# Transfusion medicine

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*The online version of this chapter contains an educational multimedia component on how to perform red blood cell compatibility testing.*

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## Introduction

Transfusion medicine encompasses blood collection, pretransfusion compatibility testing, transfusion of blood components for the appropriate indications, and recognition and evaluation of adverse reactions to transfusion. Specific hematology populations, such as patients with sickle cell disease (SCD) and hematopoietic stem cell transplant (HSCT) recipients, pose unique transfusion-related challenges that are of particular relevance to hematologists. Apheresis is another integral component of transfusion medicine that includes therapeutic and donor apheresis, which removes or modifies a constituent of whole blood, contributing to disease pathogenesis, peripheral blood stem cell (PBSC) harvesting for allogeneic or autologous HSCT, and mononuclear cell harvesting for donor lymphocyte infusion or engineered cell therapy.

## Red blood cell transfusion

### The ABO system

The ABO system is the most clinically relevant blood group system in transfusion and transplantation medicine. The ABO system is a group of carbohydrate antigens defined by their terminal saccharide moiety. A subterminal galactose with a fucose moiety defines the H antigen, which is the precursor for both A and B antigens. The ABO gene encodes transferase enzymes covalently attach the specific terminal saccharide moiety to the subterminal galactose. The addition of *N*-acetylgalactosamine or galactose to the subterminal galactose results, respectively, in A or B antigen expression. Individuals who express both sugars are group AB, whereas individuals who express neither of these sugars are group O. ABO subgroups differ in the amount of A and B antigen expressed on the red blood cell (RBC) count and are occasionally clinically significant. The most common subgroups identified in routine testing are $A_1$ and $A_2$, which differ in their glycosyltransferase enzyme activity, resulting in quantitative and qualitative differences in A antigen expression. Serologic typing for ABO is simple, fast, and inexpensive. The large number of ABO alleles (>350) has precluded the routine use of genotyping methods for ABO blood group prediction. ABO and RhD frequency in White and Black persons is shown in Table 13-1.

**Table 13-1** ABO and RhD frequency

| Blood group | Population frequency (%) | |
|---|---|---|
| | Black | White |
| O | 49 | 45 |
| A | 27 | 40 |
| B | 20 | 11 |
| AB | 4 | 4 |
| RhD | 92 | 85 |

Healthy individuals past infancy produce naturally-occurring immunoglobulin M and G (IgM, IgG) anti-A, -B, or -A,B antibodies, known as isohemagglutinins, directed against the respective ABO antigens that are not present on their own cells. Preformed recipient isohemagglutinins predictably induce acute hemolysis if ABO-incompatible RBCs are transfused. The ensuing hemolysis is intravascular and can be severe, leading to shock, renal failure, disseminated intravascular coagulation (DIC), and death.

ABO antigens are also expressed on endothelial cells. ABO compatibility is typically required for solid organ transplantation to avoid ABO antibody-mediated acute humoral rejection. A blood group O recipient transplanted with a solid organ from a group A donor is at risk of humoral rejection and destruction of the transplanted organ. ABO compatibility is not required for hematopoietic progenitor stem cell (HPSC) transplantation because ABH antigens are not expressed on HPSCs. However, ABO incompatibility occurs in many HPSC donor-recipient pairs, necessitating special attention to blood component selection for the recipient. Passenger lymphocyte syndrome may be seen in both solid organ and minor ABO-incompatible HPSC transplants. In these cases, passenger donor B-lymphocytes may continue to produce isohemagglutinins in the recipient and result in donor ABO antibody-mediated hemolysis of the recipient's RBCs. Transplantation of a liver from a group O donor would be acceptable for a group A recipient because the recipient's anti-B antibodies do not cause humoral rejection of the transplanted organ. However, if the solid organ contains passenger lymphocytes from the group O donor, which produce anti-A and anti-B antibodies, the anti-A antibody may cause hemolysis of the recipient's circulating type-A red cells. Transfusion of donor ABO-type RBC components mitigates passenger lymphocyte syndrome.

## The Rh system

The Rh blood group system is highly immunogenic, complex, and polymorphic. The *RH* locus is composed of 2 homologous genes, *RHD* and *RHCE,* which encode the D antigen and the CcEe antigens in various combinations (ce, cE, Ce, and CE), respectively. More than 60 Rh antigens have been defined serologically and over 500 *RHD* and 150 *RHCE* alleles have been reported to date. The *RH* genes are 97% identical, include 10 exons, and evolved from a gene-duplication event on chromosome 1. Individuals who are "Rh-negative" do not express D antigen (Table 13-1), either because they have a complete deletion of the *RHD* gene, which is the most common cause in individuals of European descent, or have nonfunctioning *RHD.* Nonfunctioning *RHD* results from premature stop codons, gene insertions, or other causes that are common in Asian and African individuals.

Rh immunization occurs by pregnancy, transfusion, or stem cell transplantation. Approximately 80% of $D^-$ individuals become alloimmunized if exposed to D, which results in hemolysis; although, the risk appears to be lower in the setting of massive hemorrhage. D- women are at risk of alloimmunization during pregnancy with a D+ fetus, which can lead to hemolytic disease of the newborn (HDFN) in subsequent pregnancies. Rh(D)-immune globulin (RhIg) prophylaxis is 99.9% effective in preventing maternal alloimmunization when administered to $D^-$ females at 28 weeks of pregnancy (typically as a single dose of 300 mcg). If the newborn is $D^+$, a postdelivery dose is calculated based on the estimated volume of fetal-maternal hemorrhage. The other major antigens of the Rh system—C, c, E, and e—are also relatively potent immunogens and can cause HDFN of varying severity, albeit at lower frequencies.

The *RH* genes are highly polymorphic, particularly in specific ethnic backgrounds, including individuals of African descent. DNA-based methods are recommended to distinguish weak and partial Rh antigens. For patients with weak expression of Rh, the antigenic density on the cell surface is significantly reduced. However, all common epitopes are present, so there is no risk for immunization. For blood donors, reagents and techniques to detect weak D expression are paramount so that weak D donor units are labeled $D^+$ to prevent immunization of $D^-$ recipients. Blood collection centers are required to test donor blood for weak D expression and label them as $D^+$. Conversely, when the D type of a patient is determined, a weak D test is not required except to assess the RBCs of an infant whose mother is at risk of anti-D immunization. Most hospital blood banks choose D typing reagents and methods that do not detect weak D phenotypes. Thus, an individual with weak D expression may be classified as $D^-$ as a patient but $D^+$ as a blood donor.

Individuals with partial Rh antigens lack common epitopes and are at risk of immunization. Standard serologic Rh typing does not detect the many Rh partial antigens, which are increasingly recognized for their role in Rh alloimmunization associated with SCD. As a result, a $D^+$ individual with partial D expression is at risk of anti-D with transfusion of $D^+$ units; if pregnant with a $D^+$ fetus with foreign D epitopes inherited from the father, HDFN may occur. Providing $D^-$ RBCs prophylactically to patients with partial D can be recommended on an individual basis. Women with partial D should receive RhIg to prevent RhD immunization. Unfortunately, these instances are often identified only after the patient has formed anti-D. Occasionally, an case is identified after inconsistent D typing with varied reagents that recognize different epitopes of the D polypeptide. Once anti-D has formed, $D^-$ RBCs are indicated and RhIg is no longer indicated.

## Other protein antigen blood group systems

Outside the ABO and Rh systems, most clinically significant blood group alloantibodies are directed against protein-based antigens, particularly antigens in the Kell, Kidd, Duffy, and MNSs systems (Table 13-2). In general, antibodies to these antigens are acquired only after exposure by transfusion, pregnancy, or HSCT. Differences in antigenicity and relative antigen frequencies in racial populations are major determinants of alloimmunization.

Among Kell antigens, K has a prevalence of 10% in individuals of European descent, 1.5% in African descent, and is rare in Asian descent. The k antigen is prevalent in all populations (>99%). Anti-K is the most common RBC antibody outside of the ABO and Rh systems. In some countries all units are phenotyped for Kell, and prophylactic K- RBCs are provided to all females of childbearing age. Anti-K can cause clinically significant hemolytic transfusion reactions (HTRs) and HDFN. Compared with Rh HDFN, HDFN due to anti-K typically has a lower degree of hemolysis and hyperbilirubinemia but can result in a profound anemia in the fetus and newborn. Maternal anti-K titers are a less reliable indicator of fetal risk than titers in Rh-associated HDFN. Alloantibodies to the Kell antigens $Kp^a$ and $Js^a$ are occasionally identified. $Kp^a$ is a low-prevalence antigen in most populations (<2%), while $Js^a$ is rare in Europeans but relatively common (20%) in Africans. Weakened expression of all Kell antigens is associated with a rare phenotype—the McLeod phenotype that results from a deficiency of the Kx protein. The McCleod phenotype has been associated with several mutations and deletions at the *XK* locus that lies in close proximity to deletions associated with chronic granulomatous disease on the X chromosome. Individuals with McLeod phenotype have RBCs that are acanthocytic with decreased deformability and reduced survival, leading to a chronic but often well-compensated hemolytic anemia.

**Table 13-2** Commonly occurring RBC antigens of clinical significance

| RBC antigen system | Molecule expressing antigen | Function of molecule | Antibody immune/ naturally occurring | Hemolytic transfusion reaction from antibody | HDFN from antibody |
|---|---|---|---|---|---|
| ABO | Glycoprotein or glycolipid | Unknown | Naturally occurring | Yes, acute | Yes, usually mild (IgG anti-A,B generally present in blood of group O mothers) |
| Rh | Protein | Ammonium ion transport | Immune | Yes, delayed | Yes, can be severe |
| Kell | Glycoprotein | Member of neprilysin (M13) family of zinc metalloproteases | Immune | Yes, delayed | Yes, often severe |
| Kidd | Glycoprotein | Urea transport | Immune | Yes, delayed | Yes |
| Duffy | Glycoprotein | Chemokine receptor DARC (Duffy antigen receptor for chemokines) | Immune | Yes, delayed | Yes |
| MNSs | Glycoprotein | Structural role in RBC membrane (glycophorins A and B) | Naturally occurring (anti-M/N); immune (anti-S/s) | Rare (anti-M/N); yes (anti-S/s) | Rare (anti-M/N); yes (anti-S/s) |
| P | Glycolipid | Unknown | Immune (anti-P); naturally occurring (anti-$P_1$) | Yes (anti-P); rare (anti-$P_1$) | Yes, mild |

The Kidd blood group system is located on the erythrocyte urea transporter. Antibodies directed against the Kidd system are notorious for causing delayed hemolytic transfusion reactions (DHTRs). An individual is sensitized via transfusion, but the antibody titer decreases rapidly and becomes undetectable by standard serologic techniques. The patient is then transfused with an ABO- and RhD-compatible unit and, upon reexposure to the Kidd antigen, develops a rapid anamnestic antibody response that results in clinically significant hemolysis 4 to 14 days after the transfusion. The severity of DHTRs is compounded by the fact that Kidd antibodies—although IgG—fix, complement, and result in clinically significant intravascular hemolysis as well.

The Duffy antigens on RBCs are a chemokine receptor, which are also a receptor for the malarial parasite *Plasmodium vivax*, resulting in higher Fy(a-b-) frequency in individuals of African background where malaria is endemic because of selection pressure. The Fy(a-b-) phenotype is due to a GATA site mutation in the Duffy antigen receptor for chemokines (DARC) gene promoter that results in erythroid specific lack of Fy expression and is associated with neutropenia. Duffy glycoprotein is expressed on nonerythroid tissues and represents a minor histocompatibility antigen in kidney transplantation. Alloantibodies against Duffy antigens may cause mild to severe acute or delayed hemolytic transfusion reactions and HDFN.

The MNSs blood group system is highly complex and includes 46 antigens that reside on one or both of the major RBC membrane glycoproteins—glycophorin A and glycophorin B. The RBC antigens M and N reside on glycophorin A; alloantibodies to these antigens are usually IgM antibodies that are not reactive at 37 °C and are rarely clinically significant. In contrast, alloantibodies to the S and s antigens, which reside on glycophorin B, are clinically significant IgG antibodies that can cause hemolytic transfusion reactions and HDFN. U is a high-prevalence antigen, present in ~99.9% of most populations, and U-negative individuals are primarily African. Anti-U is difficult to manage because of the scarcity of antigen-negative blood.

## Other carbohydrate antigen blood group systems

Carbohydrate antigen systems other than the ABO system are rarely significant in clinical transfusion practice but are of interest for their role in specific infections and diseases. These systems include Lewis, P, and Ii.

Lewis antigens are technically not blood group antigens because they are not intrinsic to RBCs but are passively acquired from the plasma. The primary source of Lewis glycolipid is the gastrointestinal tract, where they are receptors for *Helicobacter pylori*. The 2 main antigens are $Le^a$ and $Le^b$. Antibodies against Lewis antigens are typically IgM isotype and occur naturally, so they may be identified on routine antibody screens. In general, Lewis antibodies are not considered clinically significant, and it is not necessary to transfuse antigen-negative RBCs.

RBCs are rich in P antigen, and include $P_1$, $P_2$, and $P^k$. Rare individuals who lack all P-system antigens (pp phenotype) may produce a clinically significant antibody. These individuals are also resistant to parvovirus B19 infection because the P antigen acts as the receptor for the virus. The $P^k$ antigen is a receptor for Shiga toxins, and $P^k$ expression may also modulate host resistance to HIV infection. An autoantibody with P specificity is present in patients with paroxysmal cold hemoglobinuria (PCH), which most commonly occurs in children following a viral illness.

Similar to antibodies directed against ABO antigens, antibodies directed against these carbohydrate antigens are usually IgM. One exception to this rule is with PCH, in which Donath-Landsteiner antibodies are cold-reacting IgG autoantibodies directed against the P antigen; they can fix complement on circulating RBCs and result in intravascular hemolysis. Of note, the DAT (direct antiglobulin or Coombs test) usually has paradoxically positive results for complement and negative results for IgG in PCH because the Donath-Landsteiner IgG autoantibodies usually detach from circulating RBCs after fixing complement. PCH is now most often associated with nonspecific childhood viral infections but historically was associated with syphilis in adults.

The Ii antigens serve as a scaffold for the synthesis of ABO antigens and exhibit age-dependent expression patterns. In newborns, the predominant allele is the i antigen. After infancy, the predominant allele becomes the I antigen, which includes the same polysaccharides but in a different configuration. Activity of the "branching enzyme" that forms this structure is absent until about 6 months of age. Fetal and cord blood cells thus express strong i and weak I antigens, whereas adult RBCs express i weakly and I strongly. Individuals with infectious mononucleosis sometimes develop cold agglutinins directed against the i antigen, whereas people with *Mycoplasma pneumoniae* infections sometimes develop cold agglutinins directed against the I antigen. The I antigen is also the predominant specificity for RBC autoantibodies responsible for IgM-mediated autoimmune hemolytic anemia (AIHA) or cold agglutinin disease.

## Blood group genotyping

DNA-based genotyping is increasingly used as an alternative to serological antibody-based methods to determine ABO, Rh, and "extended" blood group antigens for matching donor to recipient. The majority of blood group polymorphisms are caused by single-nucleotide polymorphisms in genes encoding protein antigens or genes encoding glycosyltransferases for the carbohydrate antigens. Several blood group genotyping tests have been approved by the United States Food and Drug Administration (FDA). These platforms typically exclude ABO and RhD, given their allelic complexity. In the ABO system, more than 100 alleles encode the glycosyltransferases responsible for the ABO type. Genotyping methods are unlikely to replace ABO typing by hemagglutination, which is extremely reliable, inexpensive, and has a quick turnaround time. *RHD* and *RHCE* platforms to test for multiple *RH* variants have been developed and target many, but not all, known alleles.

Genotyping can be used to determine RBC antigen phenotypes in patients recently transfused or with interfering allo- or autoantibodies, to resolve discrepant serologic typing, and/or when typing antisera are not readily available. Patients with warm autoantibodies whose RBCs are coated with IgG are difficult to antigen type with conventional antisera; thus, genotyping is an alternative to obtain the extended RBC antigen profile. Molecular typing can also facilitate complex antibody evaluations and guide RBC selection for patients with AIHA, SCD and thalassemia. Patients with SCD, who most often are of African background, have a high prevalence of *RHD* and *RHCE* variants, which can lead to Rh alloimmunization despite the provision of phenotypically Rh matched blood. *RH* genotyping can identify variant *RHD* and *RHCE*, which aids antibody evaluation and donor selection for future transfusion. When serologic weak D phenotypes are detected in patients, the *RHD* genotype should be determined. If genotyping predicts weak D expression, the patient can be treated as RhD$^+$ for transfusion and Rh immune globulin (RhIG) prophylaxis.

RBC genotyping is also an efficient method for donor centers to identify RBC units with rare or uncommon antigen phenotypes, or simply to meet demands for antigen-negative units. While identification of these donor units has historically been done serologically, automated DNA-based antigen testing can potentially improve the efficiency, reliability, and extent of matching.

## Red blood cell transfusion

### CLINICAL CASE

A 29-year-old man with chronic renal failure has a hemoglobin (Hb) level of 6.7 g/dL and is seen in the emergency department for a shoulder injury. The patient has a normal heart rate and blood pressure. He states that he has chronic anemia, has recently begun therapy with darbepoietin and iron through his nephrologist, and is able to conduct his daily routines without difficulty. The attending emergency department physician orders a blood transfusion.

Most RBCs collected in the United States are obtained from healthy volunteer donors. Collection of autologous RBCs and units from directed donors is possible but contributes only a small fraction of all RBC units collected. RBCs are stored routinely for up to 42 days at 4 °C in currently available storage media. Techniques for freezing RBCs allow a shelf life of 10 years or greater and are used to cryopreserve RBC units with rare antigen combinations.

### Clinical transfusion of RBCs

Selection of an RBC unit includes typing the patient's RBCs for A, B, and D antigens; an antibody screen of the patient's serum for antibodies to clinically significant RBC antigens (antibody detection test); and performing a crossmatch, in which immunologic compatibility between the patient and the prospective RBC unit is assessed (see "Pretransfusion Testing"). Finding crossmatch-compatible blood for individuals who have been alloimmunized from prior pregnancies or transfusion may take hours to days. Alloimmunized patients require manual crossmatches, which take a minimum of 30 minutes to perform. Close communication with the blood bank about anticipated need for transfusion is critical.

Table 13-3 summarizes the most commonly available RBC products and their respective indications. RBCs and platelets are contaminated with small numbers of leukocytes. Passenger leukocytes play an important role in alloimmunization to human leukocyte antigens (HLAs), transmission of cytomegalovirus (CMV) infection, cytokine-mediated febrile nonhemolytic transfusion reactions (FNHTR), transfusion-associated graft-versus-host disease (TA-GVHD), and other adverse events. Leukoreduction results in clinically important reductions in the incidence of platelet transfusion refractoriness, alloimmunization to HLA antigens, and transfusion-transmitted CMV infection. As a result, there

**Table 13-3** Characteristics and indications for various RBC and platelet products

| Product | Characteristics | Indications |
|---|---|---|
| Whole blood | 450 mL; coagulation factors adequate; platelets low in number; not widely available | To provide increased oxygen-carrying capacity and blood volume |
| RBCs | 250-300 mL; can be stored up to 42 d | To provide increased oxygen-carrying capacity |
| Leukocyte-reduced RBCs | Contain <5 × $10^6$ leukocytes/U | To reduce the incidence of febrile nonhemolytic reactions, CMV transmission, HLA alloimmunization, and platelet transfusion refractoriness |
| Leukocyte-reduced, irradiated RBCs | Leukoreduced and irradiated | To reduce the risk of transfusion-associated graft-versus -host disease, in addition to the benefits of leukoreduction listed above |
| Washed RBCs | Saline-suspended RBCs, 200-250 mL | To provide RBC support to patients with severe or recurrent allergic or anaphylactic reactions, patients with IgA deficiency with allergic reactions, and for intrauterine transfusions |
| Deglycerolized frozen RBCs | 200 mL; rare RBCs are frozen in glycerol (to prevent hemolysis) and need to be washed and deglycerolized prior to transfusion | To support alloimmunized patients requiring RBCs with rare antigen combinations |
| Pooled platelets* | 300-325 mL, 4-6 whole-blood donors | Prophylaxis and treatment of bleeding in the setting of thrombocytopenia or platelet dysfunction |
| Single-donor apheresis platelets* | 150-350 mL, 1 apheresis donor | Same as pooled platelets; limits donor exposure |
| HLA-matched platelets* | Apheresis platelet from a donor with known HLA type, matched to patient | Immune-mediated platelet transfusion refractoriness with documented anti-HLA antibodies |

*Platelet products should be subjected to leukoreduction or irradiation for the same indications as discussed for red blood cells.

has been a trend toward the universal use of prestorage leukoreduction of both RBCs and platelets, particularly in patients who are likely to require prolonged transfusion support. Leukoreduction alone does not provide protection against TA-GVHD, so irradiation of all cellular blood products except granulocytes and stem cell products, in addition to leukoreduction, is necessary for patients at increased risk of TA-GVHD (see discussion in section "Transfusion-associated graft-versus-host disease").

Several randomized controlled trials (RCTs) have prospectively investigated differences in outcomes after the transfusion of fresher versus older stored RBCs in cardiac surgery (the RECESS trial), in intensive care unit (ICU) patients with respiratory failure (the ABLE and TRANSFUSE trials), preterm neonates (the ARIPI trial), critically ill pediatric patients (ABC-PICU), and all hospitalized patients (the INFORM trial). The results of these trials have not shown any clinical benefit in using "fresher" RBCs (generally <10 days) when compared with "older," standard-issue RBCs.

The primary goal of RBC transfusion is to improve the oxygen-carrying and delivery capacity of blood in patients with anemia. RBC transfusion can also aid in the overall treatment of hypovolemia in patients with intravascular volume depletion because of massive acute blood loss. Numerous compensatory mechanisms exist to maintain oxygen delivery in the face of anemia. These mechanisms include increased heart rate and cardiac contractility; peripheral vasodilatation; increased oxygen delivery to tissues, which results from decreased oxygen affinity of hemoglobin owing to increased erythrocyte 2,3-DPG concentration and decreased plasma pH; and altered oxygen consumption and use within the tissues. Studies in healthy people indicate that a shift to anaerobic metabolism occurs at hemoglobin levels of approximately 7.5 g/dL or lower when the blood hemoglobin concentration is reduced rapidly. Below this level, compensatory mechanisms to enhance oxygen transport are likely to be inadequate in patients with relatively rapid-onset anemia. Studies of Jehovah's Witness patients, who refuse allogeneic blood transfusion, show that mortality increases with hemoglobin levels under 6 g/dL. However, there is no fixed hemoglobin target for RBC transfusion.

A number of RCTs have been conducted to compare the effects of RBC transfusion with a restrictive policy (hemoglobin <7-8 g/dL) or a liberal transfusion threshold (hemoglobin <9-10 g/dL). The Transfusion Requirements in Critical Care (TRICC) trial found that a restrictive transfusion threshold of a hemoglobin <7 g/dL in hemodynamically stable patients in the ICU did not increase adverse clinical outcomes. Subsequent RCTs have largely shown that restrictive transfusion strategies are safe in adults with septic shock, acute gastrointestinal bleeding, orthopedic surgery, and after cardiac surgery. Even in the setting of acute myocardial infarction (MI), the Restrictive and Liberal Transfusion Strategies in Patients with Acute MI (REALITY) randomized trial found that a restrictive, compared with liberal, transfusion strategy resulted in a noninferior rate of major adverse cardiovascular events after 30 days.

For pediatric patients, a multicenter trial of restrictive versus liberal transfusion thresholds (7 g/dL versus 9.5 g/dL) in pediatric ICUs found that a restrictive transfusion strategy was noninferior in the primary outcomes (28-day mortality and new or progressive multiorgan dysfunction) and successfully avoided transfusion in 54% of patients (compared with 2% in the liberal transfusion group). In 2018, participants in the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) established transfusion guidelines based on available evidence and expert consensus when evidence is lacking. They provided guidelines for critically ill children and 8 other examination categories, and generally incorporated a hemoglobin of 7 gm/dl as the maximum transfusion threshold. However, they emphasized the need for careful consideration of the overall clinical context rather than simply relying on the laboratory values.

In the previously described clinical case, the attending physician's initial decision to administer RBCs in response to a hemoglobin value, without taking the patient's overall presentation into account, failed to consider if this individual with gradual-onset anemia could tolerate the low hemoglobin level without significant difficulty. The case illustrates the importance of using clinical judgment in making transfusion decisions in addition to considering evidence-based hemoglobin thresholds in well-studied patient populations.

## KEY POINTS

- The ABO system is the most important determinant of transfusion compatibility.
- Rh compatibility is necessary because of the high immunogenicity of the RhD antigen, the role of anti-D antibodies in HDFN, and delayed hemolytic transfusion reactions.
- Frequently relevant blood group systems include Kell, Kidd, Duffy, and MNSs.
- RCT evidence to date supports restrictive RBC transfusion strategies in many clinic settings; it is important to consider each patient as an individual when deciding to transfuse RBC's.

# Platelet transfusion

## Collection and storage of platelets

Platelets can be collected and manufactured by 2 processes: pooled and single-donor apheresis platelet (SDP). Pooled platelets are obtained by pooling individual platelet concentrates derived from whole-blood units obtained from 4 to 6 volunteers of whom are ABO-identical whole-blood donors. SDPs are collected from single donors using continual centrifugation plateletpheresis techniques in which RBCs and most plasma are returned to the donor; some residual plasma remains in the product. This is the predominant collection method for platelets in the United States. Plateletpheresis collection techniques have been refined such that a minimum of $3 \times 10^{11}$ platelets—that is, approximately the same number of platelets contained in a pool of 6 whole-blood-derived platelets—can be collected from a single donor in a single session. Anticoagulation and preservative solution, such as anticoagulant citrate dextrose solution, solution A (ACD-A), is added to optimize platelets during storage.

As with RBCs, leukoreduction of platelet products can reduce the incidence of platelet transfusion refractoriness, alloimmunization to HLA antigens, transfusion-transmitted CMV infection, and febrile nonhemolytic transfusion reactions. For optimal viability and function, platelets must be stored in constant agitation at room temperature, which increases the risk of bacterial growth and limits the storage of platelets to 5 to 7 days depending on product type and regulatory approval across jurisdictions. There are FDA-approved protocols that allows for 7-day storage and some countries, such as Canada, have moved to 7-day platelet storage with enhanced bacterial-testing protocols. Clinical studies indicate that there is relatively little loss of platelet function and viability during this time. The storage lesion primarily involves platelet activation, which is reflected in platelet shape change, adhesion, aggregation, secretion of platelet granular contents, and the expression of activation antigens.

In 2015, the FDA-approved cold-stored platelets, which are stored at 4°C without agitation for 3 days. Cold-stored platelets are used only for resuscitation in actively bleeding patients. Refrigeration activates platelets (eg, increased P-selectin expression) and renders them more immediately efficacious after transfusion, even if posttransfusion platelet increments are lower than room temperature–stored platelets.

After routine platelet collection, 2 additional modifications to platelet products are available: platelet additive solution platelets and pathogen-reduced platelets. Platelet additive solution platelets provide a metabolically optimized environment for storing platelets and also reduce the plasma content of platelet components to minimize transfusion reactions. With less plasma in the component, a lower incidence of allergic transfusion reactions has been demonstrated and there is a theoretical reduction in risk of transfusion-related acute lung injury (TRALI). Pathogen reduction is achieved by treatment of the platelet product with amotosalen (psoralen)/UV, riboflavin/UV, or UV alone. In the United States, only amotosalen is FDA approved. A primary benefit of pathogen-reduced platelets is a significant decrease in bacterial contamination (BACON), which is the primary infectious complication of platelet transfusion. The method also reduces the plasma content in the platelet product, which reduces the incidence of transfusion reactions. Pathogen-reduced platelets using riboflavin and UVB inactivation steps have been shown in a randomized trial to be noninferior to standard platelets in terms of World Health Organization (WHO) bleeding outcome; however, platelet increments after transfusion are lower with pathogen inactivation.

## Clinical transfusion of platelets

### CLINICAL CASE

A 56-year-old multiparous woman develops acute myeloid leukemia and receives induction therapy. Her platelet count decreases to <10,000/µL. The patient initially responds well to prophylactic transfusion with pooled platelet concentrates. Later in the hospitalization, her one-hour posttransfusion platelet count increments are persistently <5000/µL. Having obtained HLA typing on the patient before induction, the attending physician asks the blood bank for HLA-matched platelets.

Platelets are transfused for 2 reasons: to treat bleeding and to prevent bleeding in patients with reduced platelet number or impaired platelet function.

### Prophylactic platelet transfusion

Bleeding in thrombocytopenic patients occurs at all platelet counts, but several studies indicate that the rate of spontaneous bleeding does not dramatically increase until the platelet count is ≤5000/µL. Several prospective RCTs show no differences in hemorrhagic risks between prophylactic platelet transfusion triggers of ≤10,000 and ≤20,000/µL. Both the Association for the Advancement of Blood and Biotherapies (AABB) and International Collaboration for Transfusion Medicine Guidelines (ICMTG) issued strong recommendations to transfuse hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia and platelet count ≤10 x $10^9$ cells/L. This recommendation is based on 3 RCTs. Two large RCTs compared bleeding rates in hospitalized, hypoproliferative thrombocytopenic patients treated with prophylactic platelet transfusions to those who did not receive prophylactic platelet transfusion. Both studies found that prophylactic platelet transfusions significantly reduced the risk of clinically significant (grade 2 or greater) bleeding. In the subgroup analyses, some populations (eg, allogeneic stem cell transplant recipients) demonstrated higher bleeding risk than others (eg, autologous stem cell transplant recipients). Indications for raising the prophylactic platelet transfusion target include recent or imminent invasive procedures; qualitative platelet dysfunction because of uremia, medications, or genetic defects; concurrent coagulopathy; fever; hypertension; and acute pulmonary processes. Other recommendations around target platelet thresholds for prophylactic platelet transfusion are weak recommendations based on low quality of evidence.

In patients with significant active bleeding, most clinicians target the platelet count to 50,000 or up to 100,000/µL in patients with definite or suspected central nervous system bleeding. Realistic target counts should be set in patients who do have inadequate posttransfusion increments, such as those with splenomegaly or immune-mediated platelet transfusion refractoriness. Checking an immediate (10 to 60 minutes) postinfusion platelet count is a necessary screen for platelet refractoriness.

### Choice of platelet product

Table 13-3 summarizes the major platelet preparations and their respective indications. Apheresis single-donor platelets are more expensive to manufacture than platelets derived from whole-blood derived platelets. Current evidence indicates that apheresis platelets and pooled platelets are generally interchangeable; alloimmunization rates, acute reaction rates, and TRALI rates are not meaningfully different. Some have argued that use of apheresis platelets reduces donor exposures and would therefore reduce incidence of transfusion-transmitted infectious diseases. However, given the very low absolute magnitude of infectious risk associated with transfusion of blood products (discussed in the section "Infectious complications" later in this chapter), the cost effectiveness of requiring single-donor transfusions for all platelet transfusion recipients is questionable.

In contrast to the availability of universal RBC donors (blood group O negative) and universal plasma donors (blood group AB), universal donors for platelets do not exist because platelet products contain both platelets and a variable quantity of plasma depending on platelet type (typically ~300 mL for apheresis and whole-blood derived; ~40 mL for pathogen-reduced platelet products). For example, group O platelets suspended in group O plasma contain anti-A and anti-B isohemagglutinins that would react against the RBCs of all but type O recipients. Clinically apparent hemolysis is occasionally observed after minor (plasma) incompatible platelet transfusion; rarely, hemolysis is severe. Major (cell) incompatible transfusion (eg, A platelets transfused into an O recipient) may yield up to 20% lower posttransfusion increment because the recipient's isohemagglutinins result in immune-mediated clearance of platelets expressing the incompatible ABH antigens. Ideally, patients should receive ABO-identical platelets; in reality, platelets are in short supply with limited inventory and, less often, chosen for other characteristics (eg, HLA-matched), so ABO matching is frequently not followed. Blood banks have varying procedures and policies for selection of type-specific platelet product transfusions.

Platelet products are selected for RhD compatibility. Transfusion of a platelet product from an RhD-positive donor to an RhD-negative recipient uncommonly (<1% incidence) may result in anti-D antibody formation because of exposure to the minimal volume of residual RhD-positive RBCs in the platelet product. In situations in which Rh-negative platelets are unavailable and platelet transfusion is required, RhIG may be used to prevent alloimmunization to RhD, particularly in females of childbearing potential. However, there are centers where RhIG is not universally administered for RhD incompatible platelet transfusion.

### Platelet transfusion dose

The dose of platelets administered to a thrombocytopenic patient depends on the therapeutic goal. If the primary goal is for bleeding prevention in an uncomplicated patient, the target typically would be to transfuse when the platelet count drops below 10,000/μL. The appropriate platelet dose depends on many factors—including the size of the patient and the presence of splenomegaly, active bleeding, platelet consumption (eg, DIC), anti-HLA or other antiplatelet antibodies, and the overall clinical scenario.

FDA standards dictate that single-donor apheresis platelets must contain at least $3 \times 10^{11}$ platelets and that individual platelet concentrates prepared from single units of whole-blood must contain at least $5.5 \times 10^{10}$ platelets; that is, the equivalent of approximately $3 \times 10^{11}$ platelets per 5- or 6-pool. In an average-size patient, in the absence of any of the risk factors for poor platelet transfusion response listed previously, approximately $3 \times 10^{11}$ platelets is considered an appropriate adult dose, and is expected to increase the platelet count by 20,000 to 50,000/μL. If a patient is being treated as an outpatient, larger doses of platelets may extend the interval between transfusions. A multicenter RCT (Platelet Dose [PLADO] Trial) compared low-, typical-, and high-platelet doses of prophylactic platelets for a platelet count of 10,000/μL in patients undergoing chemotherapy or HSCT. WHO grade 2 or higher bleeding was the same in all groups, and the low dose group ($1.1 \times 10^{11}$ platelets—half of a standard dose) received significantly fewer platelets, albeit over more transfusion episodes.

## The ABO system

Platelets possess A, B, and H antigens to varying degrees. Unlike RBC or plasma transfusion, ABO compatibility does not necessarily need to be honored for platelet transfusion. About 10% of group A and B individuals have high antigen expression, which can impact platelet increments in major ABO-incompatible transfusion (see section "Choice of platelet product").

## The HLA system

Alloimmunization to HLA is the major cause of immune-mediated refractoriness to platelet transfusion in patients undergoing chronic platelet transfusion therapy. Overall, however, nonalloimmune causes of platelet refractoriness are significantly more common (eg, immune-mediated thrombocytopenia [ITP], hypersplenism, and consumptive coagulopathy).

Although only HLA class I antigens at the HLA-A and HLA-B loci have been shown to be important in causing immune-mediated refractoriness to platelet transfusion, given the high degree of polymorphism in the HLA system, large numbers of HLA-typed donors need to be available to blood centers to provide HLA-compatible platelets to individual patients. If HLA-matched platelet donors are not available, identification of the specificity of the patient's HLA antibodies may allow blood centers to provide antigen-negative platelets for transfusion (ie, platelets that do not express HLA antigens against which the patient has known antibodies). Crossmatching platelets is another technique for finding compatible units. HLA antigens can be categorized into groups with common epitopes that may cross-react with the same HLA antigen antibodies; these groups of HLA antigens are referred to as cross-reactive groups. When an exact HLA-identical platelet donor is not available, select blood centers can use cross-reactive groups to locate platelet donors in whom the risk of cross-reactivity between the recipient's antibodies and the donor's antigens may be minimized.

## Human platelet antigens

In addition to anti-HLA antibodies, antibodies to platelet-specific antigens can be a rare cause of platelet transfusion refractoriness. The human platelet antigens (HPAs) arise as a result of polymorphisms involving various platelet membrane glycoproteins. Differences in HPA allelic frequencies in different ethnic populations may partially account for differences in the rates of alloimmunization to HPA antigens reported by different investigators. There are a number of well-characterized HPA antigen systems, but alloimmunization is most commonly owing to polymorphisms involving the HPA-1a/1b system.

Alloimmunization to HPAs can cause neonatal alloimmune thrombocytopenia (NAIT) and posttransfusion purpura (PTP), and it accounts for a small proportion of immune-mediated platelet transfusion refractoriness in heavily pretransfused platelet transfusion recipients. There are case reports of alloimmune thrombocytopenia after HPA-mismatched allogeneic HSCT. PTP occurs when transfused platelets are destroyed by HPA alloantibodies through a process analogous to a delayed hemolytic transfusion reaction. However, following exposure to the HPA antigen in question through RBC or platelet transfusion, there is immune destruction of both the patient's own antigen-negative platelets and transfused antigen-positive platelets. The mechanism by which autologous platelets are destroyed in PTP is unclear; however, cross-reactivity of HPA alloantibodies to patient platelets is one of the hypothesized mechanisms. For a patient with a history of PTP, RBC units should be washed to remove any contaminating platelets that could incite an additional episode of PTP. For platelet transfusions, alloantigen-negative platelets should be selected.

## Diagnosis and management of platelet transfusion refractoriness

A commonly used bedside definition of platelet transfusion refractoriness is 2 consecutive postinfusion platelet count increments ≤10,000/µL. A more formal definition of refractoriness, which adjusts for both the size of the patient and the number of platelets actually infused, uses the corrected count increment (CCI). CCI is based on a platelet count obtained within 1 hour of transfusion, calculated as follows: CCI = body surface area (BSA; $m^2$) × platelet count increment × $10^{11}$/number of platelets transfused. For example, if 3 × $10^{11}$ platelets (standard dose, as described previously) are transfused to a patient with a BSA of 1.8 $m^2$, and the posttransfusion increase in platelet count is 23,000/µL, then the CCI = 1.8 $m^2$ × 23,000/µL × $10^{11}$/3 × $10^{11}$ = 13,800. Platelet transfusion refractoriness often is defined as 2 or more consecutive postinfusion CCIs of <5000 to 7500.

An approach to managing platelet refractoriness is summarized in Figure 13-1. A trial of fresh, ABO-matched platelets may increase the posttransfusion increment modestly. A majority of platelet refractoriness is caused by nonimmune pathophysiologic conditions that consume platelets regardless of the platelet product transfused (eg, splenomegaly, DIC, fever, hemorrhage). Among immune-mediated causes, alloimmunization to HLA antigens accounts for most cases of platelet transfusion refractoriness; rarely, HPA incompatibility is responsible. In the absence of obvious nonimmune causes of platelet transfusion refractoriness, an anti-HLA-antibody evaluation is warranted. Subsequent apheresis single-donor platelet units should be selected based on HLA matching and avoiding the antibody specificities found in the patient. Some centers perform platelet crossmatching; however, these

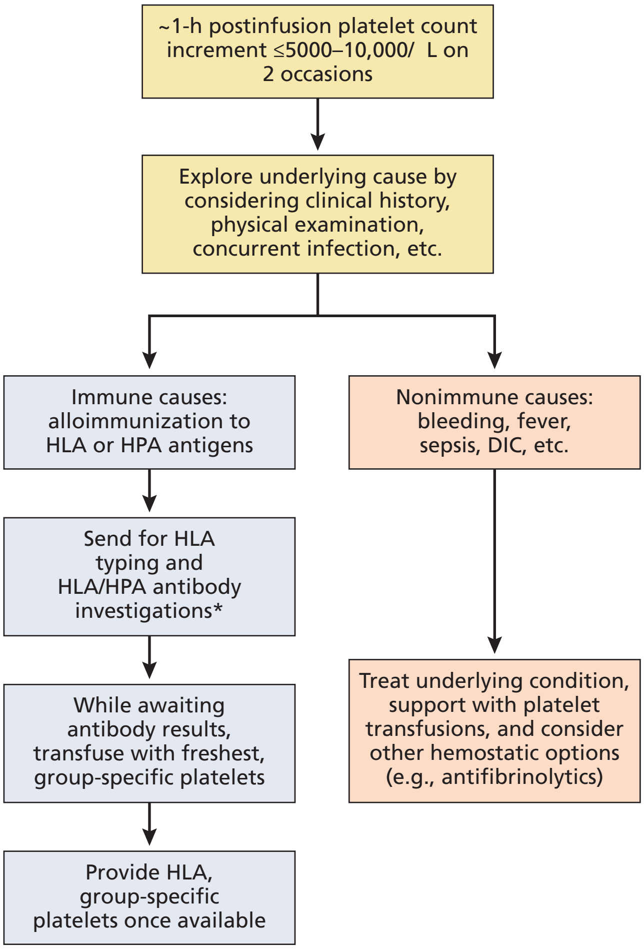
**Figure 13-1 Approach to management for platelet-refractory patients.** *HLA-antibody screen and HLA typing may be higher yield given that incidence of HPA antibodies causing transfusion refractoriness is low.

~1-h postinfusion platelet count increment ≤5000–10,000/ L on 2 occasions
Explore underlying cause by considering clinical history, physical examination, concurrent infection, etc.
Immune causes: alloimmunization to HLA or HPA antigens
Nonimmune causes: bleeding, fever, sepsis, DIC, etc.
Send for HLA typing and HLA/HPA antibody investigations*
While awaiting antibody results, transfuse with freshest, group-specific platelets
Provide HLA, group-specific platelets once available
Treat underlying condition, support with platelet transfusions, and consider other hemostatic options (e.g., antifibrinolytics)

methods do not guarantee improved platelet responses. There is no evidence that the use of single-donor or HLA-matched platelets enhances response to platelets in the absence of documented alloimmunization to HLA antigens. Alloimmunization sometimes resolves spontaneously; thus, the requirement for HLA-matched products may not persist indefinitely.

Even when a suitable HLA-matched donor is located, it can take several days to obtain a product for transfusion. The donor typically has to be called in to donate specifically for the patient in question, and the subsequent donation must undergo all routine testing before release. A variety of approaches have been taken when no compatible platelets can be found for a patient who is alloimmunized to HLA antigens. Platelet transfusion refractoriness in HSCT recipients can be managed by obtaining platelets from the original stem cell donor. In other settings, therapeutic modalities include corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIg), frequent platelet transfusion, continuous-infusion platelet transfusion, and aminocaproic acid. Clinical data do not clearly support any one of these modalities over the others. Realistic targets and infusion schedules should be set in alloimmunized patients who are not responding well to platelet transfusion or those for whom HLA-matched products are unavailable. Transfusion of multiple units of platelets from random donors, whether pooled or apheresis and with no realistic expectation of an increase in platelet count or cessation of bleeding, exposes the patient to all the risks of transfusion with no benefit.

**KEY POINTS**

- Prophylactic platelet transfusion should be considered when the peripheral blood platelet count decreases below 10,000/µL in uncomplicated patients. The platelet count target should be increased in the presence of additional risk factors for bleeding or platelet consumption.
- Platelets express ABH and HLA class I antigens, which can occasionally be clinically significant.
- Human platelet antigens are polymorphisms on platelet surface glycoproteins that may also mediate platelet transfusion refractoriness, as well as NAIT, PTP, and alloimmune thrombocytopenia following HSCT.
- Although nonimmune mechanisms are the most common causes of platelet refractoriness, antibodies directed against HLA antigens can develop following blood transfusion or pregnancy and are the most important cause of immune-mediated platelet transfusion refractoriness.

## Granulocyte transfusion

### Collection and storage of granulocytes

Approximately $10^{10}$ granulocytes can be harvested from a healthy donor during a single leukapheresis session. Pretreatment with corticosteroids induces neutrophilia in donors, increasing the granulocyte yield. Pretreatment of granulocyte donors with G-CSF significantly increases the granulocyte yield and efficacy. Several studies suggest that administering G-CSF to healthy donors does not lead to an increased incidence of hematologic disorders. Because of the short half-life of granulocytes and 24-hour expiration time of the component, granulocytes should be harvested, transported at room temperature, and infused into the intended recipient within hours.

### Clinical indications for granulocyte transfusion

Granulocyte transfusion has been performed for many decades to prevent and treat infection in neutropenic patients who are myelosuppressed from chemotherapy or hematopoietic stem cell transplant. This practice remains controversial, despite having been studied for decades. Cochrane Database systematic reviews of the literature found low-grade evidence to support prophylactic granulocyte transfusions to decrease bacteremia or fungemia risk in neutropenic, myelosuppressed patients; there is insufficient evidence of benefit on mortality rate owing to infection, all-cause mortality, or serious adverse events. In addition, there is low-grade evidence that therapeutic granulocyte transfusions may not increase the number of participants with clinical resolution of infection; there is insufficient evidence to determine whether granulocyte transfusions affect all-cause mortality.

Most cases of prolonged marrow aplasia can be treated adequately without granulocyte transfusion. The initial treatment of patients with neutropenic fever consists of broad-spectrum antibiotics and recombinant growth factors. Granulocyte transfusions should be considered only in patients with a realistic expectation of marrow recovery who have ongoing neutropenia with persistence or progression of bacterial or fungal infection despite appropriate antibiotic and antifungal therapy. Compared with conventional therapy, the RING trial studied the efficacy of high-dose granulocyte transfusion therapy in neutropenic patients with infection and did not show a benefit of granulocytes in neutropenic patients, although it was underpowered.

Once the decision to use granulocyte transfusions has been made, a minimum dose of $2 \times 10^{10}$ to $3 \times 10^{10}$ neutrophils should be given to adults. Because of the high volume of contaminating RBCs, ABO-compatible donors need to be used unless effective RBC sedimentation is performed. Granulocyte transfusions are continued, because they are available from donors, until the infection is controlled; until the patient's neutrophil count has increased to >500/µL; or until significant toxicity, particularly pulmonary toxicity, occurs. Patients with alloantibodies to granulocyte-specific antigens may not achieve a satisfactory therapeutic response to granulocyte transfusions and are at higher risk of pulmonary toxicity. Granulocyte transfusions should be separated temporally from amphotericin administration because case series evidence suggests that pulmonary toxicity is otherwise increased. Serologic testing for antineutrophil antibodies is not performed routinely, but it is indicated if significant transfusion reactions develop. If antibodies are found, leukocytes from compatible donors may be used. Leukocyte reduction filters should not be used with granulocyte products. If the potential for CMV transmission is a concern, then granulocytes collected from CMV-seronegative donors are necessary. Unlike stem cells and donor lymphocyte infusions, however, granulocytes should undergo irradiation. Because granulocytes have a short lifespan, they must be transfused as soon as possible and within 24 hours of collection. In this time, it is usually not feasible to obtain transfusion-transmitted disease testing results. To mitigate infectious transmission risk, frequent donors who have recently tested with negative results are selected, and physicians must document that they consent to the risk of transfusing an unlicensed product.

### Granulocyte transfusion risks

In addition to risks inherent to all blood product transfusions, there are more frequent and specific reactions to granulocyte transfusion:

1. Febrile nonhemolytic transfusion reactions are common.
2. Allergic reactions to reagents used for granulocyte collection such as hydroxyethyl starch can occur.
3. Pulmonary reactions can occur and be severe as a result of granulocyte transfusion; the underlying pulmonary disease can worsen.
4. Alloimmunization to HLA antigens can occur and result in platelet refractoriness.

**KEY POINT**

- Transfusion of granulocytes can be considered in patients with severe prolonged neutropenia and antibiotic-refractory infections as a bridge to endogenous granulocyte recovery.

## Transfusion of plasma products

### Plasma

Plasma can be collected through whole-blood donations or by apheresis. Collected plasma can be sent to a hospital blood bank for transfusion into a patient, or it can be sent to a fractionation plant to produce plasma protein products such as albumin or immunoglobulin. Transfusable plasma is stored frozen at -18°C and thawed prior to use. Transfused plasma must be donor-recipient ABO-compatible with the exception of universal provision of A plasma units at some trauma centers for massive hemorrhage protocols. Plasma unit volumes can range from 250 to 500 mL and should be dosed according to patient weight; 10 to 15 mL/kg. Some jurisdictions provide exclusively male plasma for transfusion (HLA-antibody negative and nulliparous female plasma may also be used) to mitigate risk of TRALI reactions.

Viral inactivation methods can be used to reduce pathogens in plasma; the most common of these techniques uses a solvent detergent method that disrupts lipid-containing viruses. Methylene blue is another method of pathogen inactivation, commonly used in Europe, in addition to the use of UV-activated psoralen derivatives. Psoralen or riboflavin-based UV treatment systems are also available in the United States.

Plasma may be indicated in the management of acquired or congenital deficiencies of virtually any individual pro- or anticoagulant factor. It is standard practice, however, to use recombinant or purified pharmaceutical preparations of coagulation-related proteins when available, and replacement of a single factor is indicated. Thus, the most common indications for plasma transfusion include treatment of bleeding or prior to an operative procedure in the presence of clinically significant levels of multiple factor deficiencies. Frozen plasma transfusion may be appropriate in bleeding patients with liver disease, DIC, dilutional coagulopathy of massive transfusion secondary to acute blood loss, or as replacement fluid for plasma exchange when indicated, such as for thrombotic thrombocytopenic purpura (TTP). Four-factor prothrombin complex concentrates composed of FII, FVII, FIX, FX, protein C, protein S and small amounts of heparin are being used instead of frozen plasma for urgent warfarin reversal in conjunction with vitamin K, particularly in the setting of intracranial hemorrhage.

Prophylactic plasma transfusions to correct mild prolongations of coagulation values before an invasive procedure usually are not indicated. RCTs to determine the appropriate indications and dosing of plasma therapy have not been completed, in part because of the low baseline bleeding risk associated with minor coagulopathies and invasive procedures, making appropriately powered trials prohibitively large. Large scale audits of plasma use show that plasma is commonly used inappropriately and/or dosed incorrectly.

## Cryoprecipitate and fibrinogen concentrate

Cryoprecipitate is prepared by thawing fresh frozen plasma to 1 °C to 6 °C, centrifuging and then separating the precipitate from the supernatant. Cryoprecipitate is a concentrated preparation of procoagulant factors, including fibrinogen, factor VIII, von Willebrand factor (VWF), factor XIII, and fibronectin. Although cryoprecipitate contains a subset of procoagulants, unlike plasma, it does not contain appreciable quantities of physiologic anticoagulants, such as protein C or protein S. Cryoprecipitate alone is not indicated in patients with disease processes that deplete both procoagulants and anticoagulants, such as DIC or severe hepatic failure. Historically, cryoprecipitate was used to treat von Willebrand disease, hemophilia A, and congenital fibrinogen disorders, but now recombinant factors and virally inactivated factor concentrates are widely available. Cryoprecipitate has also been used to treat qualitative platelet dysfunction because of uremia and life-threatening hemorrhage secondary to thrombolytic therapy. The supernatant plasma (sometimes referred to as *cryosupernatant* or *cryo-poor plasma*), which lacks the high-molecular-weight multimers of VWF, can be used in the treatment of TTP but does not appear to be superior to plasma for this indication. Cryoprecipitate is not pathogen inactivated, and a pool of 8 to 10 units of cryoprecipitate is needed to correct hypofibrinogenemia in an adult, resulting in multiple donor exposures. For children, the appropriate dose is 1 unit of cryoprecipitate per 10 kg of body weight.

In some jurisdictions, fibrinogen concentrates (FC) are being used instead of cryoprecipitate because they are pathogen-reduced and purified with standardized fibrinogen content (20 g/L). In addition, FC are lyophilized products that can be more easily stored, reconstituted, and administered. A multicenter RCT demonstrated FC to be noninferior to cryoprecipitate in the number of blood components transfused in a 24-hour period in patients undergoing cardiac surgery with clinically significant bleeding and hypofibrinogenemia after cardiopulmonary bypass. For other areas studied, such as trauma, obstetrics and gynecology, and gastrointestinal bleeding in the setting of liver disease, there is not enough evidence to support use of FC over frozen plasma; however, there are a number of RCTs underway.

## Immunoglobulin

Commercially available Ig products are typically prepared by cold ethanol fractionation of large pools of human plasma followed by viral inactivation procedures, such as solvent detergent treatment or heat pasteurization. As is the case with virally inactivated plasma, the risk of transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV appears to be negligible; however, concerns remain regarding the potential transmission of certain difficult-to-inactivate pathogens, such as parvovirus B19 and prions. There have been reports of acute renal failure occurring in association with the administration of IVIg, particularly in patients with preexisting renal insufficiency, hypovolemia, diabetes, or other risk factors. Most of the Ig in commercially available preparations is IgG itself, and the IgG immunoglobulin subtype distribution (ie, $IgG_1$ through $IgG_4$) is similar to that found in normal human plasma. Relatively small amounts of IgA and IgM also are present.

## Clinical indications for Ig

Ig is used for 2 reasons: as a replacement for those who do not make their own Ig (primary and secondary immunodeficiency) and as an immunomodulatory therapy (eg, ITP, chronic inflammatory demyelinating polyneuropathy, or Guillain-Barré syndrome). Ig is available in intravenous (IV) and subcutaneous preparations depending on the indication and dose required.

The mechanism by which IVIg ameliorates autoantibody destruction of blood cells is not clearly elucidated. Historically, it was believed that the infused IgG blocks Fc receptors on phagocytic cells of the reticuloendothelial system, but other evidence supports IVIg glycosylation driving increased inhibitory IgG receptor expression, formation of immune complexes that interact with activating dendritic cell Fc receptors, as well as direct T- and B-cell interactions.

A significant proportion of patients receiving Ig develop a positive result from DAT because of the presence of anti-A or anti-B antibodies derived from type O individuals in the donor pools. Overt, acute alloimmune hemolytic anemia can also develop, especially for blood group A and AB recipients following multiple doses of IVIg given in close proximity. Fever is a relatively common sequela of IVIg administration and does not necessarily

**Table 13-4** ABO blood group typing reaction results

| Patient's ABO type | Forward typing | | Reverse typing | |
|---|---|---|---|---|
| | Reaction of patient's RBCs with: | | Reaction of patient's serum with: | |
| | Anti-A | Anti-B | A1 RBC | B RBC |
| O | 0 | 0 | + | + |
| A | + | 0 | 0 | + |
| B | 0 | + | + | 0 |
| AB | + | + | 0 | 0 |

preclude the administration of additional IVIg. Headaches can also be common during administration of IVIg and can be mild and transient; aseptic meningitis is a severe and rare complication of IVIg.

## KEY POINTS

- The most common indications for plasma transfusion include treatment of deficiencies of coagulation factors for which specific coagulation replacement products are not available, as part of massive hemorrhage protocols and plasma exchange in patients with TTP.
- The most common indication for transfusion of cryoprecipitate is hypofibrinogenemia in the context of complex coagulopathy (eg, DIC). Fibrinogen concentrates are available for selective fibrinogen replacement.

## Pretransfusion testing

The term *pretransfusion testing* refers to the series of laboratory tests that blood banks and transfusion services perform to provide immunologically compatible blood products to patients.

### ABO/Rh(D) typing

Determining a patient's ABO blood group includes 2 independent sets of tests that are expected to yield complementary results. In the *forward typing*, patient RBCs are mixed with IgM anti-A or anti-B reagent typing sera. Agglutination of cells with either reagent indicates the presence of the A or B antigen, respectively, on the patient's RBCs. Because of the importance of determining a patient's ABO blood type with absolute certainty, a second test known as *reverse typing* is performed for confirmation. Naturally-occurring isohemagglutinins to A or B antigens occur in individuals whose RBCs lack those antigens. The patient's serum or plasma is mixed with reagent RBCs, expressing either A or B antigens, and agglutination is assessed. Table 13-4 illustrates the expected forward- and reverse-typing results for the 4 possible ABO blood types.

Discrepancies between forward- and reverse-typing reactions occur and can sometimes be explained by evaluating the patient's recent transfusion history. For example, a blood group B individual given type O red cells could continue to demonstrate only the appropriate anti-A antibodies by reverse typing but show a mixed field of RBCs, that is, both agglutinated (the patient's blood group B cells) and unagglutinated (the transfused blood group O cells) RBCs upon forward typing with anti-B reagent typing sera. Forward- and reverse-typing discrepancies are expected in newborns because isohemagglutinin production is delayed for several months while their immune systems mature. For this reason, only forward typing is performed on newborns. Forward and reverse ABO typing discrepancies also occur in patients who have undergone ABO-mismatched HSCTs, particularly during their transition from one blood type to another. Additionally, typing discrepancies can result from genetically distinct A and B blood group subtypes or rare acquired phenotypes. It is important to determine the etiology of ABO typing discrepancies to select the appropriate ABO type for different blood components.

Typing for the presence or absence of the Rh(D) antigen on RBCs is also an important part of determining a patient's blood type. Typing for D does not involve a reverse typing similar to ABO typing because anti-D is not normally expected to be present in the sera of Rh-negative individuals and develops only in response to sensitizing events from pregnancy or transfusion.

## Antibody screen and specificity identification

A patient who has never been pregnant or transfused is expected to have only the naturally- occurring isohemagglutinins based on his or her ABO type. However, it is required to test all patient sera for the presence of RBC alloantibodies. If any clinically significant alloantibodies are detected, then ABO-compatible RBCs lacking the corresponding antigens must be selected for transfusion. The antibody detection test consists of testing patient serum or plasma with 2 or 3 reagent RBCs whose extended phenotype has been characterized for all major common, clinically significant RBC antigens. If the patient's serum does not react with the screening cells, then ABO-compatible units can be selected for crossmatching. A negative-antibody detection test does not exclude all alloantibodies, such as those directed against low-prevalence antigens, but typically excludes antibodies to the common and clinically significant antigens.

If the patient's antibody detection test results are positive, further testing is required to determine the specificity of the antibody (or antibodies) present. To accomplish the determination, the patient serum is tested against a larger panel of type O reagent RBCs (typically at least 10). By comparing the resulting pattern of reactivity (ie, which cells agglutinate and which do not) with the phenotype of each of the reacting and nonreacting reagent RBCs, alloantibody specificities can be identified. Based on results of the antibody identification panel, ABO/Rh-compatible RBC units lacking the implicated antigens are selected for transfusion.

Several agglutination methods for antibody screening are available including tube, gel-based and solid-phase testing. Differences in the sensitivity, specificity, and interfering substances in the detection of clinically insignificant antibodies exist among the available methods. The gel and solid-phase methods are formulated specifically to identify IgG antibodies and not detect IgM antibodies. Therefore, if the purpose of testing is to evaluate for the presence of a cold agglutinin or other IgM antibody, consultation with a blood bank physician is important to ensure the appropriate test method is used. The antibody screen, indirect antiglobulin test, and indirect Coombs test are all different names for the same assay.

Antibody identification may take several hours to several days to complete, depending on the complexity of the reactivity. Patients with warm autoantibodies or AIHA present a significant challenge to transfusion services because of the presence of panreactive antibodies (ie, the antibodies bind to the patient's own RBCs but also to all reagent screening and panel cells). As a result, the presence of additional alloantibodies to specific blood group antigens may be masked by the autoantibodies. Time-consuming absorption techniques must be used in these cases and are discussed in the section "Autoimmune hemolytic anemia" in this chapter.

## Crossmatching

Two basic types of crossmatch procedures are used depending on results of the patient's antibody screen. If the antibody screen results are negative and the blood bank has historical records indicating no alloantibodies in the patient, then an electronic crossmatch between the donor unit and the patient's blood type to confirm ABO and RhD compatibility is performed. Computer software that performs electronic crossmatching must be validated and is under the authority of the FDA. Some blood banks do an immediate spin crossmatch, in which the patient's plasma is mixed at room temperature with an aliquot of RBCs from the prospective ABO/RhD-compatible unit, and the absence of agglutination owing to IgM isohemagglutinins is verified.

A full or Coombs crossmatch is required when the patient has a historical or current positive-antibody screen, with or without an alloantibody of known specificity. Availability of antigen-negative units varies significantly depending on the specificity of the antibody(ies) identified in the patient's plasma. After identifying prospective ABO/RhD-compatible units that are negative for the antigens against which the patient has alloantibody(ies), a full crossmatch is performed. Patient plasma is incubated with RBCs from the selected units; testing is performed from the immediate spin to the anti-human globulin phase to ensure compatibility beyond ABO. When the patient's antibody is reactive in the current sample, the Coombs crossmatch additionally ensures that the units lack the antigens for which the patient's serum contains preformed alloantibodies.

Incompatible crossmatches with multiple or all selected RBC units may be seen in a number of situations, most commonly in the presence of warm autoantibodies or panagglutinins. Understanding the reason for the incompatible crossmatch is critical to determining the risk versus the benefit of proceeding with transfusion of a crossmatch-incompatible RBC unit. Consultation with a blood bank physician is warranted in these situations.

## KEY POINTS

- For blood products to be issued to a patient, the patient's ABO/RhD blood type must be determined. For RBCs, the patient's plasma must be screened for the presence of alloantibodies that may have formed following a previous transfusion, HSCT, or pregnancy.
- If a patient's plasma lacks clinically significant RBC alloantibodies and he or she has no historical alloantibodies, then an electronic or immediate spin crossmatch is performed with prospective RBC units to ensure ABO blood group compatibility.
- If a patient's plasma demonstrates the presence of clinically significant RBC alloantibodies or he or she has historical alloantibodies, then ABO/RhD-compatible RBCs that lack the corresponding antigens must be identified. These prospective units must then undergo a full crossmatch with the patient's plasma.

# Apheresis

The American Society for Apheresis (ASFA) Journal of Clinical Apheresis (JCA) Special Issue provides robust evidence-based guidelines on the use of therapeutic apheresis in clinical practice.

## Plasma exchange

Common indications for therapeutic apheresis are given in Table 13-5. Plasma exchange typically involves centrifugation (less commonly filtration) of whole blood removed from the patient; selective removal of plasma, which is replaced with defined volumes of replacement fluid (5% albumin, plasma, saline, or various combinations of these fluids); and return of cellular blood elements from the extracorporeal circuit to the patient. Intravenous line access, number of blood volumes processed, frequency of procedure, type of replacement fluid, and duration of treatment vary depending on indication. Centrifugal apheresis typically is performed in a continuous-flow fashion so that the patient remains euvolemic throughout the procedure.

Plasma exchange can be used for depletion of unwanted autoantibodies and can be used to treat patients with antibody-mediated disorders to remove the causative antibodies, including Goodpasture syndrome, Guillain-Barré syndrome, and humoral rejection in organ transplantation. Approximately half of total IgG is intravascular. Because subsequent procedures remove plasma that has already had immunoglobulin removed, their efficiency is theoretically less than the first procedure. Allowing time in between procedures allows for redistribution of IgG back into circulation, which increases the available IgG for removal. IgM is approximately 80% intravascular and is more efficiently removed than IgG. The adverse effects of plasma exchange are primarily driven by complications related to line access or insertion, risk of reactions with plasma replacement fluid, vagal reactions, and reactions to the citrate or heparin used for anticoagulation. Many centers have apheresis protocols with strict calcium replacement orders and parameters to mitigate risk for hypocalcemia secondary to citrate toxicity.

## Extracorporeal photochemotherapy

Extracorporeal photochemotherapy (ECP or photopheresis) involves collecting peripheral blood mononuclear cells by apheresis (processing about one-third of the blood volume), adding a photoactivating agent (8-methoxypsoralen) into the mononuclear cell suspension, treating the mononuclear cells with UV-A light, and returning the treated cells to the patient. The process takes about 2 to 4 hours. ECP is an adjunctive therapy for erythrodermic cutaneous T-cell lymphoma. Patients typically are treated on 2 consecutive days every 4 weeks. The median time to response is 4 to 6 months. Response correlates with the presence of circulating clonal tumor cells and a CD8-mediated antitumor response. ECP is also used to treat acute and chronic GVHD after allogeneic stem cell transplantation. The best response rates to ECP (~70%) are seen with chronic cutaneous GVHD in steroid-refractory cases.

## RBC exchange transfusion

RBC exchange or erythrocytapheresis (RCE) is used in 2 main patient populations: neonates with severe HDFN and patients with SCD meeting certain criteria. Indications in SCD include prevention and treatment of acute complications of the disease, such as stroke and acute chest syndrome. The *American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support* details guidance around use of RCE. During RCE, the patient's erythrocytes are removed and replaced with donor erythrocytes while the patient's own plasma is continually returned to minimize disturbance of hemodynamic and coagulation parameters; however, some platelets are removed during erythrocytapheresis.

In the absence of automated RCE capacity, manual RBC exchange can be considered. Manual phlebotomy is followed by infusion of donor RBCs. This is performed particularly in small children who cannot tolerate the volume shifts associated with apheresis and/or

**Table 13-5** Abbreviated list of therapeutic apheresis procedures grouped by American Society for Apheresis indication category

| Disease/disorder | Procedure |
|---|---|
| **Category 1. Accepted as first-line therapy, stand-alone or adjunctive** | |
| Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) | Plasmapheresis |
| Cutaneous T-cell lymphoma; mycosis fungoides (erythrodermic) | Extracorporeal photopheresis |
| Familial hypercholesterolemia (homozygotes) | Selective absorption |
| Goodpasture syndrome | Plasmapheresis |
| Guillain-Barré syndrome | Plasmapheresis |
| Hyperviscosity in monoclonal gammopathies | Plasmapheresis |
| Myasthenia gravis | Plasmapheresis |
| Polycythemia vera | RBC exchange |
| Sickle cell disease (acute stroke treatment and prophylaxis) | RBC exchange |
| TTP | Plasmapheresis |
| ANCA-associated rapidly progressive glomerulonephritis | Plasmapheresis |
| Babesiosis, severe | RBC exchange |
| Antibody-mediated renal transplant rejection | Plasmapheresis |
| **Category 2. Accepted as second-line therapy, stand-alone or adjunctive** | |
| ABO-incompatible hemopoietic progenitor cell transplantation | Plasmapheresis |
| Catastrophic antiphospholipid syndrome | Plasmapheresis |
| Cold agglutinin disease, life-threatening | Plasmapheresis |
| Cryoglobulinemia | Plasmapheresis |
| Graft-versus-host disease (skin) | Extracorporeal photopheresis |
| Hyperleukocytosis/leukostasis | Leukapheresis |
| Myeloma cast nephropathy | Plasmapheresis |
| Pure RBC aplasia | Plasmapheresis |
| SCD (acute chest syndrome) | RBC exchange |
| **Category 3. Role of apheresis is not established; decision making should be individualized** | |
| Coagulation factor inhibitors | Plasmapheresis |
| Graft-versus-host disease (nonskin) | Extracorporeal photopheresis |
| Hyperleukocytosis/leukostasis (prophylaxis) | Leukapheresis |
| ITP (refractory) | Plasmapheresis |
| Malaria | RBC exchange |
| Posttransfusion purpura | Plasmapheresis |
| Warm autoimmune hemolytic anemia | Plasmapheresis |
| **Category 4. Evidence indicates apheresis to be ineffective or harmful** | |
| Amyloidosis | Plasmapheresis |
| Rheumatoid arthritis | Plasmapheresis |
| SLE nephritis | Plasmapheresis |

ANCA, antineutrophil cytoplasmic antibody; HUS, hemolytic-uremic syndrome; SLE, systemic lupus erythematosus.

those who do not have the required vascular access for chronic automated RCE. For manual exchange, serial aliquots of whole blood are removed, alternating with RBC replacement to avoid volume depletion because of excessive phlebotomy and hypervolemia/hyperviscosity owing to excessive RBC transfusion. The goal of RCE in most situations, such as acute chest syndrome, stroke, or preoperative exchange, whether performed manually or via automated RBC apheresis, is to achieve a hematocrit of 30% with a hemoglobin S of ≤30%.

### PBSC harvesting

Mobilization refers to the technique of increasing the number of circulating progenitor cells in the peripheral blood. Mobilization can be achieved through administration of single agent hematopoietic growth factors or in combination with chemotherapy and/or selective inhibitors of CXCR4. Leukapheresis refers to the collection of white blood cells using apheresis. In the context of stem cell harvest, leukapheresis refers to collection of hematopoietic stem cell collection for the purpose of transplantation. G-CSF downregulates the expression of adhesion molecules on the surface of HPSCs, progenitor cells, precursor cells, and mature neutrophils and mobilizes clinically significant numbers of HPSCs into the peripheral blood.

For autologous collection, many mobilization regimens combine chemotherapy with growth factors, whereas allogeneic donors are stimulated with growth factor alone. A mobilization regimen that has a predictable rebound phase allows for a more efficient use of apheresis and stem cell–processing staff. G-CSF is a common mobilization regimen for allogeneic PBSC donors. With this regimen, leukapheresis begins on day 5, when the white cell count is $20 \times 10^9$ to $50 \times 10^9$/L. There is correlation between the number of CD34$^+$ cells in the peripheral blood on the day of leukapheresis (or the preceding day) and the number of CD34$^+$ cells that can be collected by apheresis. In general, for each $10^6$/kg target collection of CD34$^+$ cells, the CD34$^+$ cell count in the peripheral blood is $10 \times 10^6$/L.

Although the administration of mobilizing doses of G-CSF can induce seemingly worrisome degrees of leukocytosis, transient peripheral blood leukocyte counts of 80,000/μL or higher can occur. Follow-up studies reported to date suggest that administration of short courses of G-CSF to healthy donors is not associated with any adverse long-term consequences. A rare complication of G-CSF mobilization is splenic rupture, which has been reported in healthy adult PBSC donors, most commonly after 5 daily doses of G-CSF.

A relatively common problem with PBSC harvesting is inadequate collection. The incidence of inadequate collection is much higher in heavily pretreated patients than in healthy donors. In healthy PBSC donors, increasing age, white ethnicity, and female sex were associated with lower post–G-CSF peripheral blood CD34$^+$ counts, which correlate with lower CD34$^+$ yields from collection. Risk factors for an inadequate autologous collection include multiple prior chemotherapeutic regimens, extensive prior radiation therapy, or administration of certain chemotherapeutic agents, such as fludarabine, lenalidomide, melphalan, chlorambucil, and nitrosoureas.

Plerixafor is a small-molecule reversible inhibitor of the chemokine receptor CXCR4 on stem cells. This inhibition facilitates HPSC egress from the bone marrow and is synergistic with the mobilizing effects of G-CSF. One dose of plerixafor given with G-CSF has been shown to successfully mobilize CD34$^+$ cells in patients with multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma who failed previous mobilization attempts. Plerixafor is uncommonly needed in healthy PBSC donors. The adverse effect profile of plerixafor (mostly gastrointestinal) does not appear to overlap with that of G-CSF. The use of plerixafor varies by center, with some centers routinely using it for mobilization to maximize yield and minimize apheresis collections.

**KEY POINTS**

- Apheresis selectively removes plasma, erythrocytes, or leukocytes for therapeutic benefit in a variety of hematologic diseases (eg, TTP, SCD, an HPSC collection).
- A variety of nonhematologic, antibody-mediated disorders can be successfully treated with apheresis to remove the causative antibodies, including Goodpasture syndrome, Guillain-Barré syndrome, and humoral rejection in organ transplantation.

## Transfusion support in special clinical settings and pediatric populations

**CLINICAL CASE**

A 56-year-old woman is being evaluated for matched HSCT from her brother for high-risk acute myeloid leukemia. She is A positive, and he is O negative. She is enrolled in a nonmyeloablative conditioning protocol. On day zero, the PBSC is plasma depleted and infused without incident. On day 8, she is noted to have a hemoglobin of 6 g/dL (down from 9 g/dL the day before). She is asymptomatic and without any evidence of bleeding.

### Patients who are candidates for HSCT

Many patients newly diagnosed with hematopoietic malignancies may become potential candidates for HSCT during their clinical course. Because family members may be potential HSC donors, directed-donor transfusion products from relatives should be avoided to minimize the risk of HSCT graft rejection via alloimmunization to minor histocompatibility antigens. For newly diagnosed patients with acute leukemia who are likely to require HSCT, it may be useful to perform HLA typing early in the course of induction therapy. Thrombocytopenia during the postconditioning and preengraftment phase of HSCT is expected, and in most cases is easily managed by platelet transfusion support. Multiparity places females at risk of HLA alloimmunization, which can pose challenges in adequate platelet support during HSCT.

## Transfusion support after HSCT

The intensity of transfusion support is typically less in autologous and nonmyeloablative allogeneic transplantation compared with allogeneic myeloablative regimens. In a hemodynamically stable patient without underlying cardiovascular disease, strong evidence to guide RBC transfusion strategy in this patient population is lacking; however, the hemoglobin threshold is commonly 7 to 8 g/dL. The landmark studies that support a platelet transfusion threshold of $10 \times 10^9$/L were conducted in patients undergoing leukemia induction. Risk factors for platelet refractoriness such as fever, infection, bleeding, and amphotericin are common in HSCT patients. Veno-occlusive disease increases platelet consumption, and portal hypertension and hypersplenism further increase platelet transfusion requirements.

HSCT recipients require irradiated RBC and platelet products to prevent TA-GVHD. Leukoreduced blood components reduce the risk for CMV infection in CMV-seronegative HSCT recipients. A randomized comparison of leukoreduced versus CMV-seronegative blood components in CMV-seronegative HSCT recipients (with seronegative donors) found no significant difference in the incidence of CMV infection or disease as a composite outcome. In practice, many transplantation centers use prestorage leukoreduced blood components.

## ABO-incompatible HSCTs

Allogeneic HSCTs do not require ABO matching because ABO antigens are not expressed on hematopoietic stem cells. In the unrelated donor setting, there may be multiple potential HLA matches for any given patient. ABO compatibility is a secondary consideration along with donor sex, age, and CMV status. In all cases of ABO-incompatible HSCT, the blood bank must be aware of the clinical situation and receive serial samples to correctly report ABO type and determine when the ABO switch has occurred.

In major ABO-incompatible HSCT, the recipient has preformed antibodies against donor red cell A or B antigens. Major ABO-incompatible HSCT can lead to acute hemolysis during or immediately after graft infusion. RBC depletion can be performed prior to infusion but may also reduce the stem/progenitor dose of the graft owing to processing loss. Apheresis collections typically do not require RBC depletion. Major ABO incompatibility can also lead to delayed RBC recovery but has not been shown to impact overall engraftment. Delayed RBC engraftment and prolonged anemia occur in ~10% of major ABO-incompatible HSCT when performed with reduced-intensity conditioning regimens because of the persistence of recipient-derived plasma cells.

Minor ABO-incompatible HSCT occurs when the donor anti-A or anti-B antibodies are directed against the recipient's RBC antigens. The risk of graft infusion-associated hemolysis is low but can be prevented by plasma volume reduction of the donor product. Passenger lymphocyte syndrome occurs when donor lymphocytes produce antibodies 1 to 3 weeks following HSCT, which can result in hemolysis until recipient RBCs are no longer produced. This result occurs more commonly with T-cell–depleted marrows, PBSC versus a marrow source, use of calcineurin inhibitors (immunosuppressive effect on T-cells), and reduced-intensity conditioning regimens. Clinically significant hemolysis occurs in ~10% to 15% of cases, which are supported with RBCs compatible with both donor and recipient types. Recipients of an ABO mismatch HSCT usually convert to their donor ABO blood group over ~120 days; however, only their forward blood group testing converts while their reverse testing does not.

HSCT recipients with non-ABO alloantibodies have undergone transplantation with antigen-positive grafts after RBC depletion of the product. A Rh(D)-positive recipient who undergoes HSCT from a Rh-negative donor may develop anti-D as the donor lymphocytes respond to the residual Rh-positive RBCs. For patients with multiple RBC alloantibodies, the optimal time to discontinue antigen-negative blood is unknown, but one strategy is to wait until chimerism tests show 100% donor lymphocytes because residual recipient lymphocytes may resume production of RBC alloantibodies with donor specificity. Finally, patients who reject their graft may revert to their previous ABO/Rh type. The transfusion service must be alert to subtle changes in mixed-field agglutination in ABO blood grouping during these situations. Table 13-6 provides useful guidelines for the selection of the appropriate blood group type for RBCs, platelets, and plasma for donor-recipient ABO-HSCT incompatibility.

## KEY POINTS

- RBC, platelet, and granulocyte products administered to HSCT recipients must be irradiated to minimize the risk of potentially fatal TA-GVHD and leukoreduced to minimize the risks of CMV transmission and alloimmunization to HLA antigens.
- Donor-recipient mismatches involving the ABO system usually are well tolerated but occasionally can cause delayed alloimmune hemolytic anemia or pure RBC aplasia.

## Neonatal transfusion issues

### Hemolytic disease of the fetus and newborn

HDFN is most commonly owing to maternal-fetal mismatches involving the Rh or ABO antigens. For non-ABO antigens, exposure to antigen-positive fetal RBCs or prior transfusion can cause a mother who is antigen-negative to mount an antibody response. Maternal IgG antibodies can cross the placenta and cause passively acquired immune-mediated hemolytic anemia in the fetus, potentially leading to profound anemia and in severe cases, hydrops fetalis and fetal demise. The incidence of severe HDFN has been reduced dramatically with the use of antenatal and peripartum administration of RhIg to Rh(D)-negative mothers. Most cases of HDFN are now attributed to sensitization to Rh antigens other than D, K (Kell blood group system), and ABO. Although severe cases have occurred, ABO HDFN is typically characterized by hyperbilirubinemia with mild or no anemia. The mother is usually in group O with IgG anti-A,B alloantibodies (an antibody with cross-reactivity to both A and B antigens), and the infant is most commonly in group A.

### Intrauterine transfusion

Technical expertise is currently concentrated in centers that specialize in high-risk obstetrics. In a sensitized pregnancy, middle cerebral artery Doppler ultrasonography guides the need for fetal blood sampling, which may be performed after 20 weeks of gestation. The threshold for intrauterine transfusion (IUT) for HDFN is a fetal hematocrit <25% to 30%. Group O, D-negative RBCs lacking the implicated RBC antigen are selected and crossmatched with maternal plasma. RBCs are irradiated, CMV-safe, hemoglobin S-negative, and stored for fewer than 7 days. At some institutions, the RBCs are washed and concentrated to the volume and hematocrit specified by the obstetrician performing the procedure. Once IUT is initiated, it is repeated every 3 to 4 weeks until 35 weeks of gestation to maintain a minimum fetal hematocrit at approximately 25%. Neonates who have undergone IUT may have suppressed erythropoiesis and/or persistent maternal antibody that necessitates postnatal transfusion support for up to 3 months.

**Table 13-6** Peritransplant guidelines for blood component selection in ABO-incompatible HSCT

| Recipient blood type | Donor blood type | RBC transfusion | Platelet/plasma transfusion |
|---|---|---|---|
| O | A | O | A or AB |
| O | B | O | B or AB |
| O | AB | O | AB |
| A | B | O | AB |
| A | AB | A or O | AB |
| A | O | O | A or AB |
| B | A | O | AB |
| B | AB | B or O | AB |
| B | O | O | B or AB |
| AB | A | A or O | AB |
| AB | B | B or O | AB |
| AB | O | O | AB |
| Rh neg | Rh pos | Rh neg | Rh pos or Rh neg |
| Rh pos | Rh neg | Rh neg | Rh pos or Rh neg |

neg, negative; pos, positive.

### Neonatal exchange transfusion

Advances in phototherapy and antenatal care have made exchange transfusion for HDFN an uncommon occurrence. Appropriate unit selection follows the same principles for IUT. In addition, the RBCs are concentrated and reconstituted with group AB plasma, typically in a 1:1 ratio to produce a unit of reconstituted "whole blood" (hematocrit 50%) for the exchange. A double-volume exchange removes approximately 85% of the neonate's antigen-positive RBCs but is less efficient in lowering plasma bilirubin. Complications of exchange transfusion include hypocalcemia, dilutional thrombocytopenia, and catheter-related complications.

### Neonatal alloimmune thrombocytopenia

Analogous to HDFN, maternal-fetal mismatches involving platelet-specific antigen systems may result in NAIT. Although numerous other platelet antibody specificities have been implicated, the most common antibody specificity in NAIT in European backgrounds targets HPA-1a, which resides on the platelet fibrinogen receptor GPIIb/IIIa. While HDFN typically occurs with the second pregnancy, NAIT can occur during a first pregnancy.

Prenatal treatment of these disorders often includes maternal IVIg to decrease placental transfer of antibodies and reduce platelet clearance in the fetus. Infants with NAIT are at risk of intraventricular hemorrhage and should be screened with a head ultrasonography immediately after birth. Transfusion support of NAIT is initiated with random donor platelets, which typically results in an adequate platelet increment in the majority of cases. If the neonate has a poor response, maternal platelets are considered negative for the target antigen and may be used while awaiting identification of the platelet alloantibody specificity. Some blood centers have registries of specific platelet antigen–negative donors available for donation if required. IVIg is a therapeutic option if the bleeding is mild to moderate.

## RBC transfusion in preterm neonates

Among preterm infants, physiologic anemia of infancy occurs at 4 to 6 weeks, and the nadir is 7 to 8 g/dL, factors of which may also be compounded by iatrogenic phlebotomy. Judicious laboratory monitoring can help minimize blood loss and subsequent transfusion. Delaying umbilical cord clamping for 30 to 60 seconds for infants who do not require immediate resuscitation has been advocated by some to be the first step in counteracting the anemia of prematurity. Erythropoietin has limited efficacy in preterm infants and has been associated with an increased risk of retinopathy of prematurity. Limited donor exposure can be achieved by dedicating a fresh O-negative RBC unit (≤7 days old) to 1 or 2 preterm infants and used exclusively to transfuse those infants.

Two randomized clinical trials of restrictive versus liberal RBC transfusion criteria used transfusion thresholds that varied with patients' postnatal age, respiratory, and medical status. A stable older infant in the restrictive arm, for instance, would be transfused at a hemoglobin level of approximately 7.5 g/dL; however, a younger mechanically ventilated preterm infant would be transfused at a hemoglobin level of approximately 11.5 g/dL. In both trials, the number of donor exposures from RBC transfusions alone was not reduced by restrictive transfusion criteria, presumably reflecting the efficacy of using dedicated donor units. Only one of the 2 trials demonstrated that a restrictive transfusion threshold increased the percentage of infants who avoided transfusion altogether (from 5% to 11%).

Most US centers routinely irradiate all cellular components for neonates for a variable period of time after birth (typically 4 to 6 months). Many practices are not uniform nationally or internationally, in part because of lack of evidence to guide clinical care. Some centers use criteria based on gestational age and birth weight. While leukoreduced cellular components are used to reduce the risk of CMV transmission, some centers use CMV-seronegative components for specific subgroups, such as neonates weighing <1 200 g. Washing to reduce the potassium load is not indicated in small-volume transfusions; however, use of fresh or washed RBCs may be performed for large-volume transfusion. RBCs for neonates requiring large-volume transfusion should be irradiated as close as possible to the time that they are transfused to avoid significant increases in extracellular potassium levels. Although 2,3-DPG is depleted in stored RBCs, it is rapidly regenerated after transfusion. Infants given stored RBCs have stable 2,3-DPG levels after small-volume transfusions. In the ARIPI double-blind RCT, use of fresh RBCs (mean age 5.1 days) compared with standard-issue RBCs (mean age 14.6 days) did not improve outcomes in premature and very-low-birth-weight infants requiring transfusion.

## Other component therapy in neonates

Newborns may require plasma transfusion, most commonly for DIC secondary to sepsis; 10 to 15 mL/kg produces a 15% to 20% increase in factor levels, assuming ideal recovery. If cryoprecipitate is required for persistent hypofibrinogenemia despite plasma transfusion, a dose of 1 unit should produce a 100 mg/dL increase in fibrinogen (in older infants, the cryoprecipitate dose is 1 U/5-10 kg of body weight).

Neonatal thrombocytopenia is common in preterm infants, and frequently a sign of sepsis, severe inflammation, or perinatal asphyxia/placental insufficiency. Prophylactic transfusions are often recommended in neonates with platelet counts <20,000 to 30,000/mL if otherwise stable. In unstable neonates or those requiring invasive procedures, platelets are often transfused to maintain a count of ≥50,000/µL. In preterm infants with thrombocytopenia, the PLaNeT2 trial showed that a higher platelet transfusion threshold of 50,000/$\mu L^3$ resulted in a higher rate of death or major bleeding than a restrictive threshold of 25,000/µL. Similar to RBCs, infants requiring significant platelet transfusions may also receive aliquots from a dedicated apheresis platelet unit to reduce donor exposures; however, the shelf life of platelets is quite short. Platelets should be ABO-identical to avoid the transfusion of minor incompatible plasma into the small blood volume of a neonate. If ABO-identical (or group AB) platelets are not available, platelets can be washed, or the volume can be reduced to remove incompatible plasma. Routine washing or volume reduction of platelets is not necessary or recommended because the procedure can jeopardize platelet quality.

### KEY POINTS

- The immune system in the fetus and in neonates up to the age of 4 months is immature and typically not capable of generating antibody responses to transfusions. Thus, the most crucial compatibility issues involve the passive transfer of antibodies from the mother to the fetus, as well as maintaining ABO compatibility among the donor and the fetus or neonate.
- Current blood banking practice attempts to limit the number of donor exposures to fetal and neonatal patients by using multiple transfusion aliquots from single blood products.

## Autoimmune hemolytic anemia

### CLINICAL CASE

A 69-year-old woman presents with an Hb of 6 g/dL. The DAT has positive results for IgG and negative results for complement, indicating that circulating RBCs are coated with IgG. Her reticulocyte count is <1%. She has never been transfused and has never been pregnant. The patient is started on prednisone for treatment of presumed warm (IgG-mediated) AIHA. Because of shortness of breath, an RBC transfusion is ordered. Multiple RBC crossmatches are incompatible. Two units of crossmatch-incompatible leukoreduced RBCs are transfused. The peripheral blood hemoglobin concentration increases to 8 g/dL, and she experiences no untoward reactions.

Transfusion in patients with AIHA can be challenging. Autoantibodies to RBCs can result in multiple incompatible crossmatches, which may lead blood banks to inform clinicians that no compatible RBC units are available. FDA regulations require the patient's physician to provide written consent to release incompatible units, which makes many clinicians uncomfortable. If the patient has not been previously transfused or pregnant, alloantibodies to non-ABO antigens are unlikely to be present, and patients can usually be transfused safely with ABO-compatible blood. In patients who have been previously transfused or pregnant, withholding transfusions because of incompatible crossmatches while awaiting a complete evaluation must be weighed against the patient's clinical status and need for lifesaving transfusions.

Multiply transfused patients with AIHA are at risk of alloimmunization. Thus, if a patient has received a transfusion or been pregnant, the transfusion service must perform specific testing to determine whether alloantibodies are present concurrently with the panagglutinating autoantibodies associated with AIHA. The term *panagglutinating* refers to the fact that most autoantibodies that cause AIHA agglutinate most or all RBCs, including reagent RBCs and RBCs for transfusion, because the antigenic target is typically an antigen present on the RBCs of a large proportion of the population. This antigen is often a common Rh epitope.

Some transfusion services routinely perform extended RBC typing for patients with AIHA at the time of diagnosis. Extended RBC typing can facilitate new alloantibody identification following transfusion. DNA-based methods are preferable because of the interference of positive DAT results with serologic typing, and the additional antigen information provided by these methods. In rare situations, when the presence of underlying alloantibodies cannot be excluded, transfusion of RBC units phenotypically similar to the patient's own extended RBC phenotype (Rh, K, Jk, Fy, Ss antigens) can theoretically reduce the risk of hemolysis owing to alloantibodies.

The technique for detecting alloantibodies in the presence of autoantibodies is called adsorption. With the autoadsorption technique, an aliquot of the patient's plasma is adsorbed repeatedly with the patient's own RBCs. This step removes autoantibody on the autologous RBCs and leaves any RBC alloantibody in the plasma. The remaining plasma is then tested for alloreactivity with a panel of donor RBCs in a standard antibody screen. The technique is time-intensive, and results can take several days if the antibody specificity is unusual. If the patient has undergone transfusion recently, autoadsorption cannot be reliably interpreted because the transfused RBCs present in the patient's circulation could adsorb the very same alloantibodies that the laboratory is attempting to detect. In this situation, alloadsorption is used. Differential alloadsorption, sometimes called triple adsorption, involves adsorbing aliquots of patient serum against RBCs of defined phenotypes to produce several adsorbed sera that give differential reactivity in standard antibody screens. The differential reactivity results from the fact that alloantibodies are left behind in the serum following the adsorption if the adsorbing cells are considered negative for the antigen in question. Because most warm-reacting autoantibodies react with RBC surface determinants that do not vary among individuals (ie, common antigens), adsorption with RBCs of different phenotypes removes the autoantibody but, depending on the phenotype, either removes or fails to remove alloantibody. For example, if the patient's serum contains an anti-Jk$^a$ antibody, both the autoantibody and the anti-Jk$^a$ antibody are adsorbed by Jk$^a$-positive adsorbing cells, but only the autoantibody is adsorbed by Jk$^{a-}$negative adsorbing cells.

The presence of the anti-Jk$^a$ in the patient's serum then can be deduced by demonstrating that the aliquot of the serum that was adsorbed by Jk$^a$-positive cells is nonreactive in a standard antibody screen; whereas, the aliquot of serum that was adsorbed by Jk$^a$-negative cells reacts only with Jk$^a$-positive cells in a standard antibody screen.

Warm-reacting autoantibodies occasionally demonstrate preferential reactivity against certain antigens. The apparent specificity demonstrated by autoantibodies is often directed to an antigen in the Rh blood group system, most commonly to the e (little e) antigen. For transfusion, the survival of antigen-positive donor RBCs usually does not differ from that of the patient's own RBCs; however, in some cases, RBCs that do not express the target antigen may survive longer following transfusion.

In patients with clinically significant cold-reacting autoantibodies, such as anti-I, RBCs lacking the offending antigen are often not available. Blood transfused through a blood warmer usually survives adequately if the patient is kept warm while other forms of treatment, such as cytotoxic chemotherapy or plasmapheresis, are instituted. If requested, a blood bank workup of the cold-reacting autoantibodies can include the performance of a thermal-amplitude determination in which RBC binding in vitro to the patient's autoantibodies is assessed as a function of temperature (eg, at 4 °C, 22 °C, 30 °C, and 37 °C). Autoantibodies that are reactive at body temperature are considered clinically significant. The results of such tests can give the clinician a sense of the potential clinical significance of the autoantibodies in vivo at body temperature.

In the clinical case described previously, the patient's reticulocyte count was low. A substantial minority of patients manifest at least transient reticulocytopenia early in the course of AIHA, a phenomenon that may be because of either autoantibody titers that increase more quickly than the bone marrow's reticulocyte response or rapid destruction of reticulocytes by the autoantibody. Reticulocytopenia with brisk AIHA is an emergency situation, and transfusion should not be delayed.

## KEY POINTS

- RBC transfusions in patients with life-threatening AIHA should not be withheld simply because all available units are crossmatch-incompatible. Consultation with a transfusion medicine physician may be helpful for assessment of transfusion risks in patients with complex serologic workups.
- Special blood bank techniques are available to minimize the risk of transfusion in patients with AIHA.

## Autoimmune and consumptive thrombocytopenias

Transfusion of platelets in patients with ITPs is usually not indicated because the transfused platelets are also destroyed by the antibody. As is the case with AIHA, the autoantibody in ITP often reacts with public antigens. Platelet transfusion in patients with ITP is reserved for life-threatening hemorrhages and for major surgery. Administration of IVIg may improve the survival of transfused platelets in patients with ITP, and the administration of IVIg or continuous infusions of platelets has been used in patients with life-threatening hemorrhage and those undergoing major surgery. Tpo-mimetics are usually used in the chronic duration, but they may be started earlier in the course of patients in whom acute ITP is present and who are not responsive to IVIg and/or steroids. Elective splenectomy typically is managed with preoperative IVIg or a pulse of corticosteroids. Intravenous Rh(D) IgG can be administered more quickly than IVIg, but its use is limited to Rh(D)-positive and nonsplenectomized patients.

Except in life-threatening bleeding situations, such as intracranial hemorrhage, platelet transfusions should be avoided in other consumptive thrombocytopenias as well (eg, TTP and heparin-induced thrombocytopenia) because it may exacerbate the underlying thrombotic process.

## Sickle cell disease

Indications for transfusion in SCD include stroke, acute chest syndrome, aplastic crisis, and preoperative preparation to reduce the risk of postoperative respiratory complications and vaso-occlusive events. Patients who require ongoing transfusion therapy accumulate iron much less rapidly if the transfusion occurs in the form of exchange procedures rather than simple transfusions; however, exchange transfusion carries the risk of additional donor exposures and often requires adequate vascular access.

Patients with SCD have a higher risk of alloimmunization compared with other patient populations who also require frequent or long-term transfusion. Over 25% of patients become alloimmunized, depending on the level of antigen matching, cumulative exposure history, and other recipient factors. One major reason for the high rate of alloimmunization is the differences in RBC antigen phenotypes between patients who are primarily of African descent and donors who are primarily of European backgrounds (in the United States, Canada and United Kingdom). Patients with SCD may also have a higher intrinsic immune responsiveness to blood group antigens because of underlying inflammation. Furthermore, patients with SCD are more likely to form alloantibodies when transfused during hospitalizations for acute chest syndrome or painful vaso-occlusive episodes.

Alloimmunization can be associated with delayed hemolytic transfusion reactions with varying degrees of anemia, hyperbilirubinemia, and/or pain. Hyperhemolysis is a transfusion-related complication observed in patients with SCD, often present with severe anemia and reticulocytopenia 7 to 10 days after transfusion. The hematocrit is lower than the pretransfusion level, suggesting destruction of autologous RBCs. The lower hematocrit may also reflect a lower erythropoietic drive following transfusion. The DAT result is often negative, and new alloantibodies may or may not be detectable. It is important to recognize this syndrome because its management consists of the judicious avoidance of additional transfusions in the face of severe anemia, corticosteroids, IVIg, and erythropoietin. Rituximab can be considered to prevent further RBC alloimmunization and DHTR in high-risk patients (previously immunized with history of DHTR) if a subsequent RBC transfusion is required. Eculizumab, a monoclonal anti-C5 antibody targeting terminal complement activation has been used as salvage therapy in cases of severe DHTR and hyperhemolysis.

Clinical practices for prevention and treatment of alloimmunization in patients with SCD are varied. Optimal management includes extended antigen typing for the most important antigen systems in addition to ABO and RhD, including Rh (C, c, E, e), Kell (K), Kidd ($Jk^a$, $Jk^b$), Duffy ($Fy^a$, $Fy^b$), and MNSs. DNA-based methods may be preferable, particularly in recently or multiply transfused patients. Extended RBC phenotyping facilitates identification of antibody specificities when a new antibody is detected. Prophylactic C, E, and K matching are recommended for all patients with SCD. Some institutions also match c and e antigens. Less commonly, extended RBC matching is performed and includes $Jk^a/Jk^b$, $Fy^a/Fy^b$, and Ss in addition to C, E, and K. It is not feasible to routinely match all antigens that the patient lacks with typical donor inventories. The adoption of high-throughput blood group genotyping platforms by more blood centers facilitates extended blood group matching between blood donors and patients with SCD, particularly when coupled with minority donation recruitment efforts.

## KEY POINTS

- Patients with SCD should receive ABO, D, C, E, and K-matched RBCs to minimize alloimmunization.
- There is a high incidence of DHTRs in SCD and the potential for life-threatening hyperhemolytic transfusion reactions.
- Transfusion is the standard of care for the prevention and treatment of select complications of SCD (eg, stroke, acute chest syndrome, and aplastic crisis).

## Massive transfusion

Massive transfusion is defined as the replacement of 1 BV within 24 hours, or transfusion of a certain number of RBC units within 4 to 6 hours, typically in the setting of severe trauma, major surgery, or postpartum. Coagulopathy of massive transfusion is multifactorial and includes hypothermia, acidosis, dilutional effect of blood loss, inadequate coagulation-factor replacement, reduced hepatic synthesis of coagulation factors in massive hepatic injury, DIC from hypotension and tissue injury, and consumption of coagulation factors or platelets.

Both laboratory tests and transfusion volume may not correlate well with the severity of bleeding. Thrombocytopenia is the most frequent abnormality associated with massive transfusion. When transfusions of 1 to 2.0 BVs are administered over 4 to 8 hours, mean reduction in peripheral blood platelet count is approximately 50%. One strategy for management of massive transfusion is to allow the prothrombin time, activated partial thromboplastin time, plasma fibrinogen level, and platelet counts to guide component replacement therapy. In practice, many trauma centers have adopted an empiric preemptive approach to prevent coagulopathy, based on military experience, using early aggressive plasma transfusion and/or fixed ratios of blood components in standardized massive transfusion protocols. Massive hemorrhage protocols streamline rapid access to surgical care and prompt access to blood components. The use of a massive hemorrhage protocol has been shown to decrease variability of treatment, reduce blood component wastage, facilitate multidisciplinary communication, and enable tracking of metrics for continuous quality improvement. Patients undergoing massive transfusion need to be monitored for electrolyte disturbances such as hypocalcemia (citrate in the anticoagulant used for all blood components binds free calcium), hyperkalemia or hypokalemia, and metabolic alkalosis (from citrate metabolism). Tranexamic acid should be administered as soon as IV access is established because it has been shown to decrease mortality when given immediately or within 3 hours of trauma and postpartum hemorrhage. Patients should be kept normothermic to optimize hemostasis. Fibrinogen levels should be checked regularly and maintained with fibrinogen replacement.

## Cardiopulmonary bypass

Alterations in the laboratory parameters of hemostasis are observed in virtually all patients undergoing open-heart surgery and extracorporeal circulation. Less than 10% of these patients experience severe bleeding. Dilution by priming the extracorporeal circuit with nonblood solutions may reduce the platelet count by as much as 50%. Platelet dysfunction results from platelet contact with the surfaces of extracorporeal circuits, including pumps and ventricular assist devices. Preoperative therapy with antiplatelet agents, such as aspirin, clopidogrel, and GPIIb/IIIa inhibitors, exacerbates platelet dysfunction. Changes in platelet function owing to exposure to the extracorporeal circuit may persist for several hours after discontinuation of bypass. Although plasma coagulation-factor levels are diluted by nonblood priming solutions, coagulation factor levels ordinarily remain above the minimal level needed for hemostasis. The extracorporeal circuit is not thought to consume clotting factors directly. Consequently, platelet transfusion to correct quantitative or qualitative platelet defects is the mainstay for treatment of nonsurgical bleeding associated with cardiopulmonary bypass procedures. In addition, because platelet products contain significant quantities of plasma, platelet transfusion may be effective even when the primary laboratory abnormal findings appear to be coagulation-factor related; however, particular attention should also be paid to fibrinogen replacement in this setting.

Routine transfusion of platelets to patients who are not bleeding and are not severely thrombocytopenic is not indicated. Thromboelastography offers whole-blood-based coagulation testing that can localize the coagulation defect to a deficiency in platelets, coagulation factors or fibrinogen, or excessive fibrinolysis.

## Transfusion risks

### CLINICAL CASE

Shortly after initiation of an RBC transfusion, a 63-year-old patient with melena develops pain at the infusion site followed by dyspnea, fever, chills, and low back pain. His urine is red and his plasma demonstrates free hemoglobin. Repeated testing of both the RBC product and the patient reveals that the product is type A, the patient is type O, and the crossmatch is incompatible.

Hemovigilance is defined by the WHO as "the set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and transfusion to patients, and including their follow-up." Jurisdictions vary in the way that transfusion reactions are reported. Some countries have national mandatory standardized reporting as a requirement by their regulator, while others have voluntary reporting systems. Transfusion reactions are likely underreported and the frequency varies depending on product type, processing and manufacturing method, and patient population.

Transfusion risk is often poorly understood and poorly conveyed to patients when obtaining informed consent for transfusion of blood and blood products. It is important for all medical trainees and physicians prescribing transfusion to develop an approach to understand, recognize, manage, and communicate adverse transfusion reactions. There are many ways to approach transfusion reactions: acute versus delayed; infectious versus noninfectious; immune versus nonimmune; or systems-based and symptoms-based. Regardless of which approach one uses, educating physicians, nurses, and patients is key to recognizing and managing transfusion reactions and potentially preventing them in the future. Table 13-7 lists adverse transfusion reaction differentials and frequencies organized by signs and symptoms.

For any potential transfusion reaction that occurs during a transfusion, it is important to stop the transfusion, obtain vitals, maintain IV access, and consider whether further action, investigation, and reporting are required. Please see Table 13-8 for a list of commonly used transfusion reaction abbreviations.

### Acute hemolytic transfusion reactions

The patient in this clinical case illustrates the typical presentation of an acute hemolytic transfusion reaction (AHTR): pain at the administration site, fever, chills,

**Table 13-7** Adverse transfusion reaction differentials and prevalence organized by signs and symptoms

| Symptom | Primary differential | Prevalence per 100,000 units |
|---|---|---|
| Dyspnea | TRALI | 0.4-1.0 (with mitigation strategies) |
| | TACO | 10.9 |
| | TAD | Unknown |
| Urticaria | Allergic | 112.2 |
| | Anaphylactic | 8 |
| Hypotension | AHTR | 2.5-7.9 |
| | BACON | 0.03-3.3 (septic reaction; varies by component) |
| | Bradykinin | Unknown |
| Fever | FNHTR | 1000-3000 (varies by component) |
| | AHTR | As above |
| | BACON | As above |
| Cytopenia | PTP | 1.8 |
| | DHTR | 40 |
| | TA-GVHD | Extremely rare |

**Table 13-8** Adverse transfusion event abbreviations

| Abbreviation | Event |
|---|---|
| AHTR | Acute hemolytic transfusion reaction |
| DHTR | Delayed hemolytic transfusion reaction |
| FNHTR | Febrile nonhemolytic transfusion reaction |
| TACO | Transfusion-associated circulatory overload |
| TRALI | Transfusion-related acute lung injury |
| TAD | Transfusion-associated dyspnea |
| PTP | Posttransfusion purpura |
| BACON | Bacterial contamination |
| HTLV | Human T-cell lymphotropic virus |
| TA-GVHD | Transfusion-associated graft-versus-host disease |

back pain, dark urine, and laboratory evidence of intravascular hemolysis. ABO isohemagglutinins are complement-fixing and lead to the intravascular destruction of the transfused RBCs, which can manifest as hemoglobinemia and hemoglobinuria. Often, fever is the initial sign of AHTR. Activation of complement leads to the release of cytokines, including tumor necrosis factor, accounting for fever and chills. The serologic hallmark of an AHTR is a positive DAT result that demonstrates both IgG and complement on the surface of the recipient's circulating RBCs; moreover, DIC may occur.

Patient misidentification owing to systems errors or failure to follow established hospital procedures remains the most common cause of AHTR; therefore, the importance of definitive bedside patient examination, both at the time that type and screen specimens are obtained and at the time that the product is ready to be administered, cannot be overemphasized. Barcode and radio-frequency chip technologies to ensure correct identification have been shown to reduce errors.

Acute hemolytic reactions can occur after platelet transfusions, typically involving a group A patient receiving group O platelets that contain high-titer anti-A antibody.

Treatment of acute intravascular hemolytic reactions is supportive, includes fluids and vasopressors for hypotension, and maintenance of urine output. Future transfusions should be antigen-negative for all identified alloantibodies.

## Delayed hemolytic transfusion reactions

DHTRs occur when a patient develops an alloantibody to an RBC antigen following pregnancy, transfusion, or HSCT, but the titer of the antibody falls to below the detectable limit, resulting in an apparently negative results of an antibody screen before a subsequent RBC transfusion. Following the subsequent transfusion, the patient develops an anamnestic immune response to the mismatched antigen, leading to delayed antibody-mediated destruction of the transfused RBCs. Clinical symptoms of hemolysis—including fever, anemia, and jaundice—develop five to 14 days after the transfusion; however, the link to the preceding transfusion is not always obvious. If blood bank testing is performed at this point, the DAT results are often positive for IgG, with or without complement, depending on the causative antibody. Because a positive DAT result can be nonspecific, an eluate may be performed to remove the IgG antibody coating the circulating RBCs to identify the specificity. The antibody screen may also demonstrate the presence of a new antibody; however, antibody detection may lag behind the positive DAT result by a few days. Hemolysis is usually IgG-mediated and thus extravascular. Although, IgG alloantibodies to Kidd blood group antigens may fix complement and cause intravascular hemolysis. Hemoglobinuria may occur, and occasional instances of severe complications, such as acute renal failure or DIC, have been reported. The antibodies most often implicated in DHTR are directed against antigens in the Rh (34%), Kidd (30%), Duffy (14%), Kell (13%), and MNSs (4%) antigen systems.

## Febrile nonhemolytic transfusion reactions

Febrile nonhemolytic transfusion reactions typically manifest during or within 4 hours of transfusion with fever (defined as an increase in temperature of 1 °C above the patient's baseline, typically to >38 °C) and with or without chills or rigors. Symptoms are usually self-limited and respond to symptomatic therapy, which includes antipyretics for fever and chills and meperidine for rigors. It is important to rule out other causes for the fever, including AHTR, bacterial contamination, or a cause unrelated to transfusion (eg, the patient's underlying condition). It is safe to restart a transfusion when a fever is deemed secondary to FNHTR. No additional investigation, action or reporting are generally required. There are 2 mechanisms described that cause FNHTR: presence of antileukocyte antibodies and storage-generated biologic response modifiers. Increasing adoption of universal leukoreduction has been associated with a significant reduction in FNHTRs. Studies do not demonstrate a benefit for the routine use of premedication to prevent FNHTR, but some clinicians may premedicate if a fever would change clinical management (eg, in the setting of neutropenia).

## Allergic transfusion reactions

Minor allergic reactions manifested by urticaria and pruritus are frequent. Antihistamines generally alleviate symptoms of allergic reactions, but they have not been shown to prevent them. Many urticarial reactions do not recur with subsequent transfusions. If a recipient experiences multiple urticarial reactions, premedication with antihistamines (particularly nonsedating ones) can be considered. Washed products resuspended in albumin and/or saline may be considered in severe cases of recurrent allergic reactions. Although removing plasma through washing mitigates allergic reactions, washing platelets impairs platelet function and leads to accelerated clearance after transfusion.

Severely IgA-deficient patients may make anti-IgA antibodies that can cause anaphylactic reactions, but this is a rare occurrence. There is a relatively high prevalence of IgA deficiency, some of which forms anti-IgA antibodies (~1 in 1 200); however, only a small fraction of patients may go on to develop a severe allergic reaction to blood or blood products that contain IgA. Most fatal anaphylactic transfusion reactions are not owing to IgA deficiency or anti-IgA antibodies. Washed RBCs, washed platelets, and/or platelet and plasma products from IgA-deficient donors should be transfused only when a patient has severe IgA deficiency (<0.05 mg/dL), presence of an anti-IgA antibody, and history concerning for anaphylactic reactions. Most IgA-deficient patients, even those with anti-IgA, have no adverse reactions to transfusion. There are also reports of patients with deficiencies of haptoglobin and various complement components, such as C4a (Rogers antigen) or C4b (Chido antigen), who develop anaphylactic reactions to platelets.

## TRALI

TRALI is a potentially life-threatening reaction that in many cases appears to be caused by passive transfusion of donor antigranulocyte antibodies (anti-HLA or anti-HNA antibodies), cytokines, biologically active lipids, or other substances. A consensus definition of TRALI is an acute lung injury (ALI) occurring during a transfusion or within 6 hours of completing a transfusion with no other temporally associated causes of ALI. ALI is defined as a syndrome of (1) acute onset; (2) hypoxemia ($PaO_2/FiO_2$ <300 mm Hg, $O_2$ saturation <90% on room air, or other clinical evidence); (3) bilateral pulmonary infiltrates; and (4) no evidence of circulatory overload.

Patients can present with rapid-onset and severe hypoxia: hypotension and evidence of noncardiogenic pulmonary edema with bilateral infiltrates on imaging. Aggressive respiratory support, including intubation, is often required. Approximately 80% of patients improve within 48 to 96 hours, and 100% of patients require oxygen support with approximately 70% requiring mechanical ventilation. Infrequently, antibodies in the recipient may react with donor granulocytes that are introduced by units of RBCs or platelets. In some cases of TRALI, neither recipient nor donor-derived antibodies can be identified. Other mechanisms have been proposed, such as the priming of neutrophils by bioactive lipids that accumulate during blood storage.

TRALI incidence is estimated to be 0.4-1/100,000 U, but it is likely underreported. TRALI can be difficult to distinguish from transfusion-associated circulatory overload (TACO) or from causes unrelated to the transfusion, such as progression of patients' underlying conditions (eg, congestive heart failure, or pneumonia). Clinical management is supportive. When there is question of TRALI versus TACO, treatment with a diuretic is recommended if possible, and if effective, may help support diagnosis of TACO.

In 2007, TRALI represented approximately 65% of all transfusion-related fatalities reported to the United States FDA. Since then, TRALI mitigation strategies have been implemented and include deferral of donors implicated in a TRALI reaction and routine use of male plasma (or HLA/HNA-negative plasma from nulliparous women) for transfusion. The frequency of TRALI cases has decreased but remains the leading cause of death linked to transfusion in the United States. When this approach was adopted in the United Kingdom in late 2003, where 60% of TRALI cases previously had been caused by plasma transfusions, no reports of TRALI deaths owing to plasma occurred after 2004 (6 deaths occurred in 2005, none from plasma). Cases of TRALI, in which HLA or other granulocyte-specific antibodies do not appear to be responsible, are not eliminated even with these precautions in place. Therefore, strict transfusion criteria for plasma-rich blood products, early recognition, and prompt clinical management are key to managing TRALI risk. Reporting suspected cases of TRALI to the blood bank is also important in limiting potential risk to other patients by quarantine of any cocomponents from the same donation and, if TRALI is confirmed, evaluating the donor with possible exclusion from future donation.

## Transfusion-associated circulatory overload

TACO presents with dyspnea with or without hypoxia during or after transfusion, accompanied by signs of volume overload—such as an increase in blood pressure, jugular venous distention, and elevated pulmonary arterial wedge pressure. Despite increased awareness of TACO, it remains significantly underdiagnosed or underreported to hospital blood banks as a transfusion reaction. The 2019 Fatalities Reported to FDA Following

Blood Collection and Transfusion Annual Summary listed TACO as the most common cause of death linked to transfusion. Risk factors for TACO include extremes of age, history of cardiac disease, renal failure, and transfusion of multiple blood components within a short period of time. An elevated brain natriuretic peptide may be helpful to distinguish TACO from TRALI in some cases. TACO is treated with diuretics and supplemental oxygen. TACO mitigation strategies include recognizing patients at increased risk, pretreating those patients with IV diuretics prior to the transfusion, and transfusing one product at a time over the maximum time allowable (eg, over 3.5-4 h/ RBC U).

## Transfusion-associated graft-versus-host disease

TA-GVHD is a rare but highly fatal transfusion reaction that presents with signs and symptoms of classic transplantation-associated GVHD. The symptoms include skin rash; diarrhea; liver function test with abnormal results; and other symptoms related to pancytopenia, such as infection and bleeding. The pathophysiology of TA-GVHD involves engraftment of small numbers of donor-derived passenger leukocytes into a host whose immune system is unable to recognize these cells as foreign and/or unable to eliminate them. Unlike HPSC *transplantation*-associated GVHD, in which the hematopoietic organ is donor-derived and thus relatively protected from immune assault by donor-derived T-cells, in *transfusion*-associated GVHD, the hematopoietic organ is recipient-derived. Therefore, when TA-GVHD develops, mortality approaches 100% as a result of complications of severe pancytopenia. The infusion of any cellular blood product can theoretically cause TA-GVHD. Irradiation of all cellular blood products before transfusion virtually eliminates the risk of TA-GVHD. The majority of cases of TA-GVHD occur in product stored for fewer than 10 days.

TA-GVHD has been described in both immunocompromised and immunocompetent recipients. Transfusion within relatively less HLA-diverse populations, such as in Japan, appears to increase the risk of TA-GVHD because of the increased prevalence of donors who are homozygous for an HLA haplotype shared with the recipient. This sets up a unidirectional HLA mismatch in which the recipient immune system is unable to recognize the donor-derived passenger leukocytes as being foreign and thus is unable to eliminate the passenger leukocytes. The passenger T lymphocytes recognize the nonshared HLA allele on the recipient's cells and initiate a graft-versus-host reaction. For similar reasons, directed-donor transfusions among blood relatives, such as siblings or mother to neonate, increase the risk of TA-GVHD. Therefore, all directed donations of cellular blood products from blood relatives must be irradiated.

## Infectious complications

### Bacterial and parasitic transmission by transfusion

Bacterial contamination of platelet products is a significant issue given that platelets are stored at room temperature. Before the introduction of specific precautions to reduce bacterial contamination of platelet products, as many as one in 1000 to one in 2000 platelet units were contaminated with bacteria, resulting in clinical sepsis after one in 4000 platelet transfusions. As bacterial contamination of platelets owing to an infectious source became recognized as the most common cause of transfusion-associated morbidity and mortality in the United States, methods to limit and detect the presence of bacteria in platelet components were mandated.

Since the introduction of bacterial screening, the risk of septic transfusion reactions for apheresis platelets has declined to approximately one in 75,000, and the risk of a fatal septic reaction has declined to approximately one in 500,000. Efforts to limit the introduction of bacteria into platelets include the diversion of the first aliquot of donor blood from the collection bag to remove the skin core that otherwise would be introduced by the phlebotomy needle. Practices to detect the presence of bacteria in platelet units before dispensing to a patient include incubating an aliquot of the unit in a culture system and using a rapid strip immunoassay for bacterial antigens. Pathogen inactivation platelets are becoming more widely available. The process involves addition of psoralen treatment (eg, amotosalen), UV illumination, and photosensitizers resulting in damage to pathogen nucleic acids and prevention of pathogen replication and growth. This process inactivates many viruses, gram-positive and gram-negative bacteria, spirochetes, and parasites.

While platelet products are typically contaminated by gram-positive cocci, such as coagulase-negative staphylococci, sepsis associated with transfusion of RBC units most often occurs because of gram-negative organisms, particularly *Yersinia enterocolitica*. Fatal reactions to RBCs caused by contamination with *Yersinia enterocolitica* have been reported. This gram-negative organism can survive during refrigerated storage and lead to bacteremia or septic shock.

Malarial transmission by transfusion is uncommon, but cases are occasionally reported. Currently, no FDA-approved test is available to screen donors for malaria, and therefore screening is accomplished by donor questioning. Donors with a history of residence in or travel to a malaria-endemic area are deferred for a period of time.

With the immigration of individuals from South America to the United States, there is concern that Chagas disease may emerge as a common transfusion-transmitted infection. *Trypanosoma cruzi* parasites can survive several weeks of storage in blood, and contamination of blood products with this organism is already a significant problem in parts of South America. An FDA-approved blood donor-screening test for antibodies to *T. cruzi* is available. Blood donors need to be tested only at their first donation.

Transfusion-transmitted babesiosis has been reported in New England and the upper Midwest and has been found in patients receiving platelets, refrigerated RBCs, and even frozen-thawed RBCs. Implementation of investigational tests is being evaluated for donor screening in areas where *Babesia* is endemic.

*Borrelia burgdorferi*, the etiologic agent of Lyme disease, has yet to be confirmed as having been transmitted by blood transfusions.

There is no evidence of SARS-CoV-2 transfusion transmission despite RNA detection in blood donors showing symptoms after donation.

### Viral hepatitis

Risk of HBV, HCV and HIV may have been as high as 1/100 to 1/1000 units in the early 1980s. With implementation of rigorous donor screening, testing, and hemovigilance, the risk of each HBV, HCV, and HIV is now less than one in millions. Table 13-9 summarizes the estimated risks of various transfusion-associated infections. Posttransfusion hepatitis can rarely still develop if blood donation occurs during the brief initial period (~1 to 4 weeks) of viremia after exposure with negative results in a nucleic acid test. Acute transfusion-related hepatitis C virus infection is subclinical and anicteric in most cases.

**Table 13-9** Infectious complications of transfusion

| Infectious agent | Approximate risk per transfused unit |
|---|---|
| Hepatitis B virus | 1:7.5 million |
| Hepatitis C virus | 1:12.6 million |
| HIV-1, HIV-2 | 1:21.4 million |
| HTLV-1, HTLV-2 | 1:2.7 million |
| Bacterial sepsis | 1:75,000 (platelet transfusion);<br>1:250,000 to 1:10 million (RBC transfusion) |

### HIV and human T-cell lymphotropic viruses

The risk of acquiring HIV-1 or HIV-2 infection as a result of transfusion is very small (Table 13-9). Nucleic acid amplification testing for HIV has reduced the window of serologic conversion from 16 days to about 9 days.

Human T-cell lymphotropic virus 1 (HTLV-1) is a retrovirus associated with adult T-cell leukemia or lymphoma and tropical spastic paraparesis. Because asymptomatic blood donors can transmit this virus, screening for HTLV-1 in blood donors is currently performed in the United States. Several cases of neuropathy had been reported in transfusion recipients before the availability of testing. HTLV-2, a related virus with antigenic cross-reactivity to HTLV-1, is endemic in certain Native American populations and also has been found in a high proportion of intravenous drug users. The risk of HTLV transmission by transfusion using current test methods is approximately one in 2.7 million.

### West Nile virus

During the 2002 West Nile virus (WNV) epidemic in the United States, 23 individuals acquired WNV after blood transfusion, developing fever, confusion, and encephalitis characteristic of WNV infection within days to weeks of transfusion. As a result, blood centers now use nucleic acid–based testing to screen all donations for WNV. In a survey of 2.5 million donations in 2003, 601 donations (0.02%) were found to contain WNV. A subsequent follow-up study detected no cases of transfusion-transmitted WNV infection among recipients of tested blood; however, rare breakthrough transmissions have been reported.

### Parvovirus B19

Rare transmissions of parvovirus B19 by transfusion have been recognized. Documented persistence of low levels of parvovirus B19 DNA have been shown in a high percentage of multitransfused patients. The long-term clinical implications of this finding currently are unknown. Parvovirus (and other viruses without a lipid envelope, such as hepatitis A virus) is not eliminated by solvent detergent treatment. There is no currently available blood donor-screening assay for this virus.

### Cytomegalovirus

Transfusion-transmitted CMV infection is an important issue in transfusion of cellular blood products to neonates, particularly low-birth-weight infants born to seronegative mothers, HSCT recipients, and other highly immunosuppressed patients. The risk of acquiring CMV from transfusions is particularly high when pretransplant-serologic testing reveals that neither the HPSC donor nor the recipient has previously been exposed to CMV. In addition, transplantation recipients are at increased risk for transplantation-associated CMV reactivation when either the donor or the recipient is seropositive for CMV before transplantation.

For these reasons, some institutions use blood products obtained exclusively from CMV-seronegative donors when providing blood products to neonatal recipients or recipients of HPSC transplants. However, randomized comparison of leukoreduced versus CMV-seronegative blood components in CMV-seronegative HSCT recipients (with seronegative donors) found no significant difference in the incidence of CMV infection and CMV disease as a composite outcome. Thus, many institutions provide leukoreduced blood products for all recipients, regardless of CMV status. This strategy also reduces the risk of alloimmunization to HLA antigens with subsequent refractoriness to platelet transfusions and decreases the incidence of FNHTR.

## Patient blood management

### CLINICAL CASE

A 44-year-old multiparous woman requires orthopedic surgery. Pretransfusion testing reveals antibodies to 3 RBC antigens: K (Kell system), $Fy^a$ (Duffy system), and E (Rh system). Crossmatch-compatible blood is transfused, and the patient does well. A second operation is needed. At this time, repeated screening of the patient's plasma detects an additional antibody directed against c (Rh system). Because of the multiple antibodies, a large number of donor units must be screened to find the required number of antigen-negative units. The hematologist advises the surgeon that a comprehensive blood management approach should be considered to reduce the need for further allogeneic transfusion in this patient.

Patient blood management (PBM) is widely adopted with increased recognition of poor patient outcomes associated with preoperative anemia, high costs associated with transfusion, high frequency of inappropriate use of blood products, and an increasing range of adverse effects potentially associated with transfusion. PBM aims to optimize patients' own blood, correct coagulopathies, and avoid unnecessary allogeneic transfusion by applying a patient-centered multidisciplinary approach.

### Iatrogenic and preoperative anemia

The cornerstone of decreasing the need for transfusion is appropriate medical management of anemia, particularly in the preoperative setting in which anemia is the most important predictor of perioperative transfusion. Preoperative hemoglobin optimization requires identification of anemia and investigation into underlying etiology. If nutritional deficiencies such as iron and/or B12 are found, they need rapid correction. Iron repletion can be provided with oral iron supplementation if time permits and if the patient tolerates and responds to oral iron. IV iron is safe and effective and should be considered for iron repletion in iron-deficient patients. Erythropoietin-stimulating agents may provide benefit in certain patient populations.

Iatrogenic anemia can be limited by avoiding unnecessary blood draws. In the setting of ICUs, routine blood draws have been demonstrated to result in the loss of the equivalent of one to 2 units of RBCs per week. All blood tests ordered should be justified and actively contribute to clinical decision making. The frequency, timing, and volumes of blood draws, including use of lower-volume blood collection tubes when appropriate, should be coordinated to limit the volume of patient blood collected.

In the past, preoperative autologous donation, where the patient would donate blood for his or her own use in the weeks before surgery, was a common approach to avoid allogeneic transfusion for elective surgical cases. Although the use of autologous blood may eliminate transfusion risks because of transfusion-transmitted infection (except for bacterial contamination of the unit), the risk of transfusion of ABO-incompatible blood because of a clerical error still exists (ie, the inadvertent transfusion of the wrong patient's autologous blood) as does the risk of TACO. Therefore, unless the clinical condition of the patient actually warrants transfusion, autologous units of blood should not be used simply because they are available and "won't hurt." Use of preoperative autologous blood donation is now broadly discouraged, because approximately 50% of autologous units are never transfused. Patients who donate autologous units preoperatively may present to surgery with anemia that increases their overall risk of transfusion, particularly if the interval between donation and surgery is short. Of note, directed donations from relatives or friends selected by the patient have not been shown to decrease transmission of infectious agents compared with units from the general blood supply. Directed donors are also more likely to be first-time donors, who have a higher incidence of testing positive for an infectious disease. For these reasons, directed donations are generally discouraged.

### Intraoperative techniques

A number of surgical, anesthetic, and pharmacological approaches can be used to reduce intraoperative bleeding. Use of the patient's own blood to minimize the need for, or entirely avoid, allogeneic transfusion may be accomplished through acute normovolemic hemodilution (ANH) and RBC salvage or perioperative autotransfusion. ANH involves removal of one or more units of whole blood in the operating room immediately before surgery, with adequate fluid replacement to maintain an iso- or normovolemic state. Blood shed during surgery is dilute in this case, theoretically resulting in a lower net loss of RBC mass after return of the whole-blood units to the patient toward the end of the case. The units collected by ANH may have the added benefit of providing additional platelets and coagulation factors. ANH has not been established definitively to avoid allogeneic transfusion. Conversely, intraoperative cell salvage can significantly reduce the need for allogeneic transfusion, particularly in cases associated with high-volume blood loss. In this approach, blood is suctioned from the operative field into an anticoagulated reservoir and then washed with normal saline. The washed salvaged RBCs are concentrated for reinfusion into the patient. When using cell salvage techniques, precautions must be taken to avoid potential hazards, such as air emboli and infusion of inadequately washed products. In some cases, postoperative wound drainage may be collected, filtered, and administered with or without washing. Many Jehovah's Witnesses consent to autologous transfusion using cell salvage, potentially allowing more complex operations to be performed in this patient population. The technique can also be helpful in patients for whom it is difficult to find compatible blood because of the presence of multiple RBC antibodies.

### Judicious transfusion

Restrictive transfusion practices are safe in many clinical practice areas. Care should always be taken to transfuse the smallest amount of blood products required to achieve the desired outcome. It is unnecessary to correct a cytopenia or a clotting factor deficiency to normal levels. Transfusion should be directed toward restoring only functionally adequate levels. For example, many patients with chronic anemia or thrombocytopenia tolerate much lower blood counts than patients with acute cytopenias involving the same lineages, and most patients tolerate clotting factor levels below 50% without difficulty. One of the major behavioral changes incorporated into most blood management programs is a shift in practice from transfusing RBC units in multiples to a strategy of single-unit transfusions with subsequent reassessment of patient status and need for further transfusion.

Auditing of compliance with institutional transfusion guidelines, internal and external benchmarking, and ongoing data-driven process improvement projects all contribute to improved blood product use and systematic application of blood management concepts. The institutional oversight for such activities usually is provided by hospital transfusion committees, which typically include broad multidisciplinary representation from transfusion medicine, hematology, anesthesiology, surgery, internal medicine, nursing, pharmacy, laboratory medicine, and hospital administration.

### Bloodless medicine

Currently, no licensed blood substitutes are available for clinical use in the United States. A recent meta-analysis of hemoglobin-based blood substitutes found excess myocardial infarction and mortality in surgical patients who received the blood substitute compared with controls. Patient groups included trauma, cardiac surgery, vascular surgery, and elective orthopedic surgery.

Erythropoiesis-stimulating agents can be used in patients who decline transfusion, either therapeutically to treat anemia or prophylactically before elective surgery. The treatment of Jehovah's Witness patients who require chemotherapy for hematologic malignancies or HSCT can be challenging. A comprehensive approach is required, including reduced-intensity conditioning chemotherapy, reduced phlebotomy and gastrointestinal blood loss, optimized pretransplant blood counts using iron and folate, erythropoiesis-stimulating agents, possibly thrombopoietin mimetic agents, and prophylactic use of antifibrinolytic agents during the period of thrombocytopenia.

## KEY POINTS

- Avoiding iatrogenic anemia can help reduce the need for allogeneic transfusion in all patient populations.
- Transfusion only when indicated (right product to the right patient at the right time and for the right reason) can help avoid unnecessary risks.
- Preoperative medical management of anemia before elective surgery can reduce perioperative transfusions; consider iron repletion for iron deficiency anemia.
- Preoperative autologous donation generally is discouraged because of wastage of collected units, the residual risks of clerical error, bacterial contamination, volume overload, and the preoperative anemia associated with these donations.

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