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ALLEGATO 17) TESTO IN LINGUA INGLESEPROVE ORALI

"Technical Manual" 20th Edition, Claudia S. Cohn, Meghan Delaney, Susan T. Johnson, Louis M. Katz

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CHAPTER 10
ABO and Other Carbohydrate Blood Group Systems

Martin L. Olsson, MD, PhD, and Julia S. Westman, PhD

THE 19 BLOOD GROUP ANTIGENS IN the ABO, P1PK, LE (Lewis), H, I, GLOB (Globoside), FORS, and SID blood group systems are defined by immunodominant carbohydrate epitopes on glycoproteins and glycolipids. The synthesis of these antigens requires the action of a series of enzymes known as glycosyltransferases [Fig 10-1 (A)]. These enzymes reside mainly in the Golgi apparatus and are responsible for adding specific sugars, in a particular sequence and steric or anomeric linkage (α-linked or β-linked), to growing oligosaccharide chains on glycolipids and/or glycoproteins.[1,2] Most, but not all, carbohydrate blood group antigens are located at the ends of these chains. Because of their wide tissue distribution, the carbohydrate-based systems are often referred to as "histo-blood groups."[3]

Previously, the dogma was that each glycosyltransferase typically uses one specific donor substrate molecule and one specific acceptor substrate molecule, but many examples of broader, more "promiscuous" use of acceptor substrates have come to light, including those involving carbohydrate-based blood groups. Transcriptional regulation together with the specificity of these enzymes for both their nucleotide sugar donor substrates [eg, uridine diphosphate [UDP]-galactose] and acceptor substrates (eg, type 1 chain vs type 2 chain) are responsible for the tissue-specific distribution of many blood group antigens.[4] Studies have shown that these blood groups have roles in development, cell adhesion, malignancy, and infectious disease, although many of the exact mechanisms underlying these roles are still unknown.[4,6,7]

THE ABO SYSTEM (001)

The ABO system was originally described by Karl Landsteiner in 1900 and remains the most important blood group system in transfusion medicine.[7] In blood, ABO antigens are found in substantial amounts on red cells and also to a lesser extent on platelets. In individuals who have the "secretor" phenotype, antigens are present in body fluids as well. ABO antigens are also expressed on many other tissues, including those of the endothelium, kidney, heart, bowel, pancreas, and lung.[5] This is the reason why these antigens also constitute a relative barrier against ABO-incompatible organ transplantation.[8]

Transfusion of ABO-incompatible blood can be associated with acute intravascular hemolysis and renal failure, and can be fatal.[9,10] Similarly, transplanted ABO-incompatible solid organs can

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becomes apparent if serum testing includes an incubation phase at 37 C. Hemolysis caused by ABO antibodies should be suspected when either the supernatant serum is pink to red or the cell button is smaller or absent. Hemolysis is interpreted as a positive result. The use of plasma for testing or of reagent red cells suspended in solutions that contain EDTA prevents complement activation and hemolysis.

Anti-A,B

Sera from group O individuals contain an antibody specificity known as "anti-A,B" because it is reactive with both A and B red cells. Such anti-A and anti-B reactivity cannot be separated by differential adsorption, suggesting that the antibody recognizes a common epitope shared by the A and B antigens.[7,41] This is the reason why ISBT has acknowledged A,B as the third antigen of the ABO system. Saliva containing secreted A or B substance can inhibit the activity of anti-A,B against both A and B red cells.

Anti-A1

Anti-A1 is present as an alloantibody in the serum of 1% to 8% of A_2 individuals and 22% to 35% of A_2B individuals, and is sometimes present in the sera of individuals with other weak A subgroups. Group O serum contains a mixture of anti-A and anti-A1.[40] Because of the presence of the antibody, ISBT has recognized the A1 antigen as the fourth antigen in the ABO system. Anti-A1 can cause ABO discrepancies during routine testing and lead to incompatible crossmatches with A_1 and A_1B red cells. Anti-A1 is usually of IgM isotype, reacting best at room temperature or below, and is usually considered clinically insignificant. Anti-A1 is considered clinically significant if reactivity is observed at 37 C.[40] Group A_2 patients with an anti-A1 that is reactive at 37 C should receive group A_2 or O red cells for transfusion; group A_2B patients should receive group A_2, A_2B, B, or O red cells.

Routine Testing for ABO

Donor blood samples are routinely typed for ABO at the time of donation and on receipt of red cell units in the hospital transfusion service (confirmatory typing). The latter is not always practiced outside the United States. Recipient samples are typed before transfusion. ABO grouping requires both antigen typing of red cells for A and B antigen (red cell grouping or forward type) and screening of serum or plasma for the presence of anti-A and anti-B isohemagglutinins (serum/plasma grouping or reverse type). Both red cell and serum/plasma grouping are required for donors and patients because each grouping serves as a control for the other. Reverse or serum grouping is not required in two circumstances: 1) for confirmation testing of labeled, previously typed donor red cells and 2) in infants younger than 4 months of age. As previously discussed, isohemagglutinins are not present at birth and develop only after 3 to 6 months of age.

Commercially available anti-A and anti-B for red cell typing are extremely potent and agglutinate most antigen-positive red cells directly, even without centrifugation. Most monoclonal typing reagents have been formulated to detect many weak ABO subgroups. (See manufacturers' inserts for specific reagent characteristics.) Additional reagents (anti-A1 and anti-A,B) and special techniques to detect weak ABO subgroups are not necessary for routine testing but are helpful for resolving ABO typing discrepancies.

In contrast to commercial ABO typing reagents, human anti-A and anti-B in the sera of patients and donors can be relatively weak, requiring incubation and centrifugation. Tests for serum grouping, therefore, should be performed using a method that adequately detects human anti-A and anti-B. Several methods are available for determining ABO group, including slide, tube, microplate, and column agglutination gel techniques.

ABO Discrepancies

Table 10-1 shows the results and interpretations of routine red cell and serum tests for ABO. A discrepancy exists when the results of red cell tests do not agree with those of serum tests, usually due to unexpected negative or positive results in either the forward or reverse typing. (See Table 10-3.) ABO discrepancies may arise from intrinsic problems with either red cells or

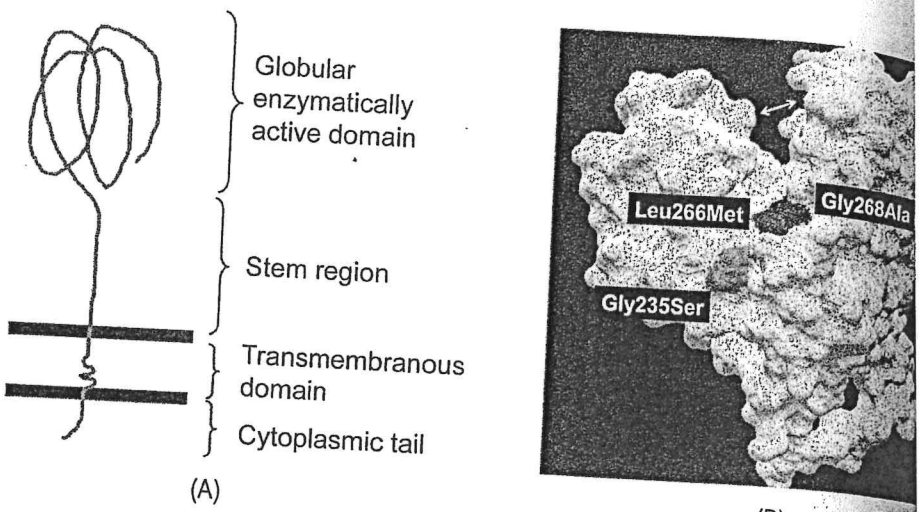

FIGURE 10-1. Model of a glycosyltransferase anchored in the Golgi membrane (A), and dimensional surface model of the human ABO glycosyltransferase (B). The arrow at the top the catalytic cleft, and the dark surfaces highlighted with black labels correspond to the ami positions that determine A vs B specificity.

undergo hyperacute humoral rejection if the patient has not been pretreated to remove naturally occurring anti-A and/or anti-B from plasma. Because of the serious clinical consequences associated with ABO incompatibilities, ABO typing and ABO compatibility testing remain the foundation of safe pretransfusion testing and a crucial part of a pretransplantation workup.

The ABO system contains four major ABO groups: A, B, O, and AB. The four phenotypes are determined by the presence or absence of two antigens (A and B) on red cells. (See Table 10-1.) The ABO system is also characterized by the presence or absence of naturally occurring antibodies, termed isohemagglutinins, directed against the missing A and B antigens. As shown in Table 10-1, an inverse relationship exists between the presence of A and/or B antigens on red cells and the presence of anti-A, anti-B, or both, in sera, a phenomenon often referred to as Landsteiner's rule. For example, group O individuals, who lack A and B antigens on red cells, possess both anti-A and anti-B. It is believed that the immunizing sources for such naturally occurring antibodies are gut and environmental bacteria, such as the *Enterobacteriaceae*, which have been shown to possess ABO-like stru on their lipopolysaccharide coats.[11,12]

Biochemistry

The A and B antigens are defined by three terminal epitopes on glycolipids and glyc teins.[7] As shown in Fig 10-2, the H antig characterized by a terminal α1,2 fucose, w is the immediate and required biosynthetic cursor for expression of either the A or B gen. The presence of this fucose is required the A and B glycosyltransferases to be able use the oligosaccharide chain as their acce substrate. In group A individuals, an *N*-acetyl lactosamine is added in an α1-3 linkage to subterminal galactose of the H antigen to fo the A antigen. In group B individuals, an α galactose is added to the same subterminal lactose to form the B antigen. In group AB in viduals, both A and B structures are synthesize In group O individuals, neither A nor B antigen are synthesized as a result of alterations in th *ABO* genes.[7,13] Consequently, group O individu als express only H antigen. A and B antigens are also absent in the very rare Bombay phenotyp

RBC transfusion also need to be balanced against the benefits of transfusion.

Hyperhemolysis refers to the development of severe anemia where the hemoglobin level following transfusion is lower than that before transfusion. Hyperhemolysis may be acute or delayed. It may be associated with a new alloantibody or a previous antibody that was not detected with antibody screening, or it may not be associated with an alloantibody. The transfused cells as well as the patient's own cells are hemolyzed, resulting in a reduction of hemoglobin to levels below the pretransfusion hemoglobin and characteristic reticulocytopenia. Subsequent RBC transfusion is also likely to result in hyperhemolysis.[46,47] Transfusion avoidance, intravenous immune globulin (IVIG), corticosteroids, and erythropoiesis-stimulating agents for anemia and reticulocytopenia have been used to treat hyperhemolysis.[48,49] Other interventions that have been described include the use of rituximab to prevent subsequent delayed hemolytic transfusion reactions in the presence of alloantibodies and potentially eculizumab for the treatment of hyperhemolysis.[49]

Hemoglobin substitutes, or hemoglobin-based oxygen carriers (HBOCs), have also been described in the treatment of sickle cell patients with contraindications to RBC transfusions, including those with rare blood types or extensive alloimmunization resulting in widespread donor incompatibility, as well as in individuals who refuse blood because of religious beliefs. Although the safety profile of early HBOCs resulted in premature withdrawal of select agents, a number of second-generation products may be better tolerated.[50] Case reports[51] have demonstrated clinical benefits in recipients, leading to growing interest in expanding the applications of HBOCs, especially in the sickle cell population. Currently, the availability of such products in the United States is confined to pharmaceutical clinical trials or expanded access (compassionate use) granted by the Food and Drug Administration (FDA).

To reduce the risk of alloimmunization, patients with sickle cell disease, similar to patients with thalassemia, often receive selected RBC units (ie, units matched for Cc, Ee, K) in addition to the usual matching for ABO and RhD.[52,53] Nonetheless, alloimmunization may still occur in these patients despite phenotype matching, due to genetic variants and heterogeneous epitope expression for any given Rh antigen. In one study, 38% of alloantibodies occurred in recipients who phenotypically expressed the corresponding Rh antigen.[44,54] Genotyping for red cell antigens has additional costs; however, the cost of genotyping needs to be balanced against the need to avoid alloimmunization in those at high risk who require frequent transfusions. For patients who have developed an alloantibody, extended-matched RBCs (ie, including antigens of the FY and JK systems and S) are also often used.[39]

RBCs can be administered to patients with SCD as a simple transfusion, by manual exchange, or by automated exchange. Automated exchange transfusion can readily deliver more volume, thereby significantly reducing hemoglobin S levels and reducing the risk of iron overload. RBCs are administered acutely or chronically as prophylaxis or for various indications, such as pulmonary hypertension.[41] Clear indications for the use of RBCs are provided by RCT evidence and, in the absence of RCTs, from clinical guidelines. Table 19-3 summarizes RBC transfusion recommendations in sickle cell disease from a recent National Heart, Lung, and Blood Institute (NHLBI) guideline.[41] The 1998 Stroke Prevention Trial in Sickle Cell Anemia (STOP trial) showed that chronic RBC transfusions significantly reduced the incidence of stroke in sickle cell patients determined to be at high risk based on transcranial Doppler (TCD) ultrasonography (middle cerebral artery or internal carotid artery flow velocity of 200 cm/sec or higher).[56] The subsequent STOP2 trial showed that discontinuing chronic transfusion in this patient population results in a reversion to baseline risk of abnormal flow velocities and stroke.[57] In the recent TCD With Transfusions Changing to Hydroxyurea (TWITCH) trial, children with sickle cell disease and abnormal TCD velocities were randomly assigned to monthly transfusion or hydroxycarbamide (hydroxyurea) for 1 year. Hydroxycarbamide was found to be noninferior to chronic transfusion for the primary outcome of stroke but was associated with an increased risk of vaso-occlusive crises.[58] RBCs are not

In certain circumstances, the FDA may determine that the product made using the change may be distributed immediately upon receipt of the Changes Being Effected Supplement (CBE) by the FDA [21 CFR 601.12 (c)(5)].

- *Minor Change:* A change that has a minimal potential to have an adverse effect on the safety or effectiveness of the product. Minor changes do not need prior approval from the FDA but must be described by the manufacturer in an annual report [21 CFR 601.12(d)].

Blood-Related Devices

CBER has the lead responsibility for devices marketed for transfusion and the collection and processing of blood products and hematopoietic progenitor cells (HPCs). These devices include apheresis machines; devices and reagents used for compatibility testing; blood establishment computer software; and blood and human cells, tissues, and cellular and tissue-based product (HCT/P) screening tests for infectious diseases.

The medical device classifications are based on the risks the device poses to the patient and the user or on the level of controls that may be necessary to ensure the device can be operated safely and effectively[15]:

- Class I medical devices represent the lowest-level risks to the patient or user. Such devices are subject to a comprehensive set of regulatory authorities called general controls. General controls are applicable to all classes of devices. Examples of Class I devices include copper sulfate solutions for hemoglobin screening, blood grouping view boxes, and heat sealers.
- Class II medical devices carry greater patient or user risks than Class I devices. These are devices for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. Most blood-related devices are in Class II and cleared through the 510(k) pathway, where a device is found to show equivalence to a predicate.
- Class III medical devices carry the g
risk of the three device classifications.
are devices for which general contr
themselves, are insufficient and for
there is insufficient information to es
special controls to provide reasonable
ance of their safety and efficacy. For
ple, tests used to determine red cell a
type by molecular methods are regula
Class III devices, requiring premarke
proval (PMA).

The FDA approves some blood-related d
es as biologics under the PHS Act and ther
requires the submission of BLAs or related
plements. These devices include reagents
for immunohematology testing by sero
methods and most donor-screening infec
disease assays [eg, tests for human immuno
ciency virus (HIV), hepatitis B virus (HBV),
hepatitis C virus (HCV)].

The FDA requires device manufacturer
register and list the products they manufac
(21 CFR 807). Each device category is assig
a code, and all cleared or approved manufac
ers and products for that code are searchabl
the Establishment Registration and Device
ing database on the CDRH website.[16]

Manufacturers and importers of medical
vices must report deaths and serious injuries
lated to medical devices to the FDA (21 C
803).[17] User facilities must report deaths and
rious injuries in which a device was or may ha
been a factor. Serious injury is defined as bei
life threatening, causing permanent impairme
or damage, or needing medical or surgical int
vention. For user facilities, reports of serious
juries are sent to the device manufacturer usi
FDA MedWatch Form 3500A within 10 wo
ing days of the event, or to the FDA if the devi
manufacturer is unknown. Deaths must be r
ported to both the manufacturer and the FD
In years when a Form 3500A report is submi
ted, the user facility must send an annual use
facility report (Form 3419) to the FDA by Janu
ary 1 of the following year.[18] Users may volun
tarily report other device-related adverse event
or malfunctions to the FDA (Form 3500). A
possible adverse events, whether reported o

nized to platelet HLA antigens either by prior pregnancy, organ transplantation, or transfusion. Platelets express HLA Class I antigens, but they are relatively poor immunogens. When immune refractoriness occurs in platelet transfusion recipients, the HLA antibody response is mainly provoked by "contaminating" white cells in the unit rather than the platelets themselves.[116] The Trial to Reduce Alloimmunization to Platelets (TRAP) confirmed that leukocyte reduction significantly reduces the risk of HLA alloimmunization.[113] Pregnancy is by far the most important risk factor for primary HLA sensitization.[117] In the era of leukocyte-reduced blood components, immune refractoriness, often reflecting a secondary immune response to HLA antigens, is a particular problem in multiparous women.[118]

Identifying HLA antibodies is a second important step in approaching immune refractoriness. HLA antibody detection is most commonly performed using flow cytometry of multiantigen-coated beads, although other methods (eg, lymphocytoxicity assays, enzyme-linked immunosorbent assays) are also used. Laboratories historically reported a panel-reactive antibody (PRA) score based on the number of reactive wells observed on cytotoxicity assays to determine the degree of HLA alloimmunization,[116] but this practice has been largely replaced by determination of the calculated PRA (cPRA) based on antigen frequencies in the United Network for Organ Sharing (UNOS) network.[119] There is no standard definition of a meaningful cPRA score, and thresholds for defining platelet refractoriness may vary by institution.

Maneuvers to mitigate platelet immune refractoriness were recently reviewed.[118,120] Options to manage immune refractoriness include providing HLA-matched platelets, HLA-antibody avoidance (ie, identifying HLA-antibody specificity and providing antigen-negative platelet units, analogous to similar strategies with RBC units), and platelet crossmatching.[121] When providing HLA-matched platelet units, donor units with closely matching Class I A and B antigens (see Chapters 15 and 16 for more information on platelet matching) have been demonstrated to result in improved transfusion response, although a failure to achieve a good increment is still seen in 20% of cases.[111] A recent systematic review[118] examined the efficacy of prophylactic HLA-matched platelet units for refractory patients. Most of the existing data come from observational studies performed before 2000, before the routine use of current HLA antibody testing methods. Posttransfusion increments were the most common outcome reported among immune-refractory patients receiving HLA-matched platelets, with varying degrees of success. A 2014 single-center observational study[122] found that providing HLA-matched units was associated with a successful increment in only 29% of transfusions to refractory patients. Although better than providing random units, transfusing HLA-matched platelets was of only limited utility. Studies powered to examine the effect of HLA-selected platelets on bleeding outcomes have not yet been performed.

When HLA-matched platelets are not available for immune-refractory patients, prophylactic transfusions of random units are unlikely to result in an effective incremental response and may cause further sensitization to additional HLA antigens. In cases of bleeding complications in such patients, unmatched HLA units may provide temporary hemostatic benefit and should not be withheld to avoid alloimmunization. IVIG and other therapeutic modalities used to treat immune thrombocytopenia (ITP) have not been demonstrated to be effective in reducing the degree of alloimmunization in both randomized and nonrandomized studies but may be effective in patients who have ITP secondary to their underlying hematologic disorder.[84] Other measures that may be considered include antifibrinolytic agents.

A minority of refractory patients who do not have an HLA alloantibody or have a poor response to HLA-matched platelet transfusions may harbor alloantibodies directed against HPAs.[119] In addition to platelet refractoriness, HPA antibodies are also associated with fetal/neonatal alloimmune thrombocytopenia (FNAIT) and posttransfusion purpura (PTP). (See Chapters 15 and 23.) Such patients may benefit from additional testing such as HPA antigen typing and HPA antibody determination. These assays may not be available outside of major blood collection centers or specialized reference laborato-

methods have been described for creating an institution-specific MSBOS derived from electronic data.[38] The actual document for that MSBOS, created as a guide for preoperative blood orders, includes 135 types of surgical procedures and the associated recommended blood order for each (Fig 20-1). Of course, these recommendations can be modified—for example, in patients with preoperative anemia or in those with red cell antibodies for whom compatible units may be difficult to find.

It has been shown that a data-driven MSBOS not only improves the blood ordering process but can also decrease costs by reducing unnecessary blood orders ($150,000-$300,000/year).[7] The crossmatch-to-transfusion ratio, a classic measure of blood-ordering efficiency, can be improved (decreased) by using an accurate MSBOS.[7] For those procedures in which blood is rarely or never transfused, the authors specify that no preoperative blood orders are needed. In the case of unexpected bleeding, the backup plan is emergency-release, uncrossmatched blood, which is much safer than many clinicians believe.[45]

Having an up-to-date MSBOS has other benefits as well. First, blood units will not be set aside unnecessarily for cases that have a low likelihood of transfusion. Overordering of preoperative crossmatches and setting aside RBC units leads to potential outdating and wastage. On the other extreme, patients who truly need blood prepared are more likely to have blood units ready when they are needed. When cases are identified that clearly should have blood ready to transfuse, the process of type and screen or type and crossmatch is best completed before the day of surgery, thereby decreasing the risk that surgery will begin before the blood is ready. The Joint Commission has recognized this particular problem as a potential performance measure,[46] and use of an MSBOS helps to reduce the problem by specifying which patients need blood prepared ahead of time. Many centers now use the 30-day time limit for expiration of the type and screen or crossmatch, as long as the patient has not been pregnant or received transfusion within the last 90 days.

Optimizing Coagulation

An important way to reduce blood loss and unnecessary transfusions is to optimize coagulation before surgery. For example, P2Y12 inhibitors such as clopidogrel should be discontinued, if possible, in time for their effect to subside before elective surgery. Often, a cardiac surgery patient needs 2 to 5 days off the medication for coagulation to normalize. Tests such as the Verify Now assay (Instrumentation Laboratories)[47] can detect residual P2Y12 inhibition, enabling the provider to determine the optimal time for surgery. Because the return to normal coagulation has significant variability when these drugs are discontinued, the test is important. Additionally, several over-the-counter herbal supplements such as garlic, ginseng, and ginkgo, have been shown to affect coagulation and should be discontinued before elective surgery.[48]

Preoperative Autologous Blood Donation

Historically, preoperative autologous blood donation (PAD) was used in an attempt to avoid allogeneic blood. However, over the last decade, there has been a significant downward trend in the number of autologous units collected in the United States. In 2017, only 10,000 units were collected, representing approximately 0.08% of the total allogeneic RBC/whole blood collection and 62% fewer units than were collected in 2015.[4,49] Major factors contributing to this decline include the increased safety of and public confidence in the blood supply, adoption of intraoperative blood-conserving techniques, high wastage of PAD blood (>45% discarded), and a higher risk for preoperative anemia after donation.[49,50] Studies showed that although patients participating in a PAD program had lower exposure to allogeneic transfusions than did patients who did not participate, they had a higher likelihood of receiving any transfusion (allogeneic and/or autologous) as a result of donation-induced anemia.[49,51] Errors related to production and handling, delays in receipt of the units at the designated hospital, and increasing acquisition costs also added to the decrease in PAD.[52] The patient also may accrue additional cost in the form of lost wages if work time is required for the donation.

HTR to be 1 in 76,000 to 80,000 and the risk of a fatal ABO HTR to be 1:1.8 million.[8] Of the transfusion-related fatalities reported to the FDA from 2012 to 2016, 8% and 10% were caused by ABO and non-ABO HTRs, respectively.[1]

Treatment

Prompt recognition of an AHTR and immediate cessation of the transfusion are crucial. The unit of blood should be returned to the blood bank for investigation. Saline should be infused to maintain venous access, treat hypotension, and maintain renal blood flow, with a goal of a urine flow rate of >1 mL/kg/hour. Consultation with transfusion medicine, critical care, renal, and hematology experts should be considered.

The addition of the diuretic furosemide promotes increased urine output and further enhances renal cortical blood flow. If urine output remains diminished after a liter of saline has been infused, acute tubular necrosis may have occurred, and the patient may be at risk of developing pulmonary edema. Oliguric renal failure may be complicated by hyperkalemia and subsequent cardiac arrest. Metabolic acidosis and uremia often necessitate the institution of dialysis.

DIC is an equally serious component of an AHTR. DIC is difficult to treat and may be the first indication that hemolysis has occurred in an anuric or anesthetized patient. Traditional therapy for DIC includes treating or removing the underlying cause and providing supportive care via the administration of platelets, plasma, and cryoprecipitate.

Unconscious or anesthetized patients may receive multiple units of incompatible blood before acute hemolysis is recognized. Because the severity of an AHTR is related to the amount of incompatible red cells transfused, exchange transfusion may be considered. Some severe reactions to a single unit of strongly incompatible blood may require exchange transfusion as well. Antigen-negative blood must be used for the red cell exchange. Likewise, plasma and platelets that will not contribute to hemolysis should be chosen.

Finally, inhibiting the complement cascade may be beneficial, especially early in the hemolytic transfusion reaction. A single case report on the use of eculizumab, a monoclonal antibody that blocks the cleavage of complement component C5, suggests that this may be a useful strategy for preventing hemolysis of incompatible red cells.[9]

Prompt initiation of therapy to aggressively manage hypotension, renal blood flow, and DIC provides the greatest chance of a successful outcome. Furthermore, consultation with appropriate medical specialists early in the course of treatment will ensure that the patient receives hemodialysis, cardiac monitoring, and mechanical ventilation when needed.

Prevention

Clerical and human errors involving patient, sample, and blood unit identification are the most common causes of mistransfusion and, therefore, AHTRs. Reported estimates place the risk of a near-miss at 1:1000, wrong blood given at 1:15,000-19,000, ABO-incompatible transfusion at 1:40,000, and error that results in harm at 1:4500.[8,10] Institutional policies and procedures must be in place to minimize the likelihood of such errors, and corrective and preventive action programs should target continual reduction of such errors. However, no one method for reducing the number of errors is foolproof.[11] Products available to increase patient safety include technology-based solutions, such as radiofrequency identification chips, handheld bar-code scanners, and "smart" refrigerators similar to systems used for pharmacologic agents.

The prevention of potential hemolysis from the administration of minor-ABO-incompatible platelets remains a challenge with constrained platelet inventories. A number of options, including anti-A or anti-B titration of the component, limiting the total amount of incompatible plasma transfused from platelets, and volume reduction may offer some benefit.[12] The use of platelet additive solutions for reducing minor-incompatible hemolysis risk has not been clinically studied, although it decreases the titers of anti-A and anti-B in the components.

improved neurodevelopmental outcome in the ESA group.[23] In contrast, earlier studies showed possible increased severity of retinopathy of prematurity[24] and increased incidence of infantile hemangiomas[25] with use of ESAs in preterm and low-birthweight infants. As compliance with strict transfusion threshold criteria has improved, clinicians have decreased phlebotomy rates and volumes and used point-of-care testing in VLBW infants, resulting in a decrease in the rates of iatrogenic anemia and need for transfusions.[26,27] Thus, in most cases, this approach combined with the use of aliquots from a single-donor blood component unit for multiple transfusions achieves the same goal (ie, decreases number of transfusions and donor exposures) without the need for EPO therapy.

Cold Stress

Hypothermia in the neonate can trigger or exaggerate several responses, including 1) increased metabolic rate, 2) hypoglycemia, 3) metabolic acidosis, and 4) potential apneic events that may lead to hypoxia, hypotension, and cardiac arrest.[28] In-line blood warmers are recommended for large-volume transfusions, including red cell exchange transfusions, to combat the effects of hypothermia. A radiant heater should never be used to warm the blood being transfused because of the risk of hemolysis. Furthermore, to prevent hemolysis in neonates undergoing phototherapy, the blood-administration tubing should be positioned to minimize exposure to phototherapy light.[29]

RBC Additive Solutions

Historically, RBCs transfused to children contained only citrate-phosphate-dextrose-adenine (CPDA)-1 anticoagulant-preservative solution.[30,31] However, as the use of additive solutions (AS) containing adenine and mannitol evolved to extend the shelf life of RBCs, many experts began to question their safety in neonates. One concern is the dose of adenine in AS and its relation to renal toxicity. Mannitol is a potent diuretic with effects on fluid dynamics that can result in fluctuations in the cerebral blood flow of preterm infants. However, because the use of AS extends shelf life, the number of aliquots that can be used from a single RBC unit is increased, which may reduce the overall donor exposure to a patient.

Luban and colleagues used theoretical calculations in a variety of clinical settings to demonstrate that red cells preserved in extended storage media present no major risk when used for small-volume transfusions.[32] Prospective randomized controlled trials to assess the outcome of longer vs shorter storage times of RBCs have been performed in this population and found that small-volume transfusion comparing older AS-1 or AS-3 units to fresher CPDA units were equivalent in terms of safety and efficacy.[33] (See next section.)

Because it is unknown whether these theoretical concerns for AS are significant for patients with renal or hepatic insufficiency, some facilities may remove the AS from RBC units, particularly if multiple transfusions from the same unit are expected; however, this is technically challenging and not possible in many facilities. The safety of AS-preserved RBCs in trauma-related massive transfusions, extracorporeal membrane oxygenation (ECMO), cardiac surgery, or exchange transfusions has not been studied. In a recent hospital survey in the United States about large-volume transfusions in neonates, 43% of responders used RBC units stored in AS-3, 29% used RBCs stored in AS-1, and 28% used RBCs stored in CPD or CPDA.[34] AS-preserved RBC units should be used with caution in settings where large volumes are being transfused.[32,34,35]

Ionized calcium and potassium levels should be monitored frequently during large-volume transfusions. A blood warmer should be used to avoid hypothermia.[36] These principles should be applied to infants and small children as well.

RBC Age and the Storage Lesion

Small-volume, simple transfusions administered slowly have been shown to have little effect on serum potassium concentrations in infants younger than 4 months despite the high potassium levels in the supernatant of stored RBCs. In calculating levels of infused potassium, Strauss mathematically determined that transfusion of an aliquot from an RBC unit that is sedimented