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118 Transfusion Therapy and Biology

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Transfusion Therapy

and Biology Transfusion encompasses the use of blood components (BCs) to pre vent or treat anemia, hemorrhage, and bleeding disorders. Occasion ally, BCs may be used to treat infection or relapse of malignant blood diseases after allogeneic hematopoietic transplantation. BCs comprise mainly red blood cell concentrates (RBCCs), platelet concentrates (PCs), and plasma for transfusion use as opposed to plasma fraction ated into medicinal products (such as immunoglobulin, albumin, and clotting factors). Alongside transfusion safety, ensuring BC quality, assessing in vivo efficacy, and promoting evidence-based transfusion practices are critical aspects of transfusion medicine. Donor medicine does not fall within the scope of this chapter. While particularly safe, blood donations can cause adverse reactions, among which are fainting reactions and iron deficiency. These reac tions require preventive approaches and appropriate treatment when needed. BLOOD COMPONENTS BC collection and manufacturing processes are described in

Table 118-1. BCs are collected as whole blood or directly as com ponents by apheresis. The vast majority of BCs are homologous. Autologous BCs, collected ahead of planned surgery, are now excep tional as they present little to no advantage over homologous BCs. Nevertheless, such donation may still be of benefit in the presence of a rare blood group phenotype. All BCs comply with common quality and performance standards and guidelines. Quality assurance encompasses well-defined process ing steps and stringent BC quality controls as defined by health author ities. Reporting of adverse reactions and events associated with blood collection, BC processing, and transfusion is highly recommended. With the obvious exception of granulocyte concentrates and mono nuclear cells, most BCs are now leukocyte-reduced, and universal prestorage leukocyte reduction has been recommended. These BCs contain <1–5.106 donor leukocytes and are associated with reduced incidence of febrile nonhemolytic transfusion reactions (FNHTRs), infections with intracellular pathogens such as cytomegalovirus (CMV), alloimmunization, and immunomodulation. BCs may undergo additional processing steps. These include irra diation to prevent graft-versus-host disease (GVHD) in immunosup pressed patients, pathogen reduction to further reduce the risk of transfusion-transmitted infections, plasma reduction in patients with

severe allergic reactions to BCs, or the manufacturing of specific units for young children, neonates, or intrauterine transfusion. BC constituents undergo centrifugation and filtration and are placed in contact with needles, plastic tubing, and bags, as well as anticoagu lants and various additive solutions. BCs are subjected to gas exchanges that are significantly different from aerobic breathing and are main tained at temperatures that are not physiologic, such as 22°C or 4°C. Any of these elements may contribute to so-called “storage lesions” and to the presence of bioactive molecules such extracellular vesicles and cell-free mitochondrial DNA in the BC. The clinical impact of such lesions is still under investigation with currently no consensus on this issue. Furthermore, plasma present in BCs contains donor antibodies (Abs). When directed toward antigens (Ags) present in the recipient, such as blood group or tissue (human leukocyte antigen [HLA]) Ags, such Abs may result in adverse events. RBCCs bring only a limited amount of donor plasma (10–30 mL), unlike PCs and obviously plasma. The use of platelet additive solution can replace two-thirds of plasma in PCs, while still leaving the equivalent of one plasma unit of 200 mL per transfused PC.

BLOOD GROUP ANTIGENS AND ANTIBODIES Red blood cells (RBCs), as well as other blood constituents such as platelets and neutrophils, express allogeneic determinants. Transfu sion may therefore result in alloimmunization and the production of alloantibodies (alloAbs). These alloAbs comprise anti-RBC Abs, antiHLA, anti-human platelet Ag (HPA) Abs, and anti-human neutrophil Ag (HNA) Abs. Anti-RBC immunization may result in hemolysis, whereas anti-HLA or anti-HPA Abs may result in complications such as fever and platelet transfusion refractoriness. Furthermore, antiHLA and anti-HNA immunization in the donor may result in a severe lung disorder called transfusion-related acute lung injury (TRALI). The Abs against red cell Ags may be IgM or IgG immunoglobulin classes. Some IgG or IgM can activate complement, and some IgG, crossing the placental barrier, may induce hemolytic disease of the fetus and newborn.

Erythrocyte blood groups refer to antigenic molecules that are expressed on the surface of RBC and other cells, genetically trans mitted, and recognized by specific Abs. The polymorphism of such molecules explains their immunizing potential in situations such as transfusion, pregnancy, and transplantation. Blood groups can also interact with the environment and with infectious pathogens, leading to individual susceptibilities. For example, malaria is less severe in type O than non-O patients. Currently, ~390 different blood group Ags have been described, classified within ~45 different systems. Blood group Ags belong to two broad categories based on their biochemical nature: carbohydrate blood groups and protein blood groups. RBC Ags may be the target of autoantibodies (autoAbs) generating autoimmune hemolytic anemia. Some of them, mostly IgG, are active at 37°C, called “warm autoAbs,” and are most often directed against Rh Ags, whereas others, most often IgM, are active at 4°C, called “cold autoAbs,” and may be directed against ABO, HI, I, i, P, and other Ags. CHAPTER 118 Transfusion Therapy and Biology Carbohydrate blood groups are headed by the ABO system, which comprises two main Ags, A and B, encoded by two alleles, which are the A and B alleles, respectively. In addition to these active alleles, there is an inactive allele: O. Depending on the genotype, four different phenotypes are produced (Table 118-2). Other carbohydrate systems (H, P1PK, Lewis, I, GLOB and SID) share many characteristics with the ABO system. The A allele encodes the A enzyme, which binds the A-type sugar (GalNac) A to the H substrate (expressed by action of the H enzyme encoded by the H allele, which happens to be inactive in the Bombay phenotype); sugars are attached to protein substrates on the surface of the RBC and so forth. Carbohydrate Ags are ubiquitously distributed in the body. The ABO Ags, expressed on endothelial cells, are genuine “tissue” groups and may be involved in graft rejection.

These Ags are not specific to humans but are shared by many species including viruses and bacteria. The presence of A and B Ags in the environment and, in particular, on the bacteria of the microbiota explains the synthesis of so-called “natural” or “regular” Abs, aside from any transfusion or pregnancy. Such Abs have a major hemolytic capacity as they bind complement and activate its cascade up to the membrane attack complex. This imposes donor-recipient stringent compatibility rules for RBCCs and whole blood transfusion and, albeit less stringently, for plasma and PC transfusion. Protein blood groups are headed by the Rh system for RBCs (Table 118-3). As these Ags are specific to humans, the occurrence of immunization can only occur upon allogeneic stimulation. Abs directed against Ags of RBC groups other than ABO must be detected before RBCC transfusion or transplantation and during pregnancy. Of the 45 RBC group systems described, five (Rh, Kell, Duffy, Kidd, and MNS) are routinely investigated due to the clinical significance of Abs and their frequency. Testing for all five types ensures routine transfu sion compatibility of 95%. The Rh system comprises nearly 56 Ags, the most immunogenic of which is the D Ag (RH1). The Rh system has two RH∗D and RH∗CE genes located on chromosome 1. The RH∗D gene codes for the RhD protein expressing the D Ag (RH1) present in 85%, 93%, and >99%

TABLE 118-1 Blood Components: Collection and Manufacturing Processes ADDITIONAL COMPONENT PROCESSING (OPTIONAL TO MANDATORY) RATIONALE BLOOD OR APHERESIS COLLECTION AND INITIAL PROCESSING BLOOD COMPONENT Whole blood collection: Separation into RBCC and platelet-rich plasma (PRP) by slow centrifugation, followed by high-speed centrifugation of the PRP to yield one unit of platelets (most often subsequently pooled) and one unit of plasma. or RBCC from whole blood or from apheresis Leukocyte reduction Deleukocytation to <1–5.106 leukocytes per unit (highly recommended): initial whole blood filtration or RBC elective filtration (highly recommended) Irradiation: X-ray or gamma, ~25–35 Gy; most often units not older than 28 days after collection Separation into a RBCC, a plasma, and a “buffy coat” containing leukocytes and platelets by high-speed centrifugation, followed by pooling and slow-speed centrifugation of the buffy coat to produce a pooled platelet unit. Alternatively, the buffy coat may undergo high-speed centrifugation to produce a granulocyte unit that will be subsequently pooled. Apheresis collection: Various apheresis devices allow for the collection of BCs either as individual BCs such as plasma or PC (possibly double, such as double RBCC) or combined BCs, such as PC and plasma, or RBCC, platelets, and plasma. Plasma reduction Prevention of allergic reactions in patients with prior severe transfusion reactions Pediatric preparation Adjustment to low-weight recipients Cryopreservation (glycerol) PART 4 Oncology and Hematology PC from whole blood (individual units or pools of 4–6 units of ABO identical units) or from apheresis Suspension in a platelet additive solution (PAS). PAS contains ingredients such as acetate, potassium, phosphate, and magnesium to sustain platelet storage Leukocyte reduction

(<1–5.106 leukocytes per unit) (highly recommended): initial whole blood filtration or PC elective filtration Pathogen reduction: Most often nucleic acid cross-linker and/or UV illumination Volume reduction Prevention of allergic reactions in patients with prior severe reactions Irradiation: X-ray or gamma, ~25–35 Gy; in general, on bags no older than 3 days after collection Pediatric Volume and content adjustment Cryopreservation (DMSO) To ensure continuous availability in remote locations To ensure availability of platelets with rare HPA groups Plasma from whole blood or from apheresis Cryopreservation at –18°C (most often)

VOLUME AND CONTENT STORAGE CONDITIONS AND DURATION Reduction of fever and chills Reduction of intracellular pathogens (including CMV) Reduction of alloimmunization 250–300 mL (including additive solution, no more than 40–50 mL of plasma) Hemoglobin: 22–40 g/dL Hematocrit: 50–70% Hemolysis ≤0.8% at issuing 4 +/– 2°C Duration depends on the additive solution:

25–42 days After irradiation: 24 h After plasma reduction:

24 h to 10 days depending on reduction methodology GVHD prevention in immunosuppressed patients or intrafamily transfusions Lesser volume, 10% reduction in RBC content Adjusted content Most often to ensure availability of RBCCs with a rare blood group for immunized “public-negative” recipients or recipients with complex alloimmunizationsa Same Hb content Hematocrit: 40–80% Glycerol ≤1 g N2 or –80°C electric freeze drying N2: unlimited; –80°C:

30 years 7 days after thawing in suitable additive solutions, 24 h without additive solution Reduction of fever and chills Plasma orientation toward fractionation From 100 to 700 mL ≥2.1011 platelets pH ≥6.4 At 20–24°C and under permanent motion:

3–7 days or At 4°C without motion:

up to 14–21 days If irradiated: <24 h Reduction of fever and chills Reduction of intracellular pathogens (including CMV infections) Reduction of alloimmunization Reduction of transfusiontransmitted infections Prevention of GVHD Prevention of GVHD 6 h after thawing (depending on cryopreservation procedure, may be resuspended in plasma) Shelf-life extension 200–300 mL Coagulation factors, including fibrinogen

(≥2 g/L), factor VIII

(≥0.5 IU/mL), protein C and S, antithrombin 1–2 years if cryopreserved Up to 28 days if kept unfrozen (Continued)

TABLE 118-1 Blood Components: Collection and Manufacturing Processes ADDITIONAL COMPONENT PROCESSING (OPTIONAL TO MANDATORY) RATIONALE BLOOD OR APHERESIS COLLECTION AND INITIAL PROCESSING BLOOD COMPONENT Leukocyte reduction (<1–5.106 leukocytes per product): Initial whole blood filtration and/or plasma elective filtration Pathogen reduction: Nucleic acid cross-linker and/or UV illumination or solvent detergent treatment (most often on pooled products) Lyophilization To facilitate transportation and storage, as well as immediate availability, in remote locations Granulocyte concentrates from whole blood (pools of 10–20 ABOidentical units) or from apheresisb Irradiation (mandatory) Prevention of GVHD ≤650 mL ≤2.1010 granulocytes Whole blood Leukocyte reduction with a platelet-sparing device Peripheral blood mononuclear cells (apheresis) May undergo cryopreservation (N2) Cryoprecipitate (collected after thawing and centrifugation of plasma) Resuspension in plasma (10–15 mL) and cryopreservation aAntigen frequency below 1% to 1/1000 of the population and contraindication for using regular blood units, depending on country-specific regulations. bGranulocyte collection by apheresis requires donor preadministration of steroids and/or hematopoietic growth factor and exposure to heparin and hydroxyethyl starch during the apheresis procedure. Abbreviations: BC, blood component; CMV, cytomegalovirus; DMSO, dimethyl sulfoxide; GVHD, graft-versus-host disease; Hb, hemoglobin;

HPA, human platelet antigen;

N2, nitrogen gas; N/A, not applicable; RBC, red blood cell; RBCC, red blood cell concentrate; PC, platelet concentrate; UV, ultraviolet. of individuals of Caucasian, African, and Asian ancestry, respectively. The RH∗CE gene codes for RhCE proteins expressing C (RH2) and/ or c (RH4), and E (RH3) and/or e (RH4) Ags. The presence of the D Ag confers Rh “positivity,” while its absence confers Rh “negativ ity.” The RH∗D and RH∗CE genes determine eight main haplotypes (DCe, DcE, Dce, DCE, dce, dCe, dcE, and dCE) whose frequencies TABLE 118-2 ABO Blood Groups and Antibodies: Transfusion Compatibility GENOTYPE(S) ENZYME(S)/IMMUNODOMINANT SUGAR(S) PHENOTYPE A/A or A/O “A” transferase/N-acetylgalactosamine (GalNac) A Anti-B A or O A, 0b, Bb, or ABb A or A,B B/B or B/O “B” transferase/galactose (Gal) B Anti-A B or O B, O, Ab, or ABb B or A,B A/B “A” transferase and “B” transferase GalNac and Gal A,B None A,B or A or B or O A,B, Ob, or Ab or Bb A,B O/O Inactive Unconverted H antigen O Anti-A and Anti-B O 0, A, B, or A,B A or B or A,B or O aOrder of priority. bWithout high-titer anti-A and/or anti-B antibody. Abbreviations: PC, platelet concentrate; RBCC, red blood cell concentrate.

(Continued) VOLUME AND CONTENT STORAGE CONDITIONS AND DURATION Reduction of fever and chills Reduction of intracellular pathogens (including CMV) Reduction of alloimmunization Reduction of transfusiontransmitted infections Room temperature ≤24 h after the end of collection CHAPTER 118 Reduction of posttransfusion fever and chills Reduction of intracellular pathogens (including CMV) Reduction of alloimmunization ~520 mL (including additive solution) At 2–4°C 21–35 days Transfusion Therapy and Biology Increased practicability Repeated administration Number of cells adjusted for a predetermined number of T lymphocytes 105–107 CD3+ cells/ recipient kg N2: unlimited Never frozen or thawed: <6 h N/A Cold-insoluble plasma proteins (fibrinogen, factor VIII, von Willebrand factor) 12 months After thawing, may be stored at 20–24°C for up to 6 h differ considerably among different geographical populations. The high diversity of the Rh Ags includes weak and/or partial expression. Identifying individuals (especially young females of childbearing potential and multitransfused patients) with a weak or partial D Ag is important to adequately select D-positive or -negative RBCs. Molecu lar biology is now routinely applied to resolve such situations. TRANSFUSION COMPATIBILITY REQUIREMENTS NATURAL ANTIBODIES RBCC PCa PLASMA

TABLE 118-3 Red Blood Cell Group Systems and Antibodies: Clinical Significance and Transfusion Recommendations ISBT NO./ SYSTEM SYMBOL/GENE(S) ANTIGENS (NO.) MAIN ANTIBODIES (ANTI-) 1/ABO ABO/ABO

A, B None to severe; immediate and/or delayed 2/MNS MNS/GYPA, GYPB, (GYPE)

M None (except in extremely rare cases if active at 37°C) N None (may be clinically significant in the case of the rare N–S–s–U– phenotype) S, s None to moderate (rare) None to severe (rare) Ag-negative RBCC U Mild to severe Mild to severe (one reported case requiring an intrauterine transfusion) 3/P1PK P1PK/A4GALT

P1 None to moderate; delayed (rare) P1, Pk, P (Tja) None to severe None to severe Ag-negative RBCC 4/Rh RH/RHD, RHCE

D, C, E, c, e Mild to severe; immediate or delayed PART 4 Oncology and Hematology 6 /Kell KEL/KEL

K Mild to severe; delayed Mild to severe (rare) Ag-negative RBCC 7/Lewis LE/FUT3

Lea, Leb None (rare cases of hemolytic reactions) 8/Duffy FY/ACKR1

Fya, Fyb Mild to severe (rare); immediate/delayed Fy3, Fy5 Mild to moderate; immediate (rare)/delayed 9/Kidd JK/SLC14A1

Jka, Jkb None to severe; immediate or delayed Jk3 None to severe; immediate or delayed 18/H H/FUT1

H (Bombay) None to severe; immediate/ delayed 20/Globoside GLOB/B3GALNT1

P None to severe None to mild Ag-negative RBCC Abbreviations: Ab, antibody; Ag, antigen; HDFN, hemolytic disease of the fetus and newborn; IAT, indirect antiglobulin test (indirect Coombs test); ISBT, International Society of Blood Transfusion; RBCC, red blood cell concentrate. The Kell system comprises 38 Ags, one of which is routinely deter mined: the K antigen (KEL1); 9% and 2% of individuals of Caucasian and African ancestry are K positive (KEL:1), respectively, whereas 91% and 98%, respectively, are K negative (KEL:–1). The immunogenicity of Kell is third behind the ABO and Rh systems. The Kell protein is linked to another blood group protein called Kx. The rare absence of this protein (controlled by a gene on X) is associated with a weak KEL Ag, acanthocytosis, shortened RBC survival, and a progressive form of muscular dystrophy that includes cardiac defects. This rare condition is called the McLeod phenotype. The Duffy system (FY) comprises five Ags, two of which are rou tinely tested: the Fya Ag (FY1), coded by the Fya allele, and the Fyb Ag (FY2), coded by the Fyb allele. Depending on the combination of alleles, three common phenotypes are expected: Fy (a+b+), which has the two alleles Fya and Fyb; Fy (a+b–), which has only the Fya allele in a double dose; and Fy (a–b+), which has only a double dose of the Fyb allele. A particular phenotype characterized by the absence of the Fya and Fyb Ags, the Fy(a–b–) phenotype, is exclusive (with some excep tions) to individuals of African ancestry where it can reach frequencies of 70–100% depending on the population. It is linked to the presence of a double dose of a silent FY*0 allele. This distribution may be related to the fact that the Fy Ags serve as receptors for Plasmodium vivax and therefore the Fy(a–b–) phenotype. However, these individuals may develop Abs against two high-frequency Ags (FY3 and FY5) after transfusion or pregnancy. They may also have low a granulocyte count but are not associated with any disease. The Kidd system (JK) comprises three Ags, two of which are routinely tested: the Jka Ag (JK1), coded by the Jka allele, and the Jkb

HEMOLYSIS CHARACTERISTICS RBCC TRANSFUSION RECOMMENDATIONS TRANSFUSION HDFN None to moderate (rarely severe) Ab-negative RBCC None (except in extremely rare cases if active at 37°C) Compatible RBCC (negative IAT at 37°C) Ag-negative red cells in the case of sickle cell disease None Compatible RBCC (negative IAT at 37°C) Ag-negative RBCC in the case of N–S–s–U– phenotype Ag-negative RBCC None Compatible RBCC (negative IAT at 37°C) Mild to severe Ag-negative RBCC None Compatible RBCC (negative IAT at 37°C) Mild to severe (rare) Ag-negative RBCC Mild (rare) (no data for anti-Fy5) Ag-negative RBCC Mild to moderate (rare) Ag-negative RBCC None to mild Ag-negative RBCC Not none Ag-negative RBCC Ag (JK2), coded by the Jkb allele.

Depending on the combinations of alleles, three common phenotypes are seen: Jk(a+b+) displaying the two alleles Jka and Jkb, Jk(a+b–) displaying only the Jka allele in a double dose, and Jk(a–b+) displaying only a double dose of the Jkb allele. A particular phenotype is characterized by the absence of the Jka and Jkb Ags: the Jk(a–b–) phenotype found in Polynesian populations. It is linked to the presence of a double dose of a silent JK∗0 allele. These people may develop Abs against the high-frequency anti-JK3 Ag after transfusion or pregnancy. The MNS system comprises 50 Ags, four of which are routinely tested. Two genes (GYPA, GYPB) encode two pairs of so-called "antithetical" Ags. The M (MNS1) and N (MNS2) pair Ags encoded by the M and

N alleles, respectively, are branched on the glycophorin A molecule. Their combination will determine whether or not they are present. M+ and N+ subjects have both alleles; an M+, N– subject is homozygous for the M allele; and an M–, N+ subject is homozygous for the N allele. The same holds true for the other pair of Ags, S (MNS3) and s (MNS4) expressed on glycophorin B. Therefore, an M+, N–, S–, s+ subject (in international nomenclature, this is written as MNS:1,–2,–3,5) will be homozygous for the M and s alleles. A rare phenotype, S–s–, found exclusively in individuals of African ancestry, can develop an Ab against the high-frequency U Ag (MNS5) after transfusion or pregnancy. ■ ■RARE RBC PHENOTYPES Some patients present with rare genotype/phenotype assortments, and their RBCs display so-called private Ags or, conversely, lack public Ags (i.e., widely shared Ags) toward which the patient may develop

an immune response when exposed to these Ags. Public-negative immunized individuals are virtually impossible to transfuse using conventional blood bank resources and require access to designated blood banks that have access to rare blood programs. Their primary responsibility is to identify and collect blood from donors exhibiting particular Ag displays on their RBCs or platelets that are uncommon in the given jurisdiction. Specific ethnic populations may be targeted, as some may display genotype specificities, such as the Bombay group in southwestern Indians. Several hemoglobinopathies, such as sickle cell disease, are more common in individuals of African ancestry. Such patients may display RBC phenotypes that are uncommon in coun tries in the Northern Hemisphere, resulting in difficulties adequately identifying donors to match the need, as a last resort, for highly valued cryopreserved BCs. CLINICAL INDICATIONS AND EFFICACY ASSESSMENT OF BLOOD COMPONENTS BCs are life-saving therapies but also scarce resources. Furthermore, transfusion may result in well-identified adverse reactions as well as more ill-defined adverse reactions, including inflammation and therapeutic inefficacy. As highlighted in patient blood management programs, transfusion should be considered within a multidisciplinary approach that includes optimization of hematopoiesis and minimiza tion of blood loss during surgical interventions. Clinical indications of BCs as well as means to assess therapeutic efficacy are detailed in Table 118-4. ADVERSE REACTIONS TO BLOOD COMPONENTS Adverse reactions to transfused BCs are most commonly non-lifethreatening, although serious reactions can present with mild symp toms. Transfused patients should be closely monitored for warning signs suggestive of adverse reactions, as described in Table 118-5. When an adverse reaction is suspected, the transfusion must be stopped while the recipient's clinical status is assessed, and supportive care is initiated as needed. An average of 37 transfusion-associated fatalities with possible to definite imputability were reported yearly to the U.S. Food and Drug Administration (FDA) between 2017 and 2021 among ~15 million transfused BCs. Most frequent causes of death were transfusion-associated circulatory overload (TACO) (32%), followed by TRALI (21%), hemolysis (21%), and microbial contamina tion (13%). Adverse reactions to BCs may result in immune and nonimmune

mechanisms. Immune-mediated reactions are often due to recipient or donor alloimmunization and the presence of preformed recipient or donor Abs. Nonimmune causes of reactions are from the physical or chemical properties of BCs or from pathogens present in the BC. ■ ■IMMUNE-MEDIATED ADVERSE REACTIONS Hemolytic Transfusion Adverse Reactions Immune-mediated acute hemolysis occurs when the recipient preformed Abs lyse trans fused donor RBCs and may occur during or 24 h after transfusion. The anti-A or anti-B Abs are responsible for most of the most severe reactions, which can be fatal. However, alloAbs directed against other RBC Ags (i.e., Rh, Kell, and Duffy) are also responsible for severe hemolytic reactions. Such dramatic reactions are usually caused by a failure in product or patient identification, erroneous blood grouping, or unidentified anti-RBC alloimmunization in the recipient. Hemoly sis, most often of lesser severity, may also occur upon transfusion of BCs containing incompatible plasma with a large amount of alloAbs directed against the recipient's RBCs. This may typically occur after transfusion of a PC containing ABO-incompatible plasma. Estimated frequencies of acute and chronic hemolytic adverse reactions are 1–10 and 5–40 per 105 transfused BCs, respectively. Mechanisms of transfusion hemolytic reactions are described in Fig. 118-1. Prevention of hemolytic reactions relies on pretransfusion test ing of potential recipients. Testing will include determination of the

ABO D phenotype (and anti-ABO Abs) as well as additional typing for the other main Rh Ags (CcEe), K Ag of the Kell system, and more rarely, Duffy (Fya and Fyb), Kidd (Jka and Jkb), and MNS (S and s) Ags, depending on the clinical setting. These determinations are most often performed by serology. However, molecular typing is increas ingly being used to predict RBC phenotype and facilitate the selection of a compatible component. Special care must be taken to verify the patient's identity and apply adequate tube labeling. A double ABO determination performed separately may be considered, especially in the absence of a systematic crossmatch.

Testing will also include the screening and identification of alloAbs directed against RBC Ags other than ABO. This screen is performed by mixing patient serum with type O RBCs expressing Ags from most blood group systems and whose extended phenotype is known. The specificity of the alloAb is identified by correlating the presence or absence of Ag with the induced—or not—agglutination. Special attention should be paid to patients receiving monoclonal Ab treat ment that may bind to erythrocytes in vivo (such as anti-CD38 IgG treatment for multiple myeloma) and therefore interfere with alloAb screening. Such interference may be offset by sample dithiothreitol pretreatment. Crossmatching between the recipient plasma/serum and the selected RBCs may be performed, especially when the recipient is alloimmu nized against RBC or is frequently transfused, as well as in specific clinical settings such as sickle cell disease, even if the Ab screening is negative. CHAPTER 118 The selection of a compatible BC should consider pretransfusion testing as well as the recipient's clinical status. In the case of D-negative patients, every attempt must be made to provide Rh-negative RBCC to prevent anti-D alloimmunization. In an emergency, D-positive RBCC can be safely transfused to a D-negative patient who lacks anti-D. How ever, an estimated 20–22% of RBCC recipients will become alloimmu nized and produce anti-D Abs after transfusion with D-positive RBCs. Such alloimmunization can occur after PC transfusion, although at a much lower frequency (~1%). Whenever possible, females with child bearing potential (to include prepubertal girls) should be transfused with D- and K-compatible RBCCs and D-compatible PCs to prevent alloimmunization and protect a future fetus/newborn from an alloimmunemediated hemolytic disease. D-negative females with childbearing potential who are transfused with BCs containing D-positive RBCs should receive anti-D Ab to prevent allosensitization. Transfusion

Therapy and Biology Hemolysis, most often of lesser severity, may also occur after trans fer of alloAbs directed against the recipient's RBC Ags. Such ABO "plasmatic" incompatibility, called "minor ABO incompatibility," will occur mainly with PC transfusions, where platelets are suspended in ~100–300 mL of plasma (depending on whether part of the plasma is substituted by additive solution). BCs containing plasma with hightiter anti-A/B Ab may induce a hemolytic reaction. When the transfu sion of ABO-identical (vs ABO-compatible) PCs is not feasible, PCs provided by donors with low-titer anti-A/B only should be preferred. While there is no universal definition of high-titer Abs, a threshold titer of 1/64 (as assessed by hemagglutination) may be appropriate. The use of an additive solution in PCs substantially mitigates this risk. Lastly, ABO plasmatic incompatibility can lead to the formation of immune complexes with soluble A and/or B Ags and ensuing inflam mation and platelet activation. Acute hemolytic reactions may present with hypotension, tachypnea, tachycardia, fever (+1–2°C), chills, chest and back pain, hemoglobin uria, and hemoglobinemia. In the most severe cases, disseminated intravascular coagulation (DIC), acute renal failure, shock, and death may occur. Delayed hemolytic reactions, with icterus and persisting or wors ening anemia as the main clinical manifestations, result from an anamnestic response. Such reactions may occur in patients previously sensitized to RBC Ags who have a negative alloAb screen at the time of transfusion due to low Ab levels. The alloAb is detectable 1–2 weeks after the transfusion. Diagnosis of transfusion-associated hemolysis relies on persis tent and/or worsening anemia, depleted plasma haptoglobin levels,

transfusion (not applicable to CCIa >7.5 to 10 within 1 h and Prevention and/or resolution 25–30 mL/kg Sickle cell disease: reduced Increased Hb (+1 g/dL) and related symptoms, clinical

> 4.5 to 5 within 24 h after COMPONENT THERAPEUTIC INDICATION GOAL DONOR/RECIPIENT COMPATIBILITY DOSAGE EFFICACY EVALUATION Reduction of anemiapercentage of HbS hematocrit (+3%) improvement of bleeding whole blood–derived PCs) 0.5–0.7 × 1010 platelets/kg

1 unit at a time (250–350 solution), repeated per mL, including additive clinical status and Hb (apheresis or pooled level Additional compatibility may be required compatible (cellular) with low-titer antiHLA compatible (negative lymphocyte depending on the clinical setting and ABO identical preferable; if not, ABO A/B Ab; RhD compatible preferred in RhC/c/E/e; Kell-compatible RBCCs if multitransfused whenever possible. Improve systemic and tissue oxygenation ABO compatible (cellular) and ABO childbearing-age females, and if RhD compatibility in young and identical when achievable. PART 4 Oncology and Hematology premenopausal women screening results. multitransfused improved hemostatic capacity compared with Replace altered RBCs with donor RBCs and Cold stored platelets, despite lower in vivo compensate for hemolysis, prevention of survival, have maintained and possibly Correct impaired primary hemostasis, sickle cell occlusive crisis including vessel healing neonates and patients with severe thrombocytopenia relation with clinical symptoms): <7 g/dL for patients with preexisting cardiovascular disease (<8 g/dL) as undergoing orthopedic surgery, cardiac surgery, or in the absence of fever or infection, ≤10,000/μL to well as for patients with acute coronary disease

Hb below a given threshold (to be considered in Platelet level below a given threshold: ≤5000/μL Thrombocytopenia-related bleeding disorders: (<9–10 g/dL). Such thresholds do not apply to Anemia and/or tissue ischemia (treatment or Not recommended: nutritional anemia (iron,

hemodynamically stable, except for patients Treatment (cold or room temperature PC) or and chronic transfusion-dependent anemia. RBC exchange: Anemia/sickle cell crisis in hemoglobinopathies (sickle cell disease, prevention (room temperature PC) vitamin B12, or folate deficiency) TABLE 118-4 Blood Components: Clinical Use thalassemia) RBCC Transfusion: prevention) blood–derived platelets or temperature (most often) single donor apheresis), PC (from pooled whole maintained at room

(Continued) Reduced antibody levels (e.g., cold/cryopreserved platelets) anti-HLA antibodies prior to ABO compatible (plasma) 45–60 mL/kg Improved disease-specific Not determined Reduced bleeding disorder recovery in case of TTP) organ transplantation) symptomatology (i.e., apyrexia and platelet Infection resolution ABO compatible (plasma) 10–15 mL/kg neonates to HPA immunized mother (fetal refractoriness related to the presence of neonatal alloimmune thrombocytopenia) crossmatch) or HLA identical in case of HPA compatible in thrombocytopenic anti-HLA Ab missing elements of coagulation or fibrinolysis cascade, as well as elements to heal injured Ab in case of TTP, excess cholesterol, etc.); and/or immunomodulatory factors such as Deplete pathogenic elements in the blood Correct impaired hemostasis by providing (autoantibodies such as anti-ADAMTS-13 plasma may also bring anti-inflammatory Provide Abs against relevant pathogens room temperature stored platelets vessel endothelium immunoglobulin Infectious disease (convalescent plasma containing Plasma exchange (plasma or combined plasma and lacking enzyme (e.g., thrombotic thrombocytopenic 20,000/μL if fever or infection; ≤50,000/μL if surgery, DIC, endoscopy, invasive procedures; ≤80,000/μL if Pathogenic Ab removal (e.g., anti-HLA Ab prior to pathogen-specific Abs): Argentina hemorrhagic Pathogenic Ab removal and supplementation of fever, viral respiratory infections (experimental) Coagulation factor–related bleeding disorders Acute hypovolemic coagulopathy (see below) Acute hypovolemic coagulopathy (see below) microangiopathy or Guillain-Barré syndrome) Immune thrombocytopenia, thrombotic microangiopathy, and heparin-induced thrombocytopenia: Not recommended neurosurgery, eye surgery, or ECMO kidney transplantation) Transfusion: albumin): Plasma (thawed frozen, at room temperature, maintained at 4°C or never frozen and freeze-dried) or at 4°C

4–5 units Increased plasma fibrinogen enhancement effect) N/A 105–107 T lymphocytes/kg Disease specific (remission) stabilization until recovery status Normovolemia; bleeding Normovolemia; bleeding clinical status Infection resolution (or from neutropenia) (0.3–1 g/L) resolution resolution ABO compatible 1–2 × 1010, repeated per PC ratio, repeated per compatibility 1 RBCC/1 plasma/0.25 Willebrand factor, and factor XIII ABO compatibility is not required 10–15 mL/unit, pool of anti-A/B Ab Repeated per clinical clinical status ABO-identical or group O with low-titer Standard RBCC, PC, and plasma transfusion Appropriate ratio is under investigation; a ratio of 1 RBCC/1 plasma/0.25 PC (platelet content relation to granulocytopenia or granulocyte maintained at 4°C and without an additive transfusion Balanced provision of blood components Correct impaired granulocyte function in hematopoietic cell transplantation Graft-versus-leukemia effect (and graft Provision of fibrinogen, factor VIII, von of a whole blood) is currently favored solution and related dilution Number of platelets transfused x 10 x Body surface area (m)

( ) ( )

dysfunction Whole blood Acute hypovolemic coagulopathy requiring massive PC, and plasma) Acute hypovolemic coagulopathy requiring massive Cryoprecipitate Acute bleeding coagulopathy, type II (dysfunctional disease, hemophilia A in the absence of factor VIII granulocytes (CGD). Neutropenia can be acquired Donor mononuclear cells Relapse of malignant hemopathy after allogeneic factor) or type III (absent factor) von Willebrand Severe refractory bacterial or fungal infection (chemotherapy) or congenital. Formal proof of (mainly soft tissues and lung) in patients with neutropenia (<100/µL) or with dysfunctional CCI Postransfusion count /µL –pretransfusion count /µL efficacy is lacking. concentrates Granulocyte concentrates Multicomponent (RBCC, (apheresis or a pool of whole blood–derived aCCI calculation: granulocytes)

Abbreviations: Ab, antibody; CCI, corrected count increment; CGD, chronic granulomatous disease; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; Hb, hemoglobin; HLA, human leukocyte CHAPTER 118 antigen; N/A, not applicable; RBC, red blood cell; RBCC, red blood cell concentrate, PC, platelet concentrate; TTP, thrombotic thrombocytopenic purpura. Transfusion Therapy and Biology

TABLE 118-5 Transfusion Adverse Reactions: Main Warning Signs Fever (≥38°C) +1–2°C within 4 h FNHTR Anti-HLA immunization and cognate Ag in the blood product TRALI (with dyspnea at the forefront) +1–2°C within 15 min +/–: • Chills • Dyspnea • Hypotension • Digestive disorders • Disseminated intravascular coagulation • Hemoglobinuria

> 2°C Transfusion-transmitted bacterial infection Hypotension (≥30 mmHg decrease in systolic blood pressure) Hemolytic shock Anaphylactic shock Septic shock TRALI (with dyspnea at the forefront) Dyspnea TRALI (within 6 h of transfusion) TACO (within 12 h of transfusion) Severe allergy (immediate; within 4 h) Hemoglobinuria Intravascular hemolysis • Immunologic • Mechanical • Toxic • Thermic PART 4 Oncology and Hematology Rash <2/3 of the body within 2–3 h Minor allergy 2/3 of the body during or within 2–3 h Severe allergy 2/3 of the body within 5 min Associated with dyspnea and shock Icterus Delayed hemolysis New alloantibody Alloimmunization Rash, diarrhea, and fever occurring 2 days to 6 weeks after transfusion GVHD Gum bleeding, purpura 5–12 days after transfusion Posttransfusion purpura Cardiac, hepatic, and/or renal insufficiency in frequently transfused patients Posttransfusion iron overload Top-down investigation after a blood donor is subsequently found to be infected Transfusion-transmitted infection Bottom-up investigation after another recipient of a same blood donation is found to be infected Infectious symptoms within 6 months Abbreviations: Ag, antigen; FNHTR, febrile nonhemolytic transfusion reaction; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related

> acute lung injury. hemoglobinemia and hemoglobinuria, and elevated plasma lactate dehydrogenase and unconjugated bilirubin. The direct antiglobulin test (DAT, or direct Coombs test) that detects immunoglobulin, and pos sibly complement (C3d), on the surface of the recipient's RBC will most often be positive (Fig. 118-2). Similarly, a positive indirect antiglobulin test (IAT, or indirect Coombs test) that detects anti-RBC alloAb in the serum will also be positive. An elution of the Ab on the surface of the RBC may allow for the identification of the culprit alloAb. The management of an immune-mediated acute hemolytic transfu sion reaction is mainly supportive. Prompt interruption of the trans fusion, biological workup, and a thorough clerical check to prevent a possible second misidentified transfusion are crucial initial steps. Vigorous hydration with isotonic saline and diuretics to maintain urine output is recommended. Although often self-limiting, acute hemolysis may also require forced alkaline diuresis, correction of elec trolyte abnormalities, and pressor support as needed. In patients with DIC and severe bleeding, PC, plasma, and cryoprecipitate or fibrino gen may be required. When transfusion of incompatible RBCCs is unavoidable, prophylaxis with steroids (100 mg of hydrocortisone) just before the transfusion and repeated 24 h later and polyvalent immunoglobulin (1.2–2.0 g/kg per day over 2–3 days, initiated just before the transfusion) have been successfully used to prevent or minimize acute and delayed hemolysis. Polyvalent immunoglobulin,

Transfusion-transmitted bacterial infection Hemolysis Anaphylaxis anticomplement (C3) Ab, anti-B-cell Ab, or plasma exchange may be considered in case of severe posttransfusion hyperhemolysis in sickle cell patients. Immune-mediated hemolysis may also occur after allogeneic hema topoietic transplantation (most often involving a peripheral blood stem cell graft) or, more seldomly, solid organ transplantation. Minor ABO incompatibility, with subsequent red cell destruction in the recipient, is the most common cause of clinically significant hemolysis in such cases. Viable donor B lymphocytes, called "passenger lymphocytes," transferred passively with the graft, may produce alloAbs (including anti-D or anti-A1 in an A2 donor) that target recipient red cells. Such hemolysis has been reported to develop 5–14 days after transplanta tion. Reduced-intensity conditioning regimens and cyclosporine as prophylaxis against GVHD or rejection have been associated with increased risk. Transfusing RBCs compatible with the graft donor and the use of GVHD prophylaxis able to target B cells (e.g., methotrex ate) have significantly reduced the incidence of passenger lymphocyte syndrome. Allogeneic hematopoietic transplantation may also result in acute hemolysis due to incompatible donor-derived red cell (and precursor) destruction by the recipient alloAbs (i.e., major ABO incompatibility). Prolonged pure red cell aplasia may occur in such a situation. Graft deserythrocytation will reduce the risk of early acute hemolysis.

A Predominantly intravascular acute hemolysis occurring during or within 24 hours following transfusion Mastocyte Cytokines Chemokines TNFa IL1, 6, 8 A C1 C3a/C5a Anti-A Ab C5/C9 A Membrane attack complex formation RBC transmembrane pore Osmotic i.v. hemolysis B Predominantly extravascular acute or delayed (3 to 10 days after transfusion) hemolysis Macrophage C1 C3b RBC lysis Anti-Jka Ab Jka C3b C3d C Predominantly extravascular acute or

delayed (3 to 10 days after transfusion) hemolysis Macrophage Anti-D Ab D FIGURE 118-1 Mechanisms of transfusion hemolytic reactions. A. Acute responses will involve preexisting antibodies (Abs), naturally occurring anti-A/anti-B IgM or IgG directed against other RBC antigens (Ags) and resulting from prior sensitization. Upon interaction with cognate antigen on transfused red blood cells (RBCs), recipient allogeneic Ab (alloAb), mostly natural anti-A/anti-B IgM, may fix and activate complement up to C5/C9. Formation of membrane attack complex (MAC) will create pores in transfused RBCs with resulting intravascular hemolysis, release of toxic moieties including free hemoglobin responsible for end-organ damage including renal failure, and tissue factors contributing to occurrence of disseminated intravascular coagulation (DIC). B. Alternatively, complement activation may be incomplete, as typically observed in a delayed hemolytic transfusion reaction involving neoformed allogeneic IgG. In such cases, complement activation up to C3 results in C3b-mediated opsonization of RBCs, extravascular hemolysis, and clearance through immunophagocytosis. Anemia and jaundice will be the primary clinical manifestations. C. Lastly, alloAb may not fix complement while ensuring antibody-dependent cellular cytotoxicity (ADCC)–mediated phagocytosis of targeted RBC. (Adapted from SR Panch et al: Hemolytic transfusion reactions. N Engl J Med 381:150, 2019.)

Endothelium alterations Capillar permeability Vasodilation/Hypotension/Shock Fever DIC Hemoglobinemia Hemoglobinuria Albumin Haptoglobin HemopexinA Vasoconstriction Acute renal failure/
tubular necrosis Elimination Nitric oxide scavenging Hemoglobin Dimers Ferric heme CHAPTER 118 Transfusion Therapy and Biology Unconjugated bilirubin

- Albumin Low-level hemoglobinemia Conjugated bilirubin Partial degradation of membrane proteins Spherocytes Microspherocytes Urobilinogen Stercobilinogen Unconjugated bilirubin
- Albumin Low-level hemoglobinemia Conjugated bilirubin RBC lysis Partial degradation of membrane proteins Spherocytes Microspherocytes Urobilinogen Stercobilinogen

Positive test result Indirect Coombs test/indirect antiglobulin test PART 4 Oncology and Hematology Direct Coombs test/direct antiglobulin test Positive test result Antihuman Abs Antigens on the red blood cell surface Human anti-RBC Abs

FIGURE 118-2 Direct and indirect Coombs test. The direct Coombs/antiglobulin test detects the presence of Abs (or complement) on the surface of erythrocytes. The indirect Coombs/antiglobulin test detects Abs in the serum that may bind Agglutination of red blood cells occurs, because human Abs are attached to RBC(s). Antihuman Abs are added to the solution. Recipient’s Abs that target the donor’s RBC(s) form antibody-antigen complexes. to donor erythrocytes. Abs, antibodies; RBC, red blood cell. (Adapted from
http://upload.wikimedia.org/wikipedia/commons/1/1c/coombs_test_schematic.png.) Donor’s blood is added to the serum. Recipient’s serum is obtained, containing Abs. Agglutination of RBC(s) occurs, because human Abs are attached to RBC(s). The patient’s washed RBC(s) are incubated with antihuman Abs. Blood sample from a patient with immunemediated hemolytic anemia: Abs are shown attached to antigens on the RBC surface.

Polyvalent immunoglobulin may contain high titers of anti-A (mostly) and/or anti-B Abs and induce acute hemolysis, most often of limited severity. Such hemolysis is particularly described in group A or AB children receiving high-dose immunoglobulin, notably for Kawasaki's disease, as well as in adults treated for thrombotic thrombo cytopenic purpura. A similar mechanism may lead to hemolysis after anti-D immunoglobulin treatment for immune thrombocytopenia in RhD-positive patients. Nonimmune mechanisms of transfusion-associated hemolysis include thermal (overheated or cold BCs), osmotic (concurrent hypoosmotic perfusion), and mechanical (pressure related to high-flow transfusion filtering during cell saver processing) mechanisms. Autoimmune and drug-induced hemolytic anemias may be exacer bated by transfusion and can therefore mimic hemolytic transfusion reactions. Transfusion of RBCs with enzymatic defects may mimic immune-mediated hemolysis as well. Notably, severe hemolytic reac tions in patients receiving long-term transfusions for hemoglobinopa thies (mainly sickle cell disease) can precipitate bystander hemolysis, in addition to clearing transfused red cells. The mechanisms of this hyper hemolytic transfusion reaction may be a mediated RBC hemolysis-related systemic inflammatory response and resulting lysis of red cell precur sors by macrophages. This process may be immediate or delayed, with hemoglobin levels falling below the pretransfusion values, often to life-threatening levels. Further RBCC transfusion typically exacerbates ongoing hemolysis, with the exogenous (transfused) allogeneic Ags probably triggering further nonspecific hemolysis. Febrile Nonhemolytic Transfusion Reaction The most fre quent reaction associated with the transfusion of cellular BCs is FNHTR (up to 300 per 105 BCs). This reaction is characterized by chills and rigors and a ≥1°C rise in body temperature and is caused by pro inflammatory cytokines in the BC or by recipient Abs directed against donor cell Ags present in the BC. FNHTR is diagnosed when other causes of fever, notably infection and hemolysis, have been excluded. Leukocyte reduction, especially prestorage, can prevent the occurrence of FNHTR. Moreover, the use of additive solutions decreases FNHTR frequency associated with PC transfusion. Premedication with anti pyretics has generally proven ineffective at decreasing the rate of such reactions and may mask relevant clinical symptoms. Allergic Reactions Most allergic transfusion reactions are mild and include rash, pruritus, urticaria, and localized edema. More rarely, allergic reactions may be severe to life-threatening with an anaphylactic reaction that can involve bronchospasm, respiratory distress, hypoten sion, nausea, vomiting, and shock. Frequencies of mild and severe allergic reactions are ~100 and ~5 per 105 BCs, respectively. Allergic reactions are related to plasma proteins found in transfused components. Mild reactions may be treated by temporarily stopping the transfusion and administering antihistamine drugs. Patients with a history of aller gic transfusion reaction may be premedicated with an antihistamine, although there is no consensus on this issue. Cellular components can be washed to remove residual plasma for extremely sensitized patients. Most of the allergic presentation may not depend on preformed Abs and may be attributable to soluble mediators triggering histamine and serotonin release from platelets and leukocytes. An anaphylactic reac tion may occur after the transfusion of only a few milliliters of the BC. Treatment includes stopping the transfusion, maintaining vascular access, and administering adrenaline (0.3–0.5 mg subcutaneously). Additional treatment with steroids, antihistamine drugs, and bronchodi lators may also be required. Patients who are IgA deficient (<1% of the population) may be sen sitized to this immunoglobulin isotype and may be at risk of anaphy lactic reactions associated with plasma transfusion. As a precaution, individuals with severe IgA deficiency should therefore receive, where available, IgA-deficient plasma and washed cellular BCs. Patients who have anaphylactic or repeated allergic reactions to BCs should be tested for IgA deficiency. It should be noted that the importance, or even the reality, of such a transfusion-related allergic risk

is currently debated.

Graft-Versus-Host Disease GVHD is an extremely rare adverse reaction caused by transfusion, although it is a frequent complication of allogeneic hematopoietic transplantation. Transfusion-related GVHD is mediated by engrafted donor T lymphocytes in a recipient unable to reject such allogenic lymphocytes (as in severely immunosuppressed patients or patients homozygous for an HLA haplotype shared with the donor). Such donor T lymphocytes interact with host HLA Ags and mount an immune response, which is manifested clinically by the development, 5–10 days after transfusion, of cytopenia, fever, a characteristic skin rash, diarrhea, and liver function abnormalities. Transfusion-associated GVHD is highly resistant to treatment with immunosuppressive therapies as well as ablative therapy followed by allogeneic bone marrow transplantation and is fatal in >90% of cases. Prevention in at-risk patients relies on the irradiation of cellular BCs (minimum of 25 Gy) or treating BCs with pathogen reduction technol ogy that will deplete all living cells in the component. At-risk patients include patients with inherited immune deficiency, patients undergo ing autologous or allogeneic hematopoietic transplantation, patients treated with immunosuppressive drugs such as purine or pyrimidine analogues, anti-CD52 Ab, or antithymocyte globulin, fetuses receiving intrauterine transfusions, and recipients of BCs provided by a blood relative. Because granulocyte concentrates contain a large number of lymphocytes, they should always be irradiated.

CHAPTER 118 Transfusion-Related Acute Lung Injury TRALI is character ized by the occurrence or worsening of hypoxia and noncardiogenic pulmonary edema with bilateral interstitial infiltrates on chest x-ray during or within 6 h after transfusion, although delayed cases may occur up to 72 h later. Frequency of TRALI is BC dependent and ranges, on average, from 0.5 to 10 per 105 BCs. TRALI may be dif ficult to distinguish from other causes of hypoxia, such as circulatory overload, and is among the most common causes of transfusion-related fatalities. Treatment is supportive only. TRALI usually results from the transfusion of donor plasma that contains high-titer anti-HLA class II Abs that bind recipient cognate Ag. Anti-HLA class I and anti-HNA Abs may also be involved. TRALI mediated by cytokines and chemo kines in the absence of an HLA-mediated interaction may occur also. Leukocytes, especially when primed by either a bacterial moiety such as lipopolysaccharide or a cytokine/chemokine, aggregate in the pul monary vasculature and release inflammatory mediators. The transfu sion of plasma and PCs from male donors and nulliparous or parous female donors without anti-HLA Abs has significantly reduced the risk of TRALI where implemented. Recipient factors associated with an increased risk of TRALI include smoking, chronic alcohol use, shock, liver surgery (transplantation), cancer surgery, mechanical ventilation, and positive fluid balance. Transfusion Therapy and Biology Posttransfusion Purpura This rare reaction (~1/105 BCs) is defined as a thrombocytopenia-related bleeding disorder developing 5–12 days after PC (and more rarely RBCC) transfusion, predominantly in women. Platelet-specific alloAbs are found in the recipient, most fre quently anti-HPA-1a in HPA-1a-negative alloimmunized individuals. The delayed thrombocytopenia is due to a secondary increased produc tion of alloAbs. The mechanisms for the destruction of the patient’s own platelets remain unclear. Management is mostly supportive but may require polyvalent immunoglobulin, glucocorticoids, or plasma exchange. Additional platelet transfusions may worsen the thrombocy topenia or be associated with poor increments. Prevention of recurrence includes use of washed BCs or BCs from HPA-compatible donors. Alloimmunization/Platelet Refractoriness A recipient may become alloimmunized to a number of Ags on cellular blood elements and plasma proteins. AlloAbs to RBC

Ags are detected during pre transfusion testing, and their presence may delay finding Ag-negative crossmatch-compatible products for transfusion. Women of childbear ing age who are sensitized to RBC Ags (i.e., D, c, E, Kell, or Duffy) are at risk of bearing a fetus with hemolytic disease of the fetus or new born. Ag matching is the only pretransfusion selection test to prevent RBC alloimmunization, which is found to occur with a frequency of

~100/105 RBCC transfusions. Alloimmunization to Ags on leukocytes and platelets, most often anti-HLA Abs, can result in refractoriness to PC transfusions (as defined by a low increase in platelet count after transfusion). Once alloimmunization has developed, HLA-compatible (crossmatched) PCs should be preferred if available. If not, repeated PCs at shortened intervals may be considered. Use of leukocytereduced cellular BCs will reduce the incidence of immunization. Transfusion refractoriness may also result from an anti-HPA alloim munization, although less commonly. Recipient factors associated with platelet refractoriness include fever, splenomegaly, bleeding, DIC, and medications such as amphotericin B. Notably, cold-stored (and cryo preserved) PCs have been found to have preserved hemostatic function in acutely bleeding patients despite poor platelet increments.

Immunomodulation Transfusion of allogeneic blood may be associated with immunosuppression, as evidenced early on by the beneficial effect of pretransplant transfusion on kidney graft survival. The intensity of such an effect is debated and, if present, is most prob ably attenuated with leukoreduced BCs. Transfusion-related immu nomodulation is indeed thought to be mainly mediated by donor leukocytes, whether transfused to the recipient or undergoing apopto sis during storage. However, leukoreduced RBCCs or PCs still release immunomodulatory mediators during storage. These mediators, along with the transfused RBCs or platelets, may exert various, possibly opposing, immune effects in vivo, including immunosuppression and inflammation. PART 4 Oncology and Hematology ■ ■NONIMMUNOLOGIC TRANSFUSION ADVERSE REACTIONS Fluid Overload TACO is a common and underrecognized transfu sion adverse reaction. Estimated frequencies vary from ~10 to 100 per 105 BCs. TACO is now the main cause of death from transfusion since the TRALI risk has been mitigated. Risk factors include older age, renal failure, preexisting fluid overload, cardiac dysfunction, administration of a large volume of BCs, and an excessive rate of transfusion in rela tion to the patient’s hemodynamic tolerance. TACO results in dyspnea, hypoxia, bilateral and predominantly alveolar infiltrates on chest x-ray, frequent systolic hypertension, and elevated brain natriuretic peptide. Fever may also exist. Prevention involves identifying at-risk patients, close monitoring, a slow transfusion rate (1 RBCC over 3–4 h), and use of diuretics in hemodynamically stable patients with a history of TACO. Treatment requires stopping the transfusion and administrat ing oxygen and diuretics. Massive Transfusion-Associated Reactions/Electrolyte and Cold Toxicity Reactions Reactions related to massive transfu sion, i.e., transfusion of 50% of the patient’s total blood volume over 3 h or >5–10 units of RBCCs (plus associated BCs), include citrate toxic ity, hypothermia, hyperkalemia, and dilutional coagulopathy. Citrate, which is commonly used to anticoagulate BCs, chelates calcium. Hypo calcemia, manifested by circumoral paresthesia, and changes in cardiac function may result from multiple rapid transfusions. Although citrate is quickly metabolized to bicarbonate, calcium infusion (through a separate line) may be required. Rapid transfusion of BCs still at 4°C can result in hypothermia and cardiac dysrhythmias. Use of an inline warmer will prevent this complication. RBC leakage during storage, longer storage, and irradiation increase the concentration of potassium in the unit. Neonates and patients with renal failure or other comor bidities (e.g., hyperglycemia or

hypocalcemia) are at risk of hyperka lemia and resulting acute cardiac toxicity. Treatment includes insulin, glucose, calcium gluconate, and furosemide, and prevention includes the use of washed or plasma-reduced RBCCs or a storage age of <7–10 days and the avoidance of RBCCs stored for >24 h after irradiation. Iron Overload Each RBCC contains 200–250 mg of iron. In fre quently transfused recipients, iron accumulation that is left untreated will affect endocrine, hepatic, and cardiac function. Death may occur from cardiac failure or arrhythmia. Iron overload can be assessed by means of serum ferritin measurements, magnetic resonance imaging,

and liver biopsy. Prevention and treatment of this frequently under reported transfusion adverse event rely on careful monitoring and iron chelation. Hypotensive Reactions Acute hypotensive transfusion reactions are defined as an abrupt drop in blood pressure of >30 mmHg early after the start of transfusion and resolving quickly once the transfusion is stopped, without further intervention. Respiratory, gastrointestinal, or mild allergic reactions may also be present. Estimated frequency is 1–10/105 BCs. These reactions may result from the generation of vaso active kinins in the BCs and are more likely to occur in hypertensive patients taking angiotensin-converting enzyme (ACE) inhibitors who are therefore less able to metabolize bradykinin. Upon resolution, the same blood product should not be restarted. Switching from an ACE inhibitor to an alternative drug should be considered for patients requiring further transfusions. Adverse Transfusion Reactions of Uncertain Imputability

Necrotizing enterocolitis, which is common in preterm and very-lowbirth-weight neonates, has been infrequently described with close tem poral association with RBC transfusion. However, the causality of any association remains to be further ascertained, as does the efficacy of withholding feeds during transfusion to prevent such a complication. Posterior reversible encephalopathy syndrome is a rare syndrome char acterized by acute reversible neurologic symptoms related to subcorti cal vasogenic brain edema. It has been described within 10 days after RBCC transfusion, mainly in women with severe (and long-standing) anemia. The prognosis is most often favorable, although irreversible neurologic disturbance has been described. Prevention may include avoiding rapid correction of chronic severe anemia. Again, causality remains to be established. ■ ■INFECTIOUS ADVERSE REACTIONS Donor screening involves the selection of healthy donors without highrisk lifestyles, medical conditions, or exposure to transmissible patho gens. Tests are performed on donated blood to detect the presence of pathogens by testing for relevant Abs or Ags or by directly detecting infectious agents by nucleic acid amplification. Increasing sensitivity of testing methods has progressively narrowed the “window” period early on after infection during which a low-titer undetectable pathogen may be present in the blood and result in a transfusion-transmitted infection. Transfusion-transmitted bacterial infection remains a significant concern, notably with PCs stored at room temperature, which allows for bacterial proliferation. However, some gram-negative bacteria such as Yersinia can grow at 4°C and therefore may be implicated in infec tions related to RBCC transfusion. Recipients of contaminated BCs may develop abrupt (during transfusion and up to several hours after) fever and chills, which can deteriorate to septic shock, DIC, and death. Endotoxin formed within the BC may be implicated. After sampling for bacterial culture, broad-spectrum antibiotics should be promptly initiated. Pathogen reduction of PC and plasma, and perhaps soon of RBCCs as well, offers an additional means of reducing transfusion infection risks. Although effective for a wide range of pathogens, such processes are most often ineffective for bacterial spores and nonenveloped viruses such as hepatitis A virus, parvovirus B19, and hepatitis E virus. Postdonation information (i.e., fever occurring within 24 h after dona tion)

allows the involved BCs to be quarantined and may provide an additional safety measure. Transfusion-transmitted infections are increasingly rare. However, new or previously unidentified infectious risks may occur, as high lighted by the emergence of the transfusion-associated West Nile virus infection and babesiosis in early 2000 in the United States, as well as transfusion-associated hepatitis E in early 2010 in Europe. Such occurrences require active surveillance programs and the appropri ate implementation of mitigation measures such as additional test ing, pathogen reduction, and travel-related deferral criteria. Along with West Nile virus, a number of other arbovirus-related infections

TABLE 118-6 Infectious Transfusion Adverse Events DONATION PREVALENCE

(/104 BLOOD DONATIONS) PATHOGEN Bacteria Pyogenic bacteria PC: 10–20 Venipuncture sepsis, diversion of the initial 10–30 mL of blood, bacterial detection, pathogen reduction (for PC) Treponema pallidum (syphilis) ~1a Serologyb,c <0.01 Virus HIV-1/2 ~0.1 Serology, NAT (+/– p24 Ag)b,c 0.1–1d HBV ~0.5 Serology, NATb,c <0.5 (3 without NAT)d HCV 0.2–1.2 Serology, NATb,c <0.1–1d HTLV-1/2 0.05–0.1a Serology, BC leukocyte reduction b,c 0.1–0.3d HEV 0–10 (in endemic regions) NAT Endemic regions: <0.1 with NAT; a transmission rate from infected donors of ~50% has been reported CMV Undetermined Serology, BC leukocyte reductionb,c <0.1 in leukocyte-reduced BCs Parvovirus B19 ~0.5 with viral DNA >106 IU/mL,e up to 100 overall West Nile virus Up to 3 in high season endemic regionsa NATb High season endemic regions: <1 with NAT Parasitef Plasmodium (malaria) ~4 (40–>50 in donors from endemic regions)a Serology (NAT soon available) <0.1 in nonendemic regions Babesia ~90 (in endemic regions)a Serology (NAT implementation underway) Trypanosoma cruzi (Chagas disease) ~0.14 in donors/mothers from endemic regionsa Serology, leukocyte reduction ND aAs assessed based on seropositivity, i.e., including a varying percentage of individuals not harboring the pathogen in their blood. bPrevention measures may also include pathogen reduction (for PC and plasma), cPrevention measures may also include a quarantine of the (cryopreserved) BC pending a negative serology on a subsequent donation (for plasma), dEstimated residual risk. eTransfusion risk deemed as absent below this threshold, fVisceral leishmaniasis is a transfusion risk as well in endemic regions, a risk that may be mitigated by leukocyte reduction. Note. Other pathogens associated with transfusion-transmitted infections at a very low frequency include arboviruses other than West Nile (dengue, Zika virus), hepatitis A, human herpesvirus-8, Japanese encephalitis virus, tick-borne encephalitis virus complex, and the prion responsible for variant Creutzfeldt-Jakob disease (4 cases in the United Kingdom, in the context of the bovine spongiform encephalopathy epidemic, before implementation of systematic leukocyte reduction). Abbreviations: Ag, antigen; BC, blood component; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HTLV, human T-cell leukemia virus; NAT, nucleic acid detection test; ND, not determined; PC platelet concentrate; RBCC, red blood cell concentrate. possibly transmissible by blood transfusion are endemic or involved in epidemic outbreaks. Despite being possibly present in the blood at asymptomatic phases of the disease, documented cases of transfusiontransmitted infections involving these arboviruses have been very rare (Zika), often without a discernible clinical impact (Dengue), or absent (Chikungunya). Route of infection (i.e., intravenous vs mosquito bite), pathogen dose, storage conditions, recipient immune status, and ongo ing treatments may all impact the ability of a pathogen in the donor to induce a disease in the recipient. Estimated frequencies of transfusionrelevant infections in donors and of transfusion-transmitted infections are reported in Table 118-6. Such frequencies depend heavily on vari ables such as local epidemiology, donor

deferral rules, risk reduction measures, and data reporting, and may vary considerably. ALTERNATIVES AND PERSPECTIVES In addition to promoting appropriate transfusion indications, patient blood management programs have highlighted several transfusionsparing strategies, such as the treatment of iron deficiency before surgery and minimization of blood loss. Antifibrinolytic agents such tranexamic acid (TXA) have been shown to be effective in preventing bleeding complications in various forms of hemorrhage. Erythropoi etin stimulates erythrocyte production in patients with anemia from chronic renal failure and other conditions. Thrombopoietin recep tor agonists may reduce platelet transfusion needs resulting from chemotherapy-induced thrombopenia. Bone marrow transplantation and gene therapy approaches, including CRISPR-Cas9-mediated gene

PREVENTION MEASURES

(IN ADDITION TO DONOR DEFERRAL) INFECTION PREVALENCE IN RECIPIENTS

(/106 BLOOD PRODUCTS TRANSFUSED) Sepsis: PC: 5–30; with bacterial detection: <1 to 10; with pathogen reduction: <1 RBCC: <0.2 NAT Most adults are immune to parvovirus B19; up to 0.12% in seronegative adults has been reported CHAPTER 118 ND (0.04% donors may be within the serology window period) Transfusion Therapy and Biology editing, dramatically reduce the transfusion needs in patients with sickle cell or major thalassemia. Stem cell–derived blood cells such as RBCs or platelets may in the future become a suitable alternative to rare blood donors. Importantly, issues surrounding transfusion safety now fully encom pass transfusion efficacy. Linked large-scale databases pertaining to blood donors and transfused patients will also be instrumental in further assessing and understanding the basis of transfusion safety and efficacy. Optimal transfusion care will soon require consideration of new criteria in relation to donor, blood product, and/or recipient characteristics. Acknowledgments The authors are indebted to Jeffery S. Dzieczkowski and Kenneth C. Anderson who co-authored the chapter in a previous edition and expertly paved the way for this chapter. ■ ■FURTHER READING Carson JL et al: Red blood cell transfusion 2023 AABB International guidelines. JAMA 330:1892, 2023. Delaney M et al: Transfusion reactions: Prevention, diagnosis, and treatment. Lancet 388:2825, 2016. Panch SR et al: Hemolytic transfusion reactions. N Engl J Med 381:150, 2019. Stanworth SJ, Shah A: How I use platelet transfusions. Blood 140:1925, 2022.

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