electronic crossmatch, as well as the use of uncrossmatched erythrocytes in situations where crossmatch-compatible units are not yet available for transfusion.

Preoperative Blood Orders

For the typical surgical patient, a determination is made preoperatively as to the level of pretransfusion testing ordered (none, type and screen only, or number of units to crossmatch). Such determinations may be based on individual physician judgment of the expected/typical amount of surgical blood loss for a given procedure, the patient's preoperative hemoglobin concentration, or on an institution's maximum surgical blood order schedule (MSBOS). The MSBOS lists the recommended extent of pretransfusion testing for common surgical procedures and is intended to optimize the amount of pretransfusion testing performed on each patient thereby reducing costs and unnecessary testing.[2]

Limitations of the traditional MSBOS include that it may not be based on local data and may be updated infrequently. More recently, advances in medical informatics have allowed the MSBOS to be updated based on institution- and procedure-specific median transfusion rates, an approach with the potential to significantly reduce unnecessary testing and crossmatching.[3] The accuracy of the MSBOS in predicting transfusion requirements may also be improved by accounting for patient-specific variables such as preoperative hematocrit and the lowest tolerable hematocrit.[4] An advantage of using a data-driven MSBOS is that once the mechanism to collect data is in place, data-driven revisions can easily be made on an annual basis or whenever there is a significant change in practice (such as using tranexamic acid in joint replacement surgeries). In any case, the MSBOS represents a guideline to direct pretransfusion testing; the number of units ordered for any given patient may need to be modified in the light of the patient's preoperative condition, coagulation status, and clinically significant antibodies that may make finding compatible erythrocytes difficult. In other words, the recommendations made in the MSBOS should be interpreted for each individual patient and their underlying disease and antibody status.

Pretransfusion Testing

Pretransfusion testing is a multistep process aimed at avoiding potentially fatal hemolytic transfusion reactions. The process begins on the clinical ward with identification of the intended recipient and collection of a properly labeled blood sample. When the sample and requisition are received in the transfusion laboratory, blood bank personnel review the recipient's transfusion history, perform the necessary testing, and if ordered, crossmatch erythrocytes.

Historical Review

The patient's electronic blood bank record is reviewed for previous ABO and RhD type results and the presence of anti-erythrocyte antibodies. Previous ABO and RhD type results are important because discrepancies between previous and current results can signal a "wrong-blood-in-tube" miscollection and prompt recollection of a patient sample. Historical antibodies are important because, although their

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titers may have decreased to below the threshold of detectability in the current specimen, they may result in a clinically significant hemolytic reaction if the recipient is transfused with erythrocytes bearing the corresponding antigen (an anamnestic immune response). Thus, the historical review is a first pass look at the patient's transfusion history and provides some information on the likelihood that the patient will present with clinically significant antibodies.

Blood Type (or Group) Determination

Determination of the recipient's ABO type is performed using both forward and reverse testing phases; these two phases of testing produce complementary information that serves to confirm each other's result. Forward typing is performed by mixing the recipient's erythrocytes with commercially available anti-A and anti-B sera and observing for agglutination (clumping together of cells indicating antibody has bound to its target on the erythrocytes). The reverse type is performed using the recipient's serum and commercially available group A and B erythrocytes. Agglutination patterns of the forward and reverse types and the compatible erythrocytes for transfusion are listed in table 1.

Typing for the RhD antigen is performed in a similar manner as the forward type, with commercially available anti-D sera reacting with RhD antigen expressed on recipient erythrocytes. Unlike the ABO blood group, antibodies directed against antigens in the Rh blood group do not occur naturally and are only made in response to a sensitizing exposure such as previous transfusion or pregnancy. Such antibodies are detected by the antibody screen.[5]

Antibody Screen

The antibody screen is an antibody detection test in which the recipient's serum is added to a reference panel of commercially available erythrocytes with a known pattern of antigen expression that, between them, include all clinically significant non-ABO antigens known to cause clinically significant hemolysis.

A positive antibody screen signifies the presence of at least one antibody directed against red cell surface antigens. Development of red cell antibodies, known as alloimmunization, occurs as a result of exposure to erythrocyte antigens during pregnancy or a previous transfusion.[6] When an antibody is detected in the antibody screen, the blood bank must perform additional testing to identify the specificity of the antibody. If the antibody is clinically significant, that is, if it can cause the premature destruction of transfused erythrocytes, antigen-negative erythrocyte units must be located. This search for compatible (*i.e.*, antigen-negative) erythrocytes can take several hours or even longer (*e.g.*, days and weeks) depending on the number and nature of the antibodies and can result in significant surgical delays (median delay of 12 h in one report).[5] To reduce surgical delays and cancellations related to unexpected antibodies, pretransfusion testing can be completed up to 30 to 45 days in advance provided the patient has not been pregnant or transfused in the preceding 90 days. If a patient has been pregnant or transfused in the preceding 90 days, a type and screen is valid for up to 72 h.[5] The patient must also commit to maintaining their identification from the blood bank (usually a bracelet applied at the time of sample collection) that links the patient to their blood bank testing.[5]

Serologic Crossmatch

Serologic crossmatching involves physically mixing donor erythrocytes with recipient's plasma and it can be performed in two ways. An "immediate spin" crossmatch was the traditional method of confirming ABO compatibility between a potential donor unit and the recipient's plasma. A more extensive crossmatch involving antihuman globulin (sometimes referred to as "Coomb's reagent") is used to ensure compatibility between antigen-negative erythrocytes and the serum of a recipient with a current or historical non-ABO antibody; incompatibility in either of these crossmatches is indicated by the presence of erythrocyte agglutination or hemolysis. Serologic crossmatching adds approximately 10 min to pretransfusion testing using the immediate spin method, and approximately 45 min to perform an antihuman globulin crossmatch (table 2).

Computer or Electronic Crossmatch

With the improved sensitivity of modern antibody screening methods for detecting nearly all clinically significant erythrocyte antibodies, it was recognized that a patient who has a negative antibody screen and no historical antibodies can safely be issued any ABO and RhD type–specific unit

Table 1. Forward and Reverse Type Agglutination Patterns of Recipient Blood Types in the ABO Antigen System

Recipient Type	Forward		Reverse		Compatible Donors
	Anti-A	Anti-B	A cells	B cells	
A	+	−	−	+	A, O
B	−	+	+	−	B, O
AB	+	+	−	−	AB, A, B, O
O	−	−	+	+	O

"+" indicates the presence of agglutination (a positive finding indicating an antibody–antigen interaction), "−" indicates no agglutination. Group O is the universal erythrocyte donor, whereas group AB recipients can receive erythrocytes from any donor blood type.

without performing an immediate spin crossmatch. Starting in the 1980s, blood banks began selectively replacing conventional immediate spin serologic crossmatching with computerized systems involving bar codes and laser wands to identify and issue ABO-compatible units.[7] The blood bank's computer has logic that recognizes when an incompatible unit has been selected for transfusion and will not permit that unit to be issued. To be eligible for erythrocyte issuing using the electronic crossmatch, the recipient must have had their ABO and RhD group determined twice, a negative antibody screen, and no prior record of non-ABO antierythrocyte antibodies.[7] As non-ABO antierythrocyte antibodies are found in only a small percentage of all recipients (*i.e.,* in approximately 5% of hospitalized surgical patients who do not have sickle-cell disease), most patients qualify for this crossmatch system. Electronic crossmatch technology allows compatible units to be issued in less than 5 min because physically mixing the recipient's plasma with the donor's erythrocytes is not required. If any of the above-mentioned requirements are not met, the electronic crossmatch cannot be used and serologic crossmatching is necessary.[8]

The main advantage of the electronic crossmatch is that erythrocytes can be issued in mere minutes. This can lead to reductions in the costs associated with laboratory testing, in the number of units ordered but not transfused, and in improved blood inventory management.

A logical extension of electronic crossmatch systems, remote electronic blood issue systems have been implemented with substantial improvements in both blood availability and system efficiency.[9] In effect, these systems are vending machines containing erythrocytes that can be accessed if and when a patient requires a transfusion; these systems incorporate a mechanism to capture essential information such as the member of the healthcare team who acquires the units, the time that the units were removed, the number of units and specific units removed as well as a mechanism for the main blood bank to be electronically contacted (signaled) when the system is accessed and/or units are removed. They can be installed in locations that are remote from the blood bank itself, such as near an operating room or intensive care unit, thereby reducing the time required to transport the units to the patient. One such electronically controlled blood refrigerator system installed in a cardiac surgical operating theater reduced the median time to delivery of urgently required erythrocyte units from 24 min to 59 s and brought about significant reductions in unnecessary requests for erythrocyte units.[10]

Emergency-release Uncrossmatched Erythrocytes

Uncrossmatched group O (universal donor) erythrocytes are issued in emergencies when transfusion is required before compatibility testing is complete. Because group O erythrocytes do not express A or B antigens, ABO-incompatibility hemolytic transfusion reactions are avoided. Blood banks maintain a supply of group O erythrocytes that can be issued immediately or even stored in a refrigerator at the point-of-care, such as in the emergency room or operating room environments. The use of uncrossmatched erythrocytes is indicated when the recipient's bleeding and/or anemia is so severe that even the typically short delay necessary to complete pretransfusion testing and provide crossmatched erythrocytes would jeopardize the patient's survival. Because the blood bank's inventory of group O erythrocytes (and perhaps to a greater extent, group AB plasma) is finite, it is of critical importance to send a bleeding patient's sample to the laboratory as soon as possible so that type-specific crossmatched erythrocytes can be issued.

The main risk associated with transfusion of uncrossmatched erythrocytes (aside from the risks common to all red cell transfusions) is the risk of a hemolytic transfusion reaction in a recipient with a preexisting red cell antibody who is transfused with erythrocytes expressing the corresponding antigen. Because uncrossmatched erythrocytes are issued before the antibody screen is complete, the uncrossmatched erythrocytes could be incompatible with a recipient's antibody leading to hemolysis of the donor unit with an associated risk of organ injury if the antibody fixes complement, or if the hemolysis is brisk. The prevalence of these clinically significant red cell antibodies was recently found to be 1.9% in a tertiary hospital emergency department population, and only 0.5% in patients younger than 30 yr, although the incidence can be higher in other populations.[11] However, estimates of the actual risk of hemolysis after the transfusion of uncrossmatched erythrocytes are lower still (typically <1%) as summarized in table 3. Again, although acute hemolysis due to ABO incompatibility

Table 2. Time Required for Various Pretransfusion Testing Methods

Test	Approximate Time Required
ABO type	10 min
Antibody screen*	45–60 min depending on the technique used
Serologic crossmatch (assuming compatible units are in inventory)	Immediate spin: 10 min antihuman globulin: 45 min
Electronic crossmatch	5 min
Emergency-release uncrossmatched erythrocytes	<5 min

* As the ABO type part of a type and screen is usually performed concomitantly with the antibody screen, the time required to complete a type and screen is usually determined by the speed at which the antibody screen is performed. Note that crossmatched erythrocytes cannot be issued until both parts of a type and screen are completed.

Table 3. Summary of Uncrossmatched Transfusion Studies

Study	Number of Recipients	Number of Uncrossmatched Erythrocyte Units Issued	Rate of Hemolysis	Rate of New Antibody Formation
Mulay, 2012[17]	1,407	4,144	1/1,407 (0.02%)	7/232* (3%)
Radkay, 2012[6]	218	1,065	1/218 (0.5%)	4/218 (1.8%)
Miraflor, 2011[15]	132	1,570	1/132 (0.8%)	1/132
Goodell, 2010[18]	262	1,002	1/262 (0.4%)	Not reported
Ball, 2009[19]	153	511	0	Not reported
Dutton, 2005[14]	161	581	0	1/161 (0.6%)
Unkle, 1991[20]	135	Not reported	0	3/135 (2.2%)
Lefebre, 1987[21]	133	537	0	Not reported
Schwab, 1986[22]	99	410	0	Not reported
Gervin, 1984[23]	160	875	0	Not reported
Blumberg, 1978[24]	46	221	0	Not reported
Total	2,906	10,916	4/2,906 (0.1%)	16/878 (1.8%)

Incidence of hemolysis and alloimmunization after emergency-release uncrossmatched blood transfusion in civilian centers.

* Denominator includes only patients with a subsequent antibody screen available.

will not occur with group O erythrocytes, there is a small chance that the recipient will have an antibody against another erythrocyte antigen. Although hemolytic reactions are infrequent and those mediated by the majority of non-ABO antibodies tend to be less severe than hemolytic reactions caused by an ABO-incompatible transfusion (or other antibodies that fix complement), close clinical and laboratory monitoring for hemolysis and indices of organ injury is advised for patients who turn out to have received antigen-incompatible units.

It should be noted that for patients with negative antibody screens, erythrocytes are not routinely matched for antigens other than ABO and RhD. Thus, uncrossmatched erythrocytes would not be expected to confer any increased risk of causing the recipient to become alloimmunized compared with crossmatched erythrocytes. Studies of uncrossmatched erythrocyte transfusions have detected new antierythrocyte antibodies after 1.8 to 3% of uncrossmatched transfusion episodes (table 3), comparable with observations with crossmatched erythrocytes.[12] Confounding of these estimates is likely due to massively transfused patients often receiving both uncrossmatched and crossmatched units during their hospital course.

Group O RhD-negative blood is typically used in emergencies when the recipient's RhD status is unknown. Because RhD-negative blood is a scarce resource, priority for its use is given to RhD-negative females with child-bearing potential to prevent alloimmunization against D antigen and subsequent risk of hemolytic disease of the fetus and newborn. RhD-positive erythrocytes can be transfused to RhD-negative patients who have not made anti-D antibodies as a result of prior exposure to RhD antigen because D-negative individuals do not constitutively produce anti-D antibodies. In experimental studies,

anti-D antibodies are detected in approximately 80% of healthy RhD-negative volunteers immunized with RhD-positive blood,[13] but the alloimmunization rate observed in clinical studies of hospitalized patients who were transfused at least one unit of RhD-positive blood ranges from only 10 to 33%.[14–16]

In summary, preoperative blood orders should be based on an MSBOS that is informed whenever possible by institution-specific data. The pretransfusion testing process demands accuracy at each step, and for maximum efficiency should be completed before the day of surgery. For most surgeries, a type and screen is sufficient, particularly given the rapidity with which blood can be issued by blood banks using the computer crossmatch. When crossmatched blood is not yet available, the published experience supports the safety of transfusing uncrossmatched erythrocytes; clinicians should not hesitate to use them when clinically indicated in the management of patients with life-threatening hemorrhage.

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Competing Interests

The authors declare no competing interests.

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References

1. Wier LM, Pfuntner A, Maeda J, Stranges E, Ryan K, Jagadish P, Collins Sharp B, Elixhauser A: HCUP Facts and Figures: Statistics on Hospital-based Care in the United States, 2009. Rockville, Agency for Healthcare Research and Quality, 2011

2. Friedman BA, Oberman HA, Chadwick AR, Kingdon KI: The maximum surgical blood order schedule and surgical blood use in the United States. Transfusion 1976; 16:380–7

3. Frank SM, Rothschild JA, Masear CG, Rivers RJ, Merritt WT, Savage WJ, Ness PM: Optimizing preoperative blood ordering with data acquired from an anesthesia information management system. ANESTHESIOLOGY 2013; 118:1286–97

4. Palmer T, Wahr JA, O'Reilly M, Greenfield ML: Reducing unnecessary cross-matching: A patient-specific blood ordering system is more accurate in predicting who will receive a blood transfusion than the maximum blood ordering system. Anesth Analg 2003; 96:369–75

5. McWilliams B, Yazer MH, Cramer J, Triulzi DJ, Waters JH: Incomplete pretransfusion testing leads to surgical delays. Transfusion 2012; 52:2139–44; quiz 2145

6. Radkay L, Triulzi DJ, Yazer MH: Low risk of hemolysis after transfusion of uncrossmatched red blood cells. Immunohematology 2012; 28:39–44

7. Butch SH, Judd WJ, Steiner EA, Stoe M, Oberman HA: Electronic verification of donor-recipient compatibility: The computer crossmatch. Transfusion 1994; 34:105–9

8. Säfwenberg J, Högman CF, Cassemar B: Computerized delivery control—A useful and safe complement to the type and screen compatibility testing. Vox Sang 1997; 72:162–8

9. Cox C, Enno A, Deveridge S, Seldon M, Richards R, Martens V, Woodford P: Remote electronic blood release system. Transfusion 1997; 37:960–4

10. Staves J, Davies A, Kay J, Pearson O, Johnson T, Murphy MF: Electronic remote blood issue: A combination of remote blood issue with a system for end-to-end electronic control of transfusion to provide a "total solution" for a safe and timely hospital blood transfusion service. Transfusion 2008; 48:415–24

11. Saverimuttu J, Greenfield T, Rotenko I, Crozier J, Jalaludin B, Harvey M: Implications for urgent transfusion of uncrossmatched blood in the emergency department: The prevalence of clinically significant red cell antibodies within different patient groups. Emerg Med (Fremantle) 2003; 15:239–43

12. Heddle NM, O'Hoski P, Singer J, McBride JA, Ali MA, Kelton JG: A prospective study to determine the safety of omitting the antiglobulin crossmatch from pretransfusion testing. Br J Haematol 1992; 81:579–84

13. Gunson HH, Stratton F, Cooper DG, Rawlinson VI: Primary immunization of Rh-negative volunteers. Br Med J 1970; 1:593–5

14. Dutton RP, Shih D, Edelman BB, Hess J, Scalea TM: Safety of uncrossmatched type-O red cells for resuscitation from hemorrhagic shock. J Trauma 2005; 59:1445–9

15. Miraflor E, Yeung L, Strumwasser A, Liu TH, Victorino GP: Emergency uncrossmatched transfusion effect on blood type alloantibodies. J Trauma Acute Care Surg 2012; 72:48–52; discussion 52–3

16. Yazer MH, Triulzi DJ: Detection of anti-D in D- recipients transfused with D+ red blood cells. Transfusion 2007; 47:2197–201

17. Mulay SB, Jaben EA, Johnson P, Badjie K, Stubbs JR: Risks and adverse outcomes associated with emergency-release red blood cell transfusion. Transfusion 2013; 53:1416–20

18. Goodell PP, Uhl L, Mohammed M, Powers AA: Risk of hemolytic transfusion reactions following emergency-release RBC transfusion. Am J Clin Pathol 2010; 134:202–6

19. Ball CG, Salomone JP, Shaz B, Dente CJ, Tallah C, Anderson K, Rozycki GS, Feliciano DV: Uncrossmatched blood transfusions for trauma patients in the emergency department: Incidence, outcomes and recommendations. Can J Surg 2011; 54:111–5

20. Unkle D, Smejkal R, Snyder R, Lessig M, Ross SE: Blood antibodies and uncrossmatched type O blood. Heart Lung 1991; 20:284–6

21. Lefebre J, McLellan BA, Coovadia AS: Seven years experience with group O unmatched packed red blood cells in a regional trauma unit. Ann Emerg Med 1987; 16:1344–9

22. Schwab CW, Civil I, Shayne JP: Saline-expanded group O uncrossmatched packed red blood cells as an initial resuscitation fluid in severe shock. Ann Emerg Med 1986; 15:1282–7

23. Gervin AS, Fischer RP: Resuscitation of trauma patients with type-specific uncrossmatched blood. J Trauma 1984; 24:327–31

24. Blumberg N, Bove JR: Un-cross-matched blood for emergency transfusion. One year's experience in a civilian setting. JAMA 1978; 240:2057–9