Red Blood Cell Transfusion

Anne M. Winkler

Blood Collection and Transfusion-Service Related Activities

Blood Collection and Manufacturing

Transfusion medicine is a highly regulated discipline. In the United States (US), the Food and Drug Administration (FDA) provides oversight for blood and blood components to ensure protection of transfusion recipients [1]. Throughout this chapter, references are made to the Circular of Information for the Use of Human Blood and Blood Components, a publication of the AABB (formerly the American Association of Blood Banks), the American Red Cross, America’s Blood Centers, and the Armed Services Blood Program; this Circular was designed as an extension of container labeling to provide specific instructions for the administration and use of blood and blood components intended for transfusion and can be a useful guide to prescribing clinicians [2].

In the US, blood donation, distribution, and transfusion services operate within a network of community and hospital-based blood collection centers, and transfusing facilities, which provide red blood cells (RBC), platelets (PLT), and plasma, derived from whole blood or apheresis donation. Allogeneic blood donation is voluntary, nonremunerated and donor screening includes a focused physical examination, hemoglobin (Hb) or hematocrit measurement, completion of a questionnaire about specific risk behaviors, travel, medications, and other factors that could affect the transfusion recipient or donor safety. Following successful eligibility and consent, whole blood is collected through a large gauge needle by gravity flow from the donor’s antecubital fossa and into the primary bag of a sterile, disposable, plastic bag set, containing an anticoagulant-preservative solution to prevent clotting. After collection, whole blood is separated into individual components by centrifugation and further processed into RBC, plasma, and PLT destined to become pooled units. In comparison, apheresis blood collection uses specialized bag sets and automated instruments that are designed to continuously draw and centrifuge small volumes of blood, remove the desired component(s) (e.g., RBC, plasma, single donor PLT, and granulocytes), and return the remainder, with minimal impact to the donor’s fluid balance. Other types of blood donation include those collected for exceptional medical need, directed, and autologous donation.

The volume of an allogeneic whole blood collection ranges from 450 mL (±10%) to 500 mL (±10%), depending on the collection system used [2]. RBC are collected into anticoagulant-preservative solutions contain-

A. M. Winkler
Instrumentation Laboratory, Bedford, MA, USA
e-mail: awinkler@ilww.com
ing the following solution combinations: citrate–phosphate–dextrose (CPD), citrate–phosphate–dextrose–dextrose (CP2D), and citrate–phosphate–dextrose–adenine (CPDA-1) [2]. Citrate chelates ionized calcium in the donor’s blood to inhibit coagulation. Phosphate and dextrose directly provide nutrients to the red cells. Adenine is a nucleic building block that is added to some RBC solutions (CPDA-1) and additive solutions (AS), allowing the RBC shelf life to exceed 3 weeks [2]. RBC collected in CPD and CP2D have a shelf life of 21 days, and those collected in CDPA-1 have a shelf life of 35 days. The volumes of RBC units vary between 225 and 350 mL with a hematocrit ranging from 65% to 80% [2].

AS contain combinations of phosphate, adenine, mannitol, dextrose (glucose), and additional citrate to provide nutrients and stabilize RBC membranes, allowing for increased storage times. As a result, AS (e.g., AS-1, AS-3, AS-5, and AS-7) are commonly added to the RBC unit to enable extension of the RBC shelf life to 42 days. These solutions add an additional 100 or 110 mL of fluid postcollection, which reduces the hematocrit to 55–60% with an increased volume of approximately 300–400 mL [2].

All donors are tested for blood type, RBC antibodies, and infectious disease markers; PLT are also tested for bacterial contamination before they are released [3]. The most recent National Blood Collection Utilization and Survey (NBCUS) reports that 12,591,000 whole blood and apheresis RBC units were collected in the US in 2015 [3]. Of those, 11,349,000 RBC units were transfused at US acute care hospitals, constituting a 13.9% decline since 2013 [3]. Nonetheless, the US continues to transfuse RBC at a greater rate than many other countries, with 35.3 transfusions per 1000 population [3].

**ABO/Rh and Compatibility**

The ABO blood group system was identified in 1900 by Landsteiner and colleagues and remains one of the most important medical discoveries, as prior to this time, there were deaths due to transfusion incompatibility [4, 5].

Codominant Mendelian inheritance of an A or B allele on chromosome 9q34 predicts blood type [6]. The A and B alleles each encode a glycosyltransferase which adds a sugar to the H antigen (FUT1, chromosome 19q13.3), an oligosaccharide chain that extends beyond the RBC surface [7]. Addition of a specific sugar, N-acetylgalactosamine or α-1, 3-galactose, results in the formation of an A or B antigen, respectively [7]. Type O results from homozygous inheritance of a nonfunctional allele most commonly caused by a frameshift mutation, resulting in no glycosyltransferase being produced, thereby leaving the H antigen unaltered [7].

Type A red cells express A surface antigen, and naturally occurring anti-B is found in plasma [8]. Conversely, type B red cells express B antigen and anti-A is present in plasma. Type O red cells lack A or B antigens and have anti-A and anti-B in the plasma. Finally, type AB red cells express both A and B antigens and lack naturally occurring anti-A and anti-B [8]. Naturally occurring blood group antibodies, also called isohemagglutinins, are not present in the newborn (apart from antibodies present due to passive maternal transmission) but develop around 4–6 months of age by a thymus-independent mechanism following exposure to carbohydrate epitopes on gut bacteria and food [8]. A and B antigens are also found on cardiac, gut, and renal endothelium (and other organs) and exist in a soluble form in secretions; for this reason, they are also known as “histo-blood group antigens” and as such are an important consideration in solid organ transplant [7] (Table 20.1).

ABO compatibility is fundamental to avoid a hemolytic transfusion reaction which may occur within minutes of the start of an RBC transfusion and possibly with fatal results. ABO antibodies are primarily IgM, which fix complement well, and can cause acute, intravascular hemolysis. ABO antibodies of the IgG subtype may cause a delayed, extravascular hemolysis. IgG subtypes may also cross the placenta from the maternal circulation to cause hemolytic disease.
of the newborn (HDN) [11]. Only one fatality resulting from ABO-mismatched RBCs was reported to FDA in 2017, accounting for 3% of the total fatalities reported in that year [12]. Undoubtedly, many more ABO-mismatching events transpire without resulting in fatality. While the ABO blood group system is best known, there are 36 blood group systems currently recognized by the International Society of Blood Transfusion. Antibodies can develop to any of these blood group antigens, some of which have been implicated in hemolytic transfusion reactions and HDN. In 2017, six fatalities were attributed to non-ABO hemolytic transfusion reactions [12]. Variations or subtypes of common blood types are occasionally seen and may present challenges to the laboratory such that even routine blood orders require extra time to fulfill.

### Pretransfusion Testing and Selection of RBC for Transfusion

#### Type, Screen, and Crossmatch

Persons with type O blood are often called the “universal donor” since their red cells are compatible with all recipients. Type O RBC is also the first choice of blood in emergency transfusion or trauma situations. Persons with A blood may receive type A or type O RBC; persons with type B blood may receive type B or type O RBC. Persons with type AB RBC may be given any blood type and are sometimes referred to as being the “universal recipient” (Table 20.2).

The Rh blood group system is composed of two genes that account for expression of 54 antigens. The D antigen is the most recognized Rh antigen and the presence or absence of the D antigen on the red cell is still commonly referred to as Rh-positive or Rh-negative, respectively. D antigen expression varies among ethnic groups (Table 20.1). With respect to transfusion, the D antigen is second in importance to the ABO blood group system. For routine RBC transfusion, every effort is made to match the ABO/Rh of the unit to the recipient. For example, a patient typing B-negative should ideally receive RBC from a donor who is B-negative (type B, RhD-negative), but O-negative RBC would also be compatible.

Anti-A and anti-B are naturally occurring antibodies and are present depending on blood type (Table 20.1). Non-ABO red cell antibodies are sometimes found in a patient’s sample and are called “unexpected” alloantibodies. About 5% of patients have unexpected alloantibodies. These antibodies have formed following exposure to red cells possessing antigens foreign to the recipient usually from transfusion or pregnancy but possibly from other blood exposure. Antibodies differ in their clinical significance or in their ability to cause hemolysis and/or HDN. Extra time may be needed by the transfusion service to locate RBC for patients with rare or multiple alloantibodies.

### Table 20.1 Frequency of ABO and Rh (D) type and expected plasma antibodies [4, 9, 10]

| ABO and RhD type by ethnicity and approximate percentages | Red cell antigen | Plasma antibody |
|----------------------------------------------------------|-----------------|----------------|
| ABO and RhD type  | Caucasian | African–American | Hispanic | Asian | ABO | Rh |
| O             | 44        | 49            | 55       | 43    | None | Anti-A and Anti-B |
| A             | 43        | 27            | 28       | 27    | A    | Anti-B          |
| B             | 9         | 20            | 13       | 25    | B    | Anti-A          |
| AB            | 4         | 4             | 4        | 5     | A and B | None |
| RhD Pos.      | 83        | 93            | 93       | 98    | None |
| RhD Neg.      | 17        | 7             | 7        | 2     | None |

### Table 20.2 Red cell type and compatibility

| Recipient blood type | Compatible red cells for transfusion |
|----------------------|---------------------------------------|
| O                    | O only                                |
| A                    | A or O                                |
| B                    | B or O                                |
| AB                   | O or A or B or AB                     |

[^11]: Reference for HDN incidence.
[^12]: Reference for ABO-mismatched fatalities.
If a “type and screen” is ordered, the “type” is the determination of the patient’s ABO and RhD type and the “screen” detects unexpected alloantibodies in the patient’s sample, such as anti-K (of the Kell blood group system), anti-Fya (of the Duffy blood group system) and so on. Multiple blood group systems are represented on screening and extended reagent red cell panels to improve the chances of detecting clinically significant alloantibodies. Once a person has formed an alloantibody, RBC negative for the offending antigen should be provided if possible, whether the alloantibody is detectable. If a “crossmatch” is ordered, this is the testing of patient plasma against the intended donor red cells and it is the last check of compatibility prior to issue. If there is agglutination or hemolysis, the unit is incompatible. Crossmatched RBC units may be reserved for a designated time, depending on the institution’s policies. Emergency-release RBC are usually O-negative or O-positive and are not crossmatched. As a result, the release of these RBC units requires a physician’s signature to approve the product, either prior to or in a specified timeframe following release. Uncrossmatched blood is not necessarily incompatible.

**Selection of RBC for Transfusion**

The first choice of RBC in a patient with an unknown blood type is O, since blood type O individuals possess no A or B red cell surface antigens and are therefore more likely to be compatible with any recipient. Upon receiving an alert of an incoming trauma or for emergency RBC needs, most hospitals automatically issue O RBC units, unless the patient’s blood type is already known. In most emergency release protocols, women of childbearing potential (or age) receive O-negative RBC until their blood type is known. What constitutes childbearing age is determined by each institution but is generally accepted to be females under the age of 45 or 50. If a woman of childbearing age is confirmed as O-negative, she should continue to receive O-negative RBC to decrease her risk of forming anti-D that is capable of crossing the placenta which can result in HDN. Another group that may automatically receive O-negative RBC is patients under 18 years of age. For women beyond childbearing potential and all males greater than 18 years, O-positive RBC may be issued before pretransfusion testing is complete. This approach has been adopted in many large, urban institutions as the need for emergency release RBC could never be sustained if only O-negative RBC were used. Once the patient’s blood type is known, type-specific or compatible RBC may be given.

**RBC Transfusion Indications and Administration**

**Indications**

RBC transfusion is used to increase oxygen carrying capacity in patients with anemia in whom physiologic compensation is inadequate to maintain tissue oxygenation. Patients may require RBC transfusion in situations including hemorrhagic shock, other blood loss such as that from surgery and symptomatic anemia. Signs and symptoms of anemia that may prompt RBC transfusion include hemodynamic instability, chest pain, shortness of breath, and tachycardia at rest. In nonbleeding patients, Hb levels are typically used to guide transfusion decisions. Unfortunately, Hb concentration alone is a poor measure of circulating RBC mass because of the physiologic compensatory mechanisms that preserve oxygen transport such as reduced blood viscosity to increase blood flow to tissues, redistribution of blood flow, increased unloading of oxygen to tissues, and maintenance of blood volume due to expansion of plasma volume. Because of this and observations made in Jehovah’s Witness patients who decline transfusion based on religious beliefs and in underdeveloped countries where RBC were unavailable or limited, readjustment of transfusion practice to a lower Hb threshold has been investigated [13–18]. In 2012, a Cochrane systematic review of prospective randomized trials compared restrictive versus liberal transfusion strategies in 19 trials.
including 6264 patients [19]. The authors found that a restrictive transfusion strategy reduced the risk of receiving an RBC transfusion by 39% without an increase in adverse events, intensive care unit or hospital length of stay, and 30-day mortality. The authors concluded that the existing evidence supported the use of restrictive transfusion triggers in most patients. For RBC transfusion, multiple prospective randomized trials have been conducted to investigate restrictive versus liberal transfusion thresholds in adult patients in critical care, cardiac surgery, hip fracture repair, acute upper gastrointestinal bleeding, and septic shock, and the results have been summarized in Table 20.3 The seminal Transfusion Requirements in Critical Care or TRICC trial was the first study to demonstrate that in critically ill, euolemic patients, a restrictive RBC transfusion approach (Hb threshold of 7 g/dL and maintenance between 7 and 9 g/dL) was at least as effective and possibly superior to a liberal strategy (maintenance Hb concentration of 10–12 g/dL). In addition, the restrictive strategy (threshold 7 g/dL) resulted in a 54% decrease in RBC transfusions and a decline of 33% in RBC exposure. As a result of these findings, clinical practice guidelines have adopted recommendation of a restrictive transfusion strategy using a Hb threshold of 7–8 g/dL; however, these recommendations may not be safe for all patients including patients with acute coronary syndrome.

Transfusion Administration

Safe administration of a blood transfusion requires multidisciplinary collaboration between healthcare providers. Informed consent must be provided and signed prior to transfusion of any blood product, by the patient receiving the transfusion or by a legally authorized representative or surrogate depending on state and local laws. If no one is available to provide consent and the transfusion is considered a medical emergency, it can be administered based upon the doctrine of implied consent; however, requirements may vary, and the emergent need must be documented in the medical record. Before a transfusion commences, a “time-out” should be performed by staff administering the transfusion to ensure the right patient is being transfused the correct blood product. Every hospital should have policies, processes, procedures, and training in place for all personnel involved in administering a transfusion. Certain religious faiths may decline blood product transfusion and their refusal should be respectfully honored and carefully documented according to hospital policy and applicable laws.

Blood components must be administered through special blood infusion filter sets, which typically have 150–260 μm filters to trap clots and particulate aggregates, but still allow blood cells to pass through [2]. No medications other than 0.9% sodium chloride should be administered through the same tubing at the same time.

Routine transfusions should be administered slowly (approximately 2 mL/min), especially in the first 15 minutes, to observe for signs and symptoms of a transfusion reaction. Vital signs should be taken prior to the transfusion and then according to institutional policy. After the first 15 minutes, the rate of transfusion should be increased to ensure the unit is transfused within 4 hours. Rapid infusion, unless medically necessary, should be avoided to mitigate the risk for transfusion-associated circulatory overload (TACO) especially in recipients with cardiac and/or respiratory compromise.

If a transfusion reaction is suspected, the transfusion should be stopped, patency of the intravenous line maintained, and health care provider notified. In addition, the transfusion service should be notified as soon as possible.

Intraoperative Blood Salvage

Specialized devices or “cell savers” may be used during planned or emergency surgery in which blood loss is excessive (equal to or greater than 20% total blood volume), for patients with religious objections to receiving allogeneic transfusion or for patients with multiple alloantibodies or rare blood types.
| Study               | Number of subjects randomized | Study setting                                                                 | Hb concentration threshold (restrictive vs liberal) | Average Hb concentration at transfusion (restrictive vs liberal) | Number of patients transfused (restrictive vs liberal) | Primary outcome                                                                                                                                 |
|--------------------|-------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Hébert et al. [20] | 838                           | Intensive care unit                                                          | 7.0 g/dL vs 10.0 g/dL                                | 8.5 g/dL vs 10.7 g/dL                                        | 67% vs 100%                                         | 30-day mortality was 18.7% in the restrictive group compared to 23.3% in the liberal group ($p = 0.11$) while in-hospital mortality was lower in the restrictive group (22.2% vs 28.1%, $p = 0.05$) |
| Hajjar et al. [21] | 512                           | Elective cardiopulmonary bypass                                               | 8.0 g/dL vs 10.0 g/dL                                | 9.1 g/dL vs 10.5 g/dL ($p < 0.001$)                          | 47% vs 78% ($p < 0.001$)                            | Restrictive strategy was noninferior to liberal in the primary composite endpoint (30-day mortality, cardiogenic shock, ARDS, or acute renal injury require dialysis or hemofiltration) occurring in 11% versus 10%, respectively ($p = 0.85$) |
| Carson et al. [22] | 2016                          | Primary surgical repair of a hip fracture with cardiovascular risk factors    | 8.0 g/dL vs 10.0 g/dL                                | 7.9 g/dL vs 9.2 g/dL ($p < 0.001$)                           | 41% vs 97% ($p < 0.001$)                            | Rates of death or inability to walk without human assistance at 60 days were similar in the restrictive versus liberal group, 34.7% versus 35.2% ($p = 0.90$) |
| Villaneuva et al. [23] | 921                           | Acute upper gastrointestinal bleeding                                         | 7.0 g/dL vs 9.0 g/dL                                 | 7.3 g/dL vs 8.0 g/dL ($p < 0.001$)                          | 49% vs 86% ($p < 0.001$)                            | 45-day mortality was reduced in the restrictive group (5%) compared to the liberal group (9%, $p = 0.02$)                                                                 |
| Holst et al. [24]  | 1005                          | Intensive care patients who fulfilled criteria for septic shock              | 7.0 g/dL vs 9.0 g/dL                                 | Daily lowest Hb differed between groups* ($p < 0.001$)       | 64% vs 99% ($p < 0.001$)                            | 43% of the restrictive group and 45% of the liberal group died at 90 days after randomization ($p = 0.44$)                                                                 |
| Mazer et al. [25]  | 5035                          | Cardiac surgery with a EuroSCORE I of 6 or more                              | 7.5 g/dL vs 9.5 g/dL in the operating room or intensive care unit or 8.5 g/dL in non-ICU ward | Postoperatively, Hb concentrations were separated by approximately 1 g/dL and remained separated from ICU admission through day 28* | 52.3% vs 72.6% ($p < 0.001$) | Composite outcome (death from any cause, nonfatal myocardial infarction, stroke, or new-onset renal failure with dialysis, occurring during the index hospitalization from the start of surgery until either hospital discharge or 28 days after surgery, whichever occurred first event) was 11.4% in the restrictive-threshold group compared to 12.5% in the liberal-threshold group ($p < 0.001$ for noninferiority) |

Hb: hemoglobin, ARDS: acute respiratory distress syndrome, EuroSCORE: European System for Cardiac Operative Risk Evaluation, MODS: multiple organ dysfunction syndrome

* Numerical means/medians not reported
Various commercially-available devices function in essentially the same manner: intraoperatively shed blood is gently suctioned to preserve red cell morphology and function, washed with isotonic solution, filtered, and reinfused either intraoperatively or postoperatively. Sponges used intraoperatively may also be washed and rinsed and that fluid can be added into the circuit. Abdominal, thoracotomy, and drain blood from other surgical sites may be processed. Extracorporeal anticoagulation is achieved with heparin (up to 30,000 units per liter of normal saline) or citrate solutions (often ACD-A) or a combination of the two. The filters used have fairly large pore sizes (40–120 μm) to remove debris such as bony spicules or cement and large cellular aggregates. Due to washing, very little plasma or its solutes (e.g., free Hb, interleukins, and coagulation factors) remain in the final product.

Depending on the processing, the final product may be kept at room temperature for up to 4 or 6 hours, or at 1–6 °C for up to 24 hours in a monitored refrigerator [26, 27]. Since the whole blood product is freshly obtained from the patient and washed, some transfusion reaction risks are reduced, but reactions may still occur, such as from fluid overload or bacterial contamination [28]. The final red cell product is of high quality, with a hematocrit between 40% and 80% depending on the device and method used and is suspended in a small amount of isotonic solution with very little remaining anticoagulant. It has been shown that red cell survival of cell saver units obtained during cardiopulmonary bypass is comparable to circulating venous blood after 24 hours [29].

The literature is not abundant regarding the consistent use of autologous salvaged blood or autotransfusion in the setting of trauma, specifically regarding the quality of shed hemothorax blood as most current autotransfusion data are obtained from scheduled cardiac surgeries. A recent prospective observational study of unwashed hemothorax shed blood from 62 subjects at a large trauma center found significantly elevated cytokine levels as compared to normal controls, suggesting the potential for deleterious effects from autotransfusion in trauma [30]. Moreover, a second study demonstrated plasma hypercoagulability and platelet dysfunction induced by hemothorax frozen plasma from 17 adult trauma patients [31]. As a result, more studies including randomized trials are needed to determine the safety and efficacy of autotransfusion in trauma patients.

**RBC Product Modifications**

Clinical indications for modified components vary and it may be advantageous to consult with the transfusion service prior to ordering these products. Not all products are readily available and considerable time may be required to manufacture or obtain these modified RBC units.

**Leukocyte Reduction and Provision of CMV-Negative RBC**

Leukocyte reduction or leukoreduction (LR) of RBC is widely performed. Prestorage LR is done during automated apheresis collections or after whole blood collection. Bedside LR or poststorage LR remains an alternate but infrequently used. The FDA requires the residual white cell count to be less than $5 \times 10^6$ per RBC unit. LR of RBC decreases the incidence of febrile nonhemolytic transfusion reactions, human leukocyte antigen (HLA) and platelet alloimmunization, and the amount of biologic response modifiers (BRM), which accumulate during storage [32–34].

The equivalency of LR to Cytomegalovirus (CMV)-negative products continues to be debated. Some physicians consider LR RBC to be adequate and essentially equivalent to LR RBC from cytomegalovirus CMV-seronegative donors. The rationale is that CMV resides within white cells, and with the efficiency of modern LR filters, any risk of CMV would be exceptionally low [35–37]. For CMV-seronegative patients, especially those who are peri- or post-transplant, or low-birth-weight infants, many clinicians request CMV-negative products and accept LR-only products if CMV-negative LR RBC are unavailable. In addition, CMV-seronegative donors who test “negative for CMV” on their
most recent donation by antibody testing carry a small but real risk of transmitting CMV to a recipient, if the donor happens to be newly infected and is in the window period (the time between infection and the time at which the infection can be detected by testing). Nucleic acid testing (NAT) testing for CMV DNA to reduce this window period is available but is not routinely used for donor screening. Indications for CMV-negative blood include low-birthweight infants born to CMV-seronegative mothers and hematopoietic stem cell or solid organ transplant recipients [2, 38].

**Washing**

Washed RBC are indicated in cases of an IgA-deficient recipient or in the rare case of an anaphylactoid/anaphylactic transfusion reaction [2]. Washed cellular products may also be requested for pediatric patients with renal impairment, elevated potassium, and related issues, to remove excess potassium in the blood product [39, 40]. However, for the vast majority of patients, the amount of potassium in the plasma should not have any untoward effects on the recipient even if the RBC are irradiated and near the outdate, if infusions are given slowly, over 2–4 hours.

Frozen RBC must also be washed prior to infusion, to remove glycerol in which they are stored [2]. RBC are washed by specialized, automated instruments that progressively wash a single unit in normal saline, and sometimes dextrose, to create a final product that is essentially devoid of plasma and which contains a minimal amount of saline. A small percentage of the product is normally lost during the washing process [2]. Washing reduces the RBC expiration date to 24 hours or the original expiration date and time, whichever comes first [2]. As a result, it is important to communicate to the transfusion service, the time frame in which the product will be needed.

**Irradiation**

Cellular blood products may be irradiated to preclude the development of transfusion-associated graft-versus-host disease (TA-GVHD), which is donor T-cell-mediated destruction of the recipient’s immune system. TA-GVHD is most commonly caused by infusion of competent donor T-lymphocytes into an immunocompromised recipient, though there have been cases involving immunocompetent recipients [41]. TA-GVHD is similar to post-transplant GVHD, affecting HLA antigen dense tissues such as the skin, gastrointestinal tract, and liver. There are, however, two findings seen with TA-GVHD: bone marrow aplasia and earlier onset, usually between day 2 and 50 following transfusion, which distinguishes it from post-transplant GVHD.

Irradiation of cellular blood products is accomplished by X-ray or gamma-ray irradiators specifically manufactured for blood establishments, or by linear accelerators used in the field of radiation oncology [42]. Whatever energy source is used, irradiation renders residual allogeneic T-lymphocytes incapable of replication by rendering the leukocyte DNA inactive to a level greater than 5 logs. Irradiation causes damage to the red cell membrane and escape of intracellular potassium, which increases with the age of the red cell and over storage, but is usually not harmful to the recipient [39, 40]. Red cells outdate at 28 days from the date of irradiation or keep the original expiration date, whichever comes first [2].

Irradiated RBC are indicated for use in patient groups at risk for TA-GVHD including intrauterine transfusion, recipients of a cellular blood component from a blood relative, HLA-matched products, patients who have received a bone marrow or hematopoietic stem cell transplant, or patients on nucleoside (purine) analogs or T-cell function altering drugs (e.g., fludarabine, clofarabine, and alemtuzumab) [2].

**Adverse Events Related to Transfusion**

Transfusion complications or transfusion reactions, may be broadly divided into infectious and noninfectious serious hazards of transfusion. To decrease transfusion-transmitted infection, the FDA requires donor screening, which includes testing for human immunodeficiency virus (HIV)
types 1 and 2, hepatitis B and C virus, human T-cell lymphotropic virus (HTLV) types I and II, Treponema pallidum (the organism that causes syphilis), West Nile Virus (WNV), and Zika Virus. Recently, the FDA called for regional testing for Babesia microti or pathogen reduction in Babesia-risk states. Donors must be negative for antibodies to the parasite Trypanosoma cruzi, which causes Chagas disease, once in their donation lifetime. In regard to other infectious diseases, the donor questionnaire is written in a way such that donors with the possible risk of transmitting diseases such as malaria or hepatitis A are deferred from donation. Testing for CMV and HLA antibodies may be additionally performed. Donors may be temporarily, indefinitely, or permanently deferred based on the criteria set by FDA or AABB [43].

Much of the infectious disease testing is antibody-based and detects the donor’s immune response to the offending agent. Adequate time, days to weeks, must pass until antibodies form; this also known as the window period. NAT detects viral nucleic acid particles and has greatly reduced the window period to just days. For example, prior to NAT testing for HIV-1, the window period for detection of antibody formation, even with third-generation tests, was 21–24 days after infection; in contrast, NAT testing reduces the window period to less than 10 days [44, 45] (Table 20.4).

| Infectious agent | Risk of infection per number of transfused units |
|------------------|-----------------------------------------------|
| HBV              | 1:800,000 to 1:1,200,000                      |
| HCV              | 1:1,100,000                                   |
| HIV              | 1:1,500,000                                   |
| WNV              | Very rare; two cases reported 2008–2014       |
| HTLV             | 1:641,000                                     |
| Chagas           | Very low, no cases since screening has been implemented (FDA 2010) |
| Syphilis         | Very low, no cases in the past 40 years       |
| Bacterial contamination of platelets | 1:3000 |

With current screening and testing measures and the relatively low risk of transfusion-transmitted infection, the focus has shifted to noninfectious serious hazards of transfusion. The rate of these adverse reactions, commonly termed transfusion reactions, has been reported as 660 per 100,000 individuals from an international registry [51]. More specifically, in the US, there were 239.5 adverse reactions reported per 100,000 units transfused. A summary of the prevalence, signs and symptoms, and management of transfusion adverse reactions is presented in Table 20.5. Transfusion-related acute lung injury (TRALI), and TACO are discussed in detail.

**Transfusion-Related Acute Lung Injury**

TRALI continues to be a significant and under-reported cause of transfusion-related morbidity and mortality in the US. TRALI has previously been reported as occurring as frequently as 1 in 3000 to 1 in 5000 transfusions, but the true incidence of TRALI is unknown as transfusion reaction reporting is voluntary [53]. Critically ill patients have up to an 8% incidence of TRALI, and has been reported in as high as 15% in patients with gastrointestinal bleeding and 30% in patients with end-stage liver disease [54, 55]. While TRALI can be fatal, the vast majority of patients recover within 96 hours, with aggressive, supportive treatment [56]. Nine TRALI-related deaths were reported in the US in 2017 [12].

Post-transfusion reactions consistent with what would now be described as TRALI were first reported in the 1950s; however, the term “TRALI” was coined by Popovsky and Moore in the mid-1980s and the constellation of findings and symptoms temporally related to transfusion were unified under one diagnosis [57]. The diagnosis of TRALI begins with the recognition of acute lung injury (ALI), defined as SpO2 < 90% or PaO2/FiO2 > 300 mmHg on room air or other demonstration of hypoxemia and bilateral pulmonary edema seen as lung infiltrates by frontal chest radiograph [58]. A combined definition of
TRALI, as defined by the National Heart, Lung and Blood Institute (NHLBI) Working Group and the Canadian Consensus Conference is an acute, noncardiogenic lung injury occurring within 6 hours of transfusion with respiratory symptoms of tachypnea, dyspnea, and pulmonary edema which may be mild to severe and sometimes seen as complete “white-out” on frontal chest X-ray [59]. Frothy secretions are sometimes seen coming from the patient’s mouth or endotracheal tube. If measured, the pulmonary artery wedge pressure should be less than 18 mmHg and there must not be any new, abnormal cardiac function [59]. Per this definition, TRALI may also be diagnosed in a patient with worsening preexisting pulmonary insufficiency (unique to the NHLBI definition), such as chronic obstructive pulmonary disease or pulmonary fibrosis [59]. A diagnosis of possible TRALI may apply to patients with preexisting clinical risk factors for ALI, such as recent surgery, burn injury, coagulopathy, chronic alcoholism, sepsis, and carcinoma [59]. Hypotension, fever, chills, nonproductive cough, and transient decreases in

| Reaction                                         | Prevalence (per 100,000 units transfused) | Signs and symptoms                                                                 | Management                                                                 |
|--------------------------------------------------|------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Allergic transfusion reaction                    | 112.2                                    | Urticaria, rash, skin itching, and swelling (throat, eye, tongue, etc.)            | Antihistamines                                                              |
| Anaphylactic transfusion reaction                | 8                                        | Bronchospasm, dyspnea, angioedema, hypotension, and tachycardia                    | Epinephrine, corticosteroids, antihistamines, fluid bolus                    |
| Acute hemolytic transfusion reaction             | 2.5–7.0                                  | Fever, chills, dyspnea, hypotension, tachycardia, back pain, nausea, vomiting, oliguria/anuria, hemoglobinuria, and positive direct antiglobulin test (DAT) | Symptomatic treatment, diuretics and fluid administration For future transfusion, antigen negative RBC will be provided |
| Delayed hemolytic transfusion reaction           | 40                                       | Occurs 2–14 days after transfusion; jaundice, anemia, elevated bilirubin, reticulocytosis, spherocytosis, increased lactate dehydrogenase, positive antibody screen, and positive DAT | Symptomatic treatment For future transfusion, antigen negative RBC will be provided |
| Delayed serologic transfusion reaction           | 48.9–75.7                                | Occurs 2–14 days after transfusion; positive antibody screen, and positive DAT    | Symptomatic treatment For future transfusion, antigen negative RBC will be provided |
| Febrile nonhemolytic transfusion reaction        | 1000–3000                                | Occurs within 4 hours of transfusion; temperature of 100.4 °F (38 °C) or increase of 1.8 °F (1 °C) from pretransfusion value with or without chills and rigors | Antipyretic or close observation                                             |
| Post-transfusion purpura                         | Unknown (varies by component)            | Occurs 2–14 days after transfusion; severe thrombocytopenia, petechiae, purpura, and identification of platelet antibodies | Self-limiting, intravenous immunoglobulin with or without corticosteroids For future transfusion, antigen negative platelets will be provided |
| Septic transfusion reaction                      | 0.03–3.3                                 | Fever, chills, hypotension, tachycardia                                          | Antipyretic, empiric, antibiotics Culture blood product                      |
| Transfusion-associated circulatory overload      | 10.9                                     | Occurs within 2 hours of transfusion; dyspnea, tachycardia, hypertension, headache, and jugular venous distension | Diuretic administration, reduce fluid intake                                 |

Table 20.5  Adverse reactions to transfusion [52]
white cell counts, especially neutrophils may also occur [59–61].

TRALI is a diagnosis of exclusion and septic transfusion reaction, volume overload, severe anaphylaxis, or a newly manifesting problem are often in the differential. If TRALI is suspected during the infusion of multiple consecutive products, all products given within a 6-hour time frame are implicated. All routinely transfused blood products (whole blood, RBC, PLT, plasma, and cryoprecipitate) have been implicated in cases of TRALI [53].

The pathophysiology of TRALI is attributed to factors present in both the recipient and the transfused blood product. Up to 85% of TRALI cases may be explained by the infusion of donor antibodies as demonstrated in an ex vivo animal model using isolated perfused rabbit lungs [62]. In these studies, antibodies against HLA or human neutrophil antigens (HNA) had the ability to bind to neutrophils which expressed the cognate antigen and induced pulmonary edema. However, the antibody, the cognate antigen on the leukocyte surface, and the source of complement had to be present in order for ALI to occur and if any component was omitted, lung damage was obviated [62]. This model has been refined and demonstrated; a minimum number of antigen sites are needed to be present on neutrophils such that antibody binding must reach a threshold before ALI occurs [63]. This work was also relevant in showing that priming with N-formylmethionine-leucine-phenylalanine, a component of bacterial cell walls allowed anti-HNA antibodies to directly activate neutrophils in the absence of complement [63].

In vivo TRALI models have demonstrated that a specific monoclonal antibody could cause ALI at a concentration seemingly similar to relatively well patients who receive a transfusion and develop TRALI [64]. However, in an animal model, when mice were housed in a pathogen-free environment TRALI was not demonstrated indicating a likely two-event model [64, 65]. Such an in vivo two-event pathogenesis was confirmed in a rat model which also demonstrated that lipids and other BRM could cause TRALI in older, stored RBC irrespective of LR [66]. Both antibodies to major-histocompatibility-complex (MHC) class I and the lipids from stored RBC were capable of priming quiescent neutrophils (PMN), activating primed PMN, and inducing ALI [66]. Specifically, rats that were infused with endotoxin (lipopolysaccharide, or LPS) alone did not develop ALI; however, those rats that received LPS and then a lipid extraction from 42-dayold RBC did develop ALI [66]. Importantly, extractions from fresh RBC or plasma did not result in ALI [66]. In addition, antibodies to common MHC class I or even class II antibodies caused ALI as the second event in this animal model of TRALI, indicating that TRALI, whether caused by antibodies to specific leukocyte antigens or due to BRM that directly prime PMN, appears to be the result of two distinct events [66]. The first event is the clinical condition of the patient, which predisposes to TRALI and the second event is the infusion of the specific antibody or BRM into the patient which activates the sequestered PMN inducing damage to the vascular endothelium, resulting in capillary leak and ALI [53, 66].

TRALI mitigation strategies are vital to reducing morbidity and mortality related to this transfusion complication. During the 1990s, the UK National Blood Service created a voluntary hemovigilance program and was the first to collect plasma from donors, after noting that TRALI or probable TRALI was seen almost seven times more frequently with plasma transfusion and about eight times more frequently with PLT transfusion when these products were collected from female donors [67]. Their efforts were rewarded following the adoption of this collection strategy for PLT and plasma, and reports of TRALI from plasma transfusion fell from 15.5 cases per million units transfused (1999–2004) to 3 per million (2005–2006) for plasma and from 14 cases per million to just under six cases per million for PLT products [67]. Densmore and colleagues also showed that HLA antibody formation increased with pregnancy, with about 8% of never-pregnant females showing sensitization, increasing to 15% after one pregnancy, and to about 26% after three pregnancies [68]. Never-transfused men and never-pregnant women have a 1.7% prevalence of HLA antibodies [69]. The American Red Cross also examined hemovigilance data and subse-
quently adopted a similar strategy of collecting plasma from predominantly male donors (95%) and saw a significant (80%) decrease in TRALI cases related to plasma infusion [70].

Effective April 2014, AABB Standards state that the collection of plasma and whole blood for allogeneic donation must be from males, never-pregnant females, or females with a history of pregnancy only if they have been tested for HLA antibodies since their last pregnancy and are found to be negative.

Additional mitigation strategies include the use of licensed, pooled, and solvent-detergent-treated plasma products (Octaplas™ Pooled Plasma (Human) Solvent/Detergent Treated; OctaPharma, Lachen, Switzerland). European hemovigilance systems have not yielded any TRALI cases after using these products for 10–20 years’ time. This may be explained because the pooling of numerous units dilutes the concentration of antibody and by the presence of soluble HLA antigen which is able to bind free antibody.

Transfusion-Associated Circulatory Overload

TACO is an acute, hydrostatic pulmonary edema which occurs in the setting of transfusion. Especially vulnerable populations include the very young, older patients (over 70 years of age), and those with compromised vascular systems or renal failure. TACO closely followed TRALI in the number of FDA-reported transfusion-related deaths, with 11 confirmed cases in the fiscal year 2017, comprising 30% of transfusion-related deaths [12].

There are several distinguishing factors between TRALI and TACO (Table 20.6). Pulmonary wedge pressure is an invasive measurement to determine the backpressure from the heart, or filling (“wedge”) pressure of the left atrium, by a catheter in the pulmonary artery, and unless the patient already has a Swan-Ganz catheter in place it is not likely to be performed. Brain natriuretic peptide (BNP) is a 32 amino acid polypeptide secreted in response to stretched cardiac ventricles, to counteract the renin–angiotensin–aldosterone system. Baseline BNP is not likely to be measured unless the patient is already being monitored for heart failure and may not be useful unless the differences are marked. In general, two of the most helpful distinguishing features are that TACO responds quickly to diuresis, whereas this approach should be avoided in TRALI unless the patient is also fluid overloaded, and, though fever may or may not be seen with TRALI, it is never a feature of TACO. It may be helpful to make the patient sit upright; oxygen should be given as needed. It is possible that TRALI and TACO may occur together.

| Table 20.6 Some distinguishing features between TRALI and TACO [2, 71] |
|-------------------------------------------------|
| **Feature**                              | **TRALI**       | **TACO**       |
| Pulmonary edema, bilateral               | Yes             | Yes            |
| Fever                                   | Possibly        | No             |
| Tachypnea, dyspnea                       | Yes             | Yes            |
| Leukopenia                              | Possibly        | No             |
| PWP (pulmonary wedge pressure)           | Normal          | Increased      |
| BNP (brain natriuretic peptide)          | <200 pg/mL      | Greatly elevated |
| Blood pressure                           | Usually hypotension | Usually hypertension |
| Increased vascular congestion/heart size | No              | Yes            |
| Diuresis                                | Hypoperfusion   | Resolution of symptoms |

Red Cell Storage

RBC anticoagulant-preservation solutions are approved for use by the FDA based upon testing to demonstrate a minimum RBC recovery of 75%, 24 hours after transfusion and less than 1% hemolysis in the RBC unit. However, there is no requirement to assess the clinical efficacy of an RBC transfusion. As a result, hospitals typically transfuse the “oldest” units in inventory first as not to outdate an expensive, often limited resource. Throughout storage, red cells acquire
deleterious metabolic and structural changes which include increased levels of lactate, pH less than 6.5, reduced adenosine triphosphate and nicotinamide adenine dinucleotide levels, depletion of 2,3-diphosphoglycerate, impairment of sodium and potassium exchange, increased oxidative stress by oxidation of Hb to methemoglobin, disruption of the RBC cytoskeletal membrane, and microvesicle formation [72]. However, the association of this red cell storage lesion with clinical outcomes remains controversial. Initial observational studies have demonstrated associations of the age of RBC with risk for infection, thromboembolic events, multi-organ failure, increased ventilator time, increased ICU and hospital length of stay, and increased mortality [73]. Unfortunately, most of these studies were fraught with bias and confounding. As a result, several large, randomized, controlled clinical trials have been completed [74–78]. The results of the completed studies are summarized in Table 20.7, but none have found a difference in clinical outcomes following transfusion of fresh or old RBC across a variety of clinical settings.

Table 20.7  Key randomized, controlled clinical trials investigating clinical outcomes with red cell storage

| Study               | Number of subjects randomized | Study population                                                                 | RBC randomization                        | Mean age of blood (fresh vs standard) | Percent nonconformance to RBC group | Primary outcome                                                                 |
|---------------------|-------------------------------|--------------------------------------------------------------------------------|------------------------------------------|--------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Fergusson et al. [74] | 377                           | Premature infants with a birth weight less than 1250 grams and required one or more RBC transfusions | 7 days or less vs standard practice (dedicated donor unit per patient up to the expiration of the unit) | 5.1 days vs 14.6 days               | 15.2% in fresh group, 0% in standard | 52.7% of infants in the fresh RBC group compared to 52.9% in the standard RBC group experienced composite primary outcome (mortality and major neonatal morbidities associated with acute organ dysfunction or failure) |
| Steiner et al. [75]  | 1481                          | Individuals 12 years of age or older, weight 40 kg or more undergoing complex cardiac surgery with median sternotomy; patients 18 and older were required to have a likelihood of receiving a RBC transfusion of 60% or more during or within 24 hours of surgery | 10 days or less vs 21 days or more       | 7.8 days vs 28.3 days               | 11% in the fresh group and 13% in the standard group | No difference in MODS or mortality                                               |

(continued)
Table 20.7 (continued)

| Study          | Number of subjects randomized | Study population                                                                 | RBC randomization | Mean age of blood (fresh vs standard) | Percent nonconformance to RBC group | Primary outcome                                                                 |
|---------------|-------------------------------|--------------------------------------------------------------------------------|-------------------|--------------------------------------|------------------------------------|--------------------------------------------------------------------------------|
| Lacroix et al. [76] | 2510                          | Critically ill adults who had a RBC transfusion ordered within 7 days of ICU admission and were expected to require mechanical ventilation for at least 48 hours | 8 days vs standard issue | 6.1 days vs 22 days (p < 0.001)       | 16% in the fresh group, 0% in standard | No difference in 90-day mortality between fresh (37%) and standard (35.3%) RBC transfusion |
| Heddle et al. [77]   | 31,497                        | Adult hospitalized patients who required a RBC transfusion                   | Freshest RBC vs oldest RBC available | 13.0 days vs 23.6 days (p < 0.001)    | protocol required a minimum 10-day difference in mean red cell storage duration between treatment groups | No difference in in-hospital mortality between short-term (9.1%) and long-term (8.7%) stored RBC |
| Cooper et al. [78]    | 4994                          | Critically ill adults who had an anticipated ICU stay of at least 24 hours, and in whom the medical staff had decided to transfuse one or more RBC | Freshest, compatible, allogeneic RBC vs the oldest, compatible RBC | 11.8 days vs 22.4 days (p < 0.001)    | 1.5% in the short-term, 0.5% in the long-term group | No differences in 90-day mortality between short-term (24.8%) and long-term (24.1%) stored RBC |

*RBC* red blood cell, *MODS* multiple organ dysfunction syndrome

**Summary**

Transfusion is one of the most commonly performed procedures in hospitalized patients and a basic understanding of RBC transfusion is important for all ordering clinicians. This chapter reviewed blood product collection, manufacturing, storage, pretransfusion testing, and selection of appropriate RBC for transfusion including RBC modifications. Transfusion-related adverse events are not infrequent and clinicians should be aware of the noninfectious hazards of transfusion, especially TRALI and TACO. Last, this chapter which addressed two ongoing controversies regarding RBC transfusion thresholds and clinical outcomes associated with red cell storage were reviewed. Transfusing in the setting of hemorrhagic blood loss adds additional challenges including the utility of whole blood transfusion and optimum transfusion ratios, which are discussed in Chaps. 25 and 28, respectively.

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