Transfusion and transplantation 5563 22.8.1 Blood

Transfusion and transplantation 5563 22.8.1 Blood transfusion 5563 D.S. Giovanniello and E.L. Snyder

CONTENTS 22.8.1 Blood transfusion 5563 D.S. Giovanniello and E.L. Snyder 22.8.2 Haemopoietic stem cell transplantation 5579 E.C. Gordon-Smith and Emma C. Morris 22.8.1 Blood transfusion D.S. Giovanniello and E.L. Snyder ESSENTIALS Transfusion of blood components is a life-saving treatment for pa- tients with severe haemorrhage and can also be used to replace co- agulation factors and to ameliorate the effects of severe anaemia, thrombocytopenia, and impaired platelet function. However, blood transfusion has many hazards, hence its use should always be con- sidered carefully and restricted to those who will gain benefit that outweighs the risks. General considerations Safe administration of blood components requires secure processes from vein to vein to prevent the incorrect blood product from being given to the wrong patient. Reduction in transfusion risks is also achieved by (1) robust arrangements for the collection, storage, and delivery of appropriate supplies of blood products to their point of need; (2) better understanding of the antigenic structures on blood cells and the widespread introduction of advanced blood-group typing methods, screening for antibodies, and testing for compati- bility before transfusion; (3) identification and screening for agents present in donors, as well as the use of sterile disposable materials; and (4) comprehending the benefit of treating anaemia with the need to avoid unnecessary transfusion, with its associated costs and potential harm. Blood group systems—these include (1) the ABO system—the codominantly expressed A and B genes code for

glycosyltransferases that add either N-acetyl-d-galactosamine (A gene) or -d-galactose (B gene) to the common precursor H antigen. Anti-A and Anti-B anti- bodies are ‘naturally occurring’ and responsible for most haemolytic transfusion reactions. (2) The Rh system—the most clinically im- portant Rh antigen is D because it is strongly immunogenic; anti-D is responsible for immune reactions including haemolytic disease of the newborn and immune-mediated transfusion reactions. (3) Other clinically significant blood group antigens—these include Kell (K), Duffy (Fy), Kidd (Jk), and the MNS systems; multiple antibodies can develop when the range of red cell antigens in the donor population differ from that of patients who require repeated transfusion. Clinical use of blood components Cellular components, namely those containing red blood cells, platelets, and white blood cells, have specific clinical use and in- dications. These products and their respective indications include (1) red blood cells—symptomatic anaemia; (2) leucocyte-reduced components (red blood cells and platelets)—symptomatic an- aemia, reduce febrile reactions from leucocyte antibodies, alterna- tive to cytomegalovirus (CMV)-negative components, prevent HLA alloimmunization; (3) washed components (red blood cells and platelets)—remove harmful plasma substances that contribute to al- lergic transfusion reactions and remove antibodies that may lead to adverse reactions; (4) platelet components—thrombocytopenia with bleeding, prophylactic transfusion, platelet function abnormalities; and (5) granulocytes (obtained by apheresis)—for neutropenic pa- tients with an infection unresponsive to antibiotics but who have a reasonable expectation for recovery (rarely used, given increased use of haemopoietic growth factors in haematological practice); donor lymphocyte infusions can induce remission of disease and improve survival by exerting a graft-versus-leukaemia effect in some bone marrow transplant recipients. Noncellular products include plasma, cryoprecipitate, and plasma derivatives. Respective indications include (1) fresh frozen plasma—replacement of plasma coagulation factors for which spe- cific factor concentrates are not available, liver disease, dissemin- ated intravascular coagulation, hypofibrinogenaemia, thrombotic thrombocytopenic purpura, dilutional coagulopathy, and reversal of vitamin K antagonists or vitamin K deficiency in the setting of major bleeding;
(2) cryoprecipitate—fibrinogen and factor XIII re- placement, factor VIII and von Willebrand factor replacement when recombinant and virus-inactivated concentrates are not available;
(3) albumin—used principally in specialized surgical practice, replace- ment fluid in therapeutic plasma exchange, and in the treatment of

 liver disease; and (4) intravenous immunoglobulin—used principally for immunodeficiency syndromes, autoimmune rheumatic/vascu- litic diseases, Guillain–Barré syndrome, and autoimmune haemo- lytic anaemias; specific Rh (D) immunoglobulin is used to prevent alloimmunization in D-negative mothers; specific immunoglobulin preparations are used as antivenoms and to treat viral infections (e.g. hepatitis A and B). Complications of transfusion therapy Complications of transfusion therapy can be divided into two broad categories—immune and nonimmune complications. Immune complications include (1) acute intravascular haemolytic reactions— usually caused by transfusions of ABO-incompatible blood resulting from patient identification or clerical errors; manifest with sudden onset of back pain, hypotension, tachycardia, fever, chills, diaphor- esis, and dyspnoea; treatment consists of immediately stopping the transfusion and providing supportive care, but can be fatal despite best management; (2) delayed haemolytic reactions—usually caused by an antibody that is initially of a titre below the limits of detection on routine screening; (3) febrile nonhaemolytic reactions—usually attributed to the development of antibodies in the recipient dir- ected against HLA and/or leucocyte-specific antigens on donor white blood cells and platelets, or alternatively, may be

attributed to the passive transfusion of cytokines, such as interleukin (IL)-1, IL-6, IL-8, and tumour necrosis factor-α, which are generated and accumulate during the storage of blood components; (4) allergic reactions—IgE mediated; IgA-deficient patients are particularly prone to anaphylactic reactions; (5) transfusion-related acute lung injury, most commonly attributed to the passive transfusion of blood donor antibodies directed against HLA antigens to the recipient, or less commonly, attributed to the passive transfusion of blood donor antibodies directed against human neutrophil antibodies; and (6) transfusion-associated graft-versus-host disease, resulting from an attack by viable immunocompetent donor lymphocytes on the recipient's antigen presenting tissues. This immunological assault is manifested clinically by damage to skin, liver, gastrointestinal tract, and bone marrow. Nonimmune complications include (1) infection and septic trans- fusion reactions, with organisms commonly implicated including Gram-positive (staphylococci) and Gram-negative (enterobacter, yersinia, pseudomonas) bacteria. Other infections that may be trans- mitted from the donor include malaria, babesiosis, syphilis, leish- mania, toxoplasmosis, and viral infections such as hepatitis B and C, HIV-1, HIV-2, and West Nile virus. Immunocompromised recipi- ents are also at risk from human cytomegalovirus and parvovirus (erythrovirus) B19. A few patients have been shown to have acquired variant Creutzfeldt–Jacob disease, probably as a result of transfu- sion from latently affected donors.
(2) Other complications—acute problems can include circulatory overload, dilutional coagulopathy, hypocalcaemia, and hypothermia; complications of multiple blood transfusions include iron overload. The focus of many haemovigilence programmes has been in the prevention of these aforementioned complications. Risks of alloimmunization from donor erythrocytes and leucocytes and trans- mission of viruses can be avoided or reduced by (1) autologous blood salvage during surgery or acute normovolaemic haemodilution im- mediately before surgery; and (2) improved methods for leucocyte reduction and inactivation of infectious agents (pathogen reduction/ pathogen inactivation). Despite much research, the introduction of blood substitutes has yet to be realized in clinical practice. Use of purified recombinant haematopoietic growth factors (e.g. erythro- poietin, granulocyte colony-stimulating factor) has reduced the need for transfusion of blood products in many patients. Introduction Transfusion medicine and blood banking is a speciality that has evolved over the years. With greater understanding of red cell, platelet, and leucocyte antigen structure and function, transfu- sion therapy has improved. In addition, understanding current and emerging infectious agents ensured patient safety. Blood banking involves donor eligibility and testing, collection, processing, and storage of blood components. The transfusion medicine service in a hospital maintains necessary and vital activities contrib- uting to successful blood transfusion. These functions include pretransfusion testing, compatibility testing, additional processing (e.g. washing, irradiation), and the evaluation of transfusion reac- tions. Transfusion medicine has expanded over recent decades to include multiple disciplines, such as therapeutic apheresis, cellular therapy, and tissue banking. One of the most important techno- logical improvements in transfusion therapy was the development of sterile, disposable, and flexible plastic containers that allow sep- aration of whole blood into cellular (e.g. red cells, platelets) and noncellular (e.g. plasma, cryoprecipitate) components, known as apheresis, derived from Greek word aphaeresis, meaning 'to take away.' This technology allows the blood of a donor or patient to pass through an apparatus that separates out one particular constituent and returns the remainder to the circulation. Anticoagulants and additives currently used to collect blood allow storage of liquid sus- pensions of concentrated red cells for 35 to 42 days. These advances have essentially eliminated the use of whole blood. Blood transfu- sion is used to treat patients with severe anaemia, haemorrhage, thrombocytopenia, and coagulation disorders. Although the haz-

ards of blood replacement are relatively small, the expected benefit of a transfusion must outweigh the risk to the patient. Therefore, a thorough understanding of the indications of blood transfusion is required to minimize unnecessary blood replacement and to pre- vent wastage of limited blood resources. Clinicians who prescribe blood transfusion must also be familiar with the risks and be able to recognize and treat transfusion reactions. Blood collection and processing Blood donation is either autologous or allogeneic, collected and processed from whole blood or by apheresis procedure. Most of the red blood cells (RBCs) and plasma manufactured in the United States of America are from whole blood collections. Conversely, the majority of the platelets manufactured in the United States of America are collected by an apheresis procedure. The donor se- lection process includes a health history, a directed mini phys- ical exam, and donor questionnaire, which contains questions to protect the recipient from acquiring a transfusion-transmitted

22.8.1 Blood transfusion 5565 infection or immune-mediated transfusion reaction, and to pro- tect the donor from suffering an adverse reaction after donation. This process also helps to ensure the donor's ability to tolerate the collection procedure. Whole blood is collected and subsequently undergoes processing and separation into its components by cen- trifugation. There are two schemata in processing whole blood: the United States of America uses the platelet-rich plasma method, while Canada and Europe uses the Buffy coat method. The differ- ence between them relates to use of different g forces during the primary and secondary centrifugation steps. This is illustrated in Fig. 22.8.1.1. Pretransfusion testing Pretransfusion testing is performed to prevent the transfusion of incompatible blood that could result in a haemolytic transfusion reaction. It includes ABO and Rh D typing, antibody detection, identification, and compatibility testing. The steps of pretransfusion testing prior to issuing a unit of RBCs are illustrated in Fig. 22.8.1.2. When a patient blood sample is delivered to the blood bank and appropriate patient identification is performed, the specimen is centrifuged and tests are performed on either serum or plasma. Processing schemas WBD USA Canada and Europe High centrifugation g force High centrifugation g force Low centrifugation g force Low centrifugation g force White blood cells RBC PC Plasma PC PC PC PC PC PC Pooled platelets Cryoprecipitate Cryo-reduced plasma Plasma Plasma RBC PRP Buffy coat Fig. 22.8.1.1 Processing schemas. WBD, whole blood donation; PRP, platelet rich plasma; PC, platelet concentrate; RBC, red blood cell. Transfusion order Blood sample collection ABO and Rh D typing Antibody screen Positive screen Autocontrol Positive Autoantibody Coombs' test IgG Warm Cold Eluate Phenotype Identify the AB Panel of cells Alloantibody Negative C3 Crossmatch compatible Negative screen Crossmatch compatible/ Least incompatible/ Phenotypically matched Antigen negative/ Crossmatch compatible Fig. 22.8.1.2 The steps of pretransfusion testing prior to issuing a unit of RBC.

section 22 Haematological disorders 5566 The tests in the blood bank are serological, based on the agglutin- ation reactions that result from antigens on the RBCs interacting with antibodies. The first test is identifying patient ABO and Rh D type, using commercially available reagents. During 'front typing', red cells are reacted with antibodies directed against the A, B, and D antigens. Blood grouping is confirmed during 'back typing' in which serum/plasma is tested for the presence of expected anti-A and anti- B antibodies. This is followed by an antibody screen (known as the indirect antiglobulin test or indirect Coombs' test) performed by incubating patient serum/plasma with two to four reagent red cells with a predetermined antigen phenotype that in sum will cover all common and clinically significant alloantibodies. If an antibody is present in the serum/plasma, it will react with the screening cell(s) and cause red cell agglutination. Antibody screening is

commonly performed at room temperature (immediate phase), after incu- bating serum/plasma and test red cells at 37°C, and after incuba- tion with antihuman globulin serum (Coombs' phase). The screen will detect the presence of antibodies formed against foreign RBC antigens (i.e. alloantibody) or against self (i.e. autoantibody). When an alloantibody is suspected by a positive screen and a negative autocontrol (patient plasma/serum mixed with patient RBCs), an antibody identification panel is performed that is an indirect antiglobulin test using serum/plasma tested against a larger com- mercial 'panel' of group O reagent red cells from donors with pre- determined phenotypes. If a pattern is detected, the specificity of the alloantibody can usually be identified. This is followed by per- forming a patient phenotype to detect the presence or absence of the antigen on the patient RBCs to which the antibody is directed. The patient phenotype in the case of an alloantibody should be nega- tive. In some cases, a patient's serum may react with all panel cells. These 'panagglutinins' can be caused by (1) a single antibody dir- ected against a high incidence antigen present on all panel test red cells; (2) multiple antibodies that in total react with all test cells; or (3) an autoantibody, in which case the patient's serum will also react with his or her own red cells. Autoantibodies will have a positive screen, a positive autocontrol, and a positive direct antiglobulin test (Coombs' test). If complement is coating the RBCs (C3), the auto- antibody is a cold reacting IgM. In the case of an IgG coating the RBCs, it is a warm autoantibody and an eluate should be performed to identify the specificity of the antibody that is coating the RBCs. This is performed by dissociating antibodies from the sensitized RBC (elution) and performing an antibody identification panel. Once the antibody is identified, compatibility testing will follow prior to issuing RBCs. Blood bank tests are performed using the tube testing system in which red cell agglutination is identified in standard test tubes. A number of newer systems are being used to detect antigen–antibody reactions. These include gel systems based on the differential mobility of red cell agglutinates through gel col- umns and capture systems in which test red cells are immobilized on microtitre plates. Newer automated and semiautomated systems are rapidly replacing tube testing for the majority of ABO grouping, Rh typing, antibody screening, and crossmatching. Blood group systems Blood group antigens are proteins and carbohydrates attached to lipids or proteins. These antigens are found on the surface of the RBCs. Some of these antigens are found on other blood cells, tissues, and secretions in addition to the RBCs. There are 33 blood group systems known to date and over 290 antigens identified. ABO system The most clinically important blood group antigens belong to the ABO system. The codominantly expressed A and B genes, located on chromosome 9, code for glycosyltransferases that add either N- acetyl-d-galactosamine (A gene) or -d-galactose (B gene) to the common precursor H antigen (Table 22.8.1.1). Group O individ- uals lack functional transferases due to a single base deletion in the A gene that eliminates its production. The AB antigens are of critical importance because individuals who lack the A and/or B antigens form IgM and IgG antibodies directed against the missing antigen(s). Circulating A and B antibodies can fix complement and cause intravascular haemolysis. Anti-A and Anti-B antibodies are 'naturally occurring', that is, they are formed without prior clinical antigenic stimulation. Presumably, individuals become immunized following exposure to carbohydrate ABO antigenic determinants commonly found in the bacterial environment. Accordingly, group A individuals produce anti-B, group B produce anti-A, and group O produce both anti-A and anti-B, as well as anti-A,B, an IgG anti- body. It is worth noting that this anti-A,B antibody produced by group O individuals can cross the placenta and potentially lead to haemolytic disease of the newborn in non-group O neonates. Circulating A and B antibodies are of critical importance in blood therapy because they are responsible for most major haemolytic transfusion reactions. Rh system The Rh blood group system is composed of at least 50 distinct antigens. The five major

antigens in the Rh system (D, C, c, E, and e) are responsible for most Rh-related transfusion incompatibility. It is now known that the D polypeptide is encoded at the RHD locus, whereas the CcEe polypeptide is coded by alleles at the RHCE locus; both are found on chromosome 1. Based on the D gene frequency in Table 22.8.1.1 ABO blood group system ABO type Gene(s) Enzyme coded by gene Resulting antigen Antibody present in plasma Frequency (white population) O H L-fucosyl transferase H Anti-A, anti-B, anti-A,B 0.43 A H,A L-fucosyl transferase and N-acetyl-d-galactosamine transferase H,A Anti-B 0.45 B H,B L-fucosyl transferase and d-galactosyl transferase H,B Anti-A 0.09 AB H,A and B L-fucosyl transferase and N-acetyl-d-galactosamine and d-galactosyl transferase H,AB None 0.04

22.8.1 Blood transfusion 5567 North America and Europe, approximately 15% of individuals will not produce D antigen and are 'Rh negative'. Very rare individuals who lack all Rh antigens are termed 'Rh-null'. Rh-null red cells are morphologically abnormal and typically have shortened survival, resulting in a mild haemolytic anaemia. The most clinically important Rh antigen is D because it is strongly immunogenic; the likelihood of a D-negative person developing anti-D following exposure to as little as 0.1 ml of D-positive red cells is extremely high. Anti-D is responsible for immune reac- tions including haemolytic disease of the newborn and immune- mediated transfusion reactions. Despite widespread use of Rh immune globulin, anti-D remains a most common cause of serious haemolytic disease of the newborn. Rh-negative women most com- monly produce anti-D after exposure to D-positive red cells during pregnancy, a miscarriage, or abortion. The anti-D formed is of the IgG class and therefore can cross the placenta where it may cause po- tentially fatal intrauterine haemolysis in an Rh-positive fetus. Other blood groups Other well-characterized, clinically significant blood groups in- clude Kell (K), Duffy (Fy), Kidd (Jk), and MNS systems. Antibodies to these blood group antigens may form following exposure to the corresponding antigens during transfusion or pregnancy and are associated with immune-mediated red cell destruction of trans- fused cells and haemolytic disease of the newborn (Table 22.8.1.2). In most cases, compatible blood can be found for patients with red cell alloantibodies. Based on the high incidence of some red cell antigens among specific donor populations, however, some patients may be difficult to transfuse if they have developed multiple anti- bodies. This is particularly true in patients with sickle cell disease and other red cell disorders who require frequent transfusions. Table 22.8.1.2 lists the antigen frequencies of the most clinically relevant blood groups. Certain blood groups are known to have particular disease asso- ciations. The Kell system is linked to chronic granulomatous dis- ease, a congenital disease in which a decreased oxidative capacity of neutrophils leads to recurrent, severe bacterial infections. The genetic defect seen in chronic granulomatous disease is located on the X chromosome near the Kx Kell locus, mutation at that locus re- sults in depressed expression of the Kell antigens. Abnormalities de- scribed in this disease include acanthocytic red cells that are prone to mild haemolysis, cardiomyopathy, areflexia, and skeletal myop- athies: this is known as the McLeod phenotype. The Duffy antigens, which occur at a much lower incidence among African populations, have an interesting association with malaria. Specifically, Fy(a–b–)- negative red cells are resistant to Plasmodium vivax and P. knowlesi infection. Red cells from most West African black people are Fy(a– b–) and therefore resistant to these forms of malaria. The antibodies to the Kidd antigens are unusual in that once formed, they often fall below the level of detection and may not be detected in an already immunized patient. In this situation, trans- fusion of additional Kidd-positive red cells may cause a rapid, sec- ondary immunological response, leading to formation of high-titre anti-Kidd with subsequent haemolysis and delayed transfusion re- actions; this is illustrated in Fig. 22.8.1.3.

Antibodies Alloantibodies Alloantibodies are antibodies formed against foreign antigens present on donor RBCs but absent on recipient RBCs. Some alloantibodies are naturally occurring and some are formed fol- lowing exposure to transfusion or by pregnancy. The clinical sig- nificance of different alloantibodies varies. Antibody significance is determined by their class and subclass, quantity, ability to activate Table 22.8.1.2 Clinically significant blood groups Red cell antigen Antigen frequencya Risk of haemolysis (immediate or delayed) Risk of haemolytic disease of the newborn A, B Variable High (immediate) Moderate (anti-A) Low (anti-B) Rh Variable High (immediate and delayed) Variable High to low K 0.09 High (immediate and delayed) High k 0.998 High (immediate and delayed) Low Fya White 0.66 High (delayed) Low Black 0.10 Fyb White 0.83 Low (delayed) None Black 0.23 Jka 0.77 Moderate (immediate and delayed) Rare Jkb 0.73 Moderate (immediate and delayed) None M 0.78 Low Rare N 0.72 None None S 0.55 Moderate (immediate and delayed) Rare s 0.89 Low (delayed) Rare a Antigen frequency in white population unless otherwise specified.

section 22 Haematological disorders 5568 complement, its thermal amplitude, the characteristics of the RBC antigen, and the patient’s clinical status. A clinically significant alloantibody can cause a haemolytic transfusion reaction or haemo- lytic disease of the newborn. If a clinically significant alloantibody is identified, crossmatched compatible RBCs units that lack the antigen should be provided. Autoantibodies Autoantibodies consist of immunoglobulins that react with a wide range of self-antigens including membrane and intracellular com- ponents, adsorbed plasma proteins, and nuclear antigens. The presence of an autoantibody does not necessarily cause increased RBC destruction; up to 15% of hospitalized patients have a positive Coombs’ test with no signs or symptoms of haemolysis. However, patients with warm autoimmune haemolytic anaemia often require transfusion. In this case, the blood bank may have difficulty finding a ‘compatible’ unit of red cells because the patient’s serum not only reacts with their own red cells, but also those of all donor red cells. Additional time may be required by the blood bank to exclude the presence of a significant underlying alloantibody that is obscured by the autoantibody. Upwards of 25% of previously transfused patients with warm autoimmune haemolytic anaemia may have an under- lying alloantibody which can cause red cell haemolysis. Autoimmune antibodies often appear to have specificity for Rh antigens (e.g. anti- e), but the transfusion of antigen negative red cells (e.g. e-negative) is not indicated, as in vivo red cell survival of antigen-negative cells is usually no better than antigen-positive cells. Compatibility testing Routine compatibility testing is performed only on red cell units, whole blood, and granulocytes prior to transfusion. Specifically, donor red cells are reacted with patient serum, and if no reac- tion is observed, the unit is considered ‘crossmatch compatible’. In emergency situations, there may be insufficient time to perform compatibility testing. Many hospitals will supply group O Rh- negative red cells until a patient sample is obtained and tested. If a patient’s ABO Rh status is known with certainty, then type-specific uncrossmatched blood can be provided. In either case, compati- bility testing is performed on these transfused units as soon as pos- sible. It is critically important to realize that supplies of O-negative blood are limited and some centres adopted the strategy of trans- fusing males with O Rh D-positive units in an emergency situation and preserve the O Rh D-negative units for children and females. ‘Computer crossmatches’ have been instituted at many hospitals in North America using a validated computer system. Patients with known ABO and Rh type, and who have a negative antibody screen, are provided with ABO-compatible blood while omitting the cross- match step described earlier. Although a true serological crossmatch is not performed, the computer crossmatch is safe in the vast ma- jority of transfusions. Clinical use of blood components Blood

component therapy refers to transfusing only the specific component that is required by a patient. Individual components are stored under optimal conditions, which maintain the integrity and potency of each respective blood component. RBCs are stored re- frigerated at 1 to 6°C, platelets at room temperature, 22 to 24°C, due to loss of function with refrigeration, and plasma is frozen at tem- peratures equal to or less than −18°C to maintain functional clotting factors, especially labile factors, which deteriorate with time. The difference in storage requirements among blood components is one of the reasons why whole blood usage has dropped. Other reasons include the requirement to provide the best blood component for the patient, cost, manufacturing logistics at the blood centre, and Secondary response Primary response Alloantibody titers First exposure to antigen Second exposure to antigen Time Threshold of detection Fig. 22.8.1.3 The antibodies to the Kidd antigens are unusual in that once formed, they often fall below the level of detection and may not be detected in an already immunized patient. In this situation, transfusion of additional Kidd-positive red cells may cause a rapid, secondary immunological response, leading to formation of high-titre anti-Kidd with subsequent haemolysis and delayed transfusion reactions.

22.8.1 Blood transfusion 5569 a limited blood supply. Plasma separated from whole blood can be further fractionated into coagulation factor concentrates, albumin, or gamma globulin. Cell separators (apheresis devices) capable of collecting platelets, plasma, granulocytes, peripheral blood stem cells, and RBCs, are also in widespread use across the United States of America and Europe. Red blood cells RBCs account for approximately 75% of the annual cost of transfu- sion therapy in the United Kingdom. Red cell units, prepared from whole blood by removing most of the plasma, are indicated for pa- tients with acute haemorrhage or chronic anaemias (Table 22.8.1.3). Earlier preservative solutions composed of citrate, dextrose, and phosphate buffers allowed storage of red cells from 21 to 35 days. It was later observed that adenine improved cell viability by increasing intracellular ATP levels. The haematocrit of RBC units varies from 55 to 70% depending on the specific anticoagulant/preservative so- lution used. Citrate contained in blood preservatives binds calcium to inhibit clotting and may cause hypocalcaemia and alkalosis in neonates and massively transfused patients. Units of red cells stored refrigerated at 1 to 6°C have a shelf- life of 35 to 42 days depending on the ingredients of the preser- vative. During storage, the following changes are observed in red cell units: (1) a fall in pH, (2) decreases in red cell ATP and 2,3- diphosphoglycerate, (3) increased supernatant potassium, and (4) decreased supernatant glucose. RBCs with uncommon antigen profiles can be frozen within 6 days of collection and stored for up to 10 years. They are frozen with glycerol to avoid cell dehydration and damage during the freezing process. The patient’s overall clinical status and laboratory parameters should be considered as a whole when deciding to transfuse a pa- tient. A decision should not be based on the haematocrit alone. Younger patients will usually tolerate a given degree of hypoxaemia and hypotension better than older patients who may have underlying coronary or myocardial disease. Evidence of symptomatic anaemia includes excessive fatigue, malaise, headache, tachycardia, hypoten- sion, and end-organ damage. Hypovolaemic shock typically ensues with acute loss (<24 h) of more than 30% of total blood volume. Initially, the haematocrit will be falsely elevated in acute haemor- rhage, but will then fall with fluid resuscitation. Slowly developing, chronic anaemias are usually better tolerated than rapid-onset anaemias due to the ability of the body’s fluid compensatory mech- anisms. Transfusion is rarely indicated when the haemoglobin (Hb) level is greater than 100 g/litre, and is often not considered until the Hb level is less than 70 g/litre.
A patient’s cardiac and pulmonary status must be considered when determining transfusion thresh- olds. Patients with unstable angina or acute myocardial infarction may require transfusion when

the Hb level is less than 100 g/litre. In the absence of active red cell destruction, transfusing a single unit will typically increase the Hb level by 10 g/litre (haematocrit by 3%). RBCs are administered through a transfusion administration- infusion set containing a standard screen filter designed to remove particles that are over 150 μm in size. Platelets Platelets are in most cases a by-product of red cell and plasma separ- ation. When manufactured from whole blood they are called platelet concentrates. In the United States of America, platelets are prepared by the platelet-rich plasma method, whereas the buffy coat method is used in Europe (Fig. 22.8.1.1). Each unit of ‘random donor’ plate- lets prepared by differential centrifugation of a single whole-blood collection typically contains at least 5.5 × 1010 platelets suspended in 50 ml of plasma or additive solution, the latter used mainly in Europe. Platelets stored under agitation at 20 to 24°C in plastic con- tainers that allow oxygen diffusion have a shelf life of 5 days. The risk of bacterial growth and development of platelet function abnormal- ities (platelet storage defect) has precluded longer storage. However, in the United States, all platelets are now tested for bacterial contam- ination using culture or surrogate methods (see ‘Septic reactions’). ‘Random donor’ whole blood-derived platelets are usually admin- istered in pools of 4 to 6 units. In the absence of conditions associ- ated with decreased platelet survival, each unit can be expected to raise the recipient’s platelet count by 5000 to 10 000/μl. Pooled and stored, leucoreduced, whole blood-derived platelets are available Table 22.8.1.3 Uses of blood transfusion components Component Indication for use Red blood cells Symptomatic acute and chronic anaemias, and as the replacement product in erythrocytopheresis (red cell exchange) Red blood cells frozen and deglycerolized Symptomatic anaemia, storage of red cells of rare antigen composition for up to 10 years Leucocyte-reduced components (red blood cells and platelets) Symptomatic anaemia and thrombocytopenia, reduce febrile reactions from leucocyte antibodies, alternative to CMV-seronegative components, prevent HLA alloimmunization Washed components (red blood cells and platelets) Prevent graft-versus-host disease in immunocompromised patients Irradiated blood products (red blood cells and platelets) Remove harmful plasma antibodies Platelet components (pooled platelets and pheresis platelets) Thrombocytopenia with bleeding, prophylactic transfusion, platelet function abnormalities HLA matched/selected platelets and crossmatch-compatible platelets HLA-alloimmunized thrombocytopenic patients with decreased platelet survival Fresh frozen plasma Replacement of plasma coagulation factors for which specific factor concentrates are not available, liver disease, DIC, hypofibrinogenaemia, TTP Cryoprecipitate Fibrinogen and factor XIII replacement, factor VIII and VWF replacement when recombinant and virus-inactivated concentrates are not available Granulocytes by apheresis Neutropenic patient with infection unresponsive to antibiotics DIC, disseminated intravascular coagulation; TTP, thrombocytopenic purpura, VWF, von Willebrand factor.

section 22 Haematological disorders 5570 in the United States of America. Licensed by the Food and Drug Administration (FDA) in 2006, these products are usually manufac- tured in pools of 5 units and offer the benefit of allowing the use of culture techniques to detect bacterial contamination. Additionally, platelets can be collected and manufactured by apheresis resulting in single donor platelets. These products contain more than 3 × 1011 platelets suspended in about 200 ml plasma or additive solu- tion and they are equivalent to 4 to 6 average random donor pooled platelet units. Platelets are not normally crossmatched with the recipient’s serum. ABO type-specific platelets should be provided whenever possible because transfusing out-of-type platelets may result in poor platelet survival in the patient’s circulation. Rh antigens present on the small number of contaminating red cells found in platelet concentrates are capable of immunizing

a Rh-negative recipient. If Rh-negative platelet concentrates are not available for a Rh-negative patient, Rh-positive platelets can be transfused followed by adminis- tration of Rh immune globulin within 72 h of transfusion. Platelets are provided to thrombocytopenic patients who are bleeding or to severely thrombocytopenic patients as a prophylactic measure. Spontaneous bleeding is rare when a patient’s platelet count is above 20 000/μl, and studies suggest that patients who re- ceive chemotherapy can tolerate platelet counts as low as 5000 to 10 000/μl. Postsurgical patients may require platelet transfusions to control or prevent postoperative bleeding when the platelet count is over 50 000/μl. Overall coagulation status should also be considered because patients with plasma coagulation factor disorders are more likely to bleed at marginal platelet counts. Actively bleeding patients receiving antiplatelet agents such as aspirin or clopidogrel, irre- versible inhibitors of platelet function, may require transfusions at higher platelet counts; however, transfused platelets will also be af- fected if the drug is not discontinued. Platelet refractoriness is a major issue for patients who are de- pendent on platelet transfusions. Immune and nonimmune fac- tors may be responsible for platelet refractoriness. Common causes of diminished platelet survival post transfusion include spleno- megaly, disseminated intravascular coagulation, bleeding, medi- cation, and sepsis. Patients may become refractory to platelet transfusions through either HLA or platelet alloimmunization. Once platelet alloimmunization is documented, crossmatch- compatible platelets or HLA-matched platelets should be con- sidered. However, these special products are not readily available in most blood banks. Increasing the dose of standard platelet con- centrates can be considered until compatible platelets are identified. Leucocyte reduced blood products should be provided to patients who will require many platelet transfusions to decrease the risk of HLA alloimmunization. Plasma, cryoprecipitate, and plasma derivatives Plasma therapy started in the late 1940s when fractionation tech- niques were developed to separate plasma proteins from large pools of human plasma. Fresh frozen plasma is prepared by separating plasma from whole blood by centrifugation and then freezing the plasma within 8 h of collection. This process maintains the activity of labile coagulation factors, particularly factors V and VIII. Many blood suppliers also prepare plasma that is frozen within 24 h of collection; this product is considered an effective alternative to fresh frozen plasma in most instances when plasma transfusion is necessary. Plasma should not be transfused for volume expansion because of the risk associated with plasma including transfusion- transmitted disease, transfusion-related lung injury, and allergic transfusion reactions, and because of the availability of other, safer nonplasma substitutes. The indications for plasma transfu- sion include inherited deficiencies of coagulation factors when no factor concentrate is available. However, the primary indica- tion is for acquired coagulopathies, such as deficiency of multiple coagulation factors seen in liver disease, dilutional coagulopathy, and disseminated intravascular coagulation. It has been used to re- verse warfarin anticoagulation urgently though prothrombin com- plex concentrate is preferred. Plasma is not particularly effective in replacing individual clotting factors because of the large vol- umes that would be required to obtain adequate factor levels. The patient’s fluid and cardiovascular status may preclude the use of large amounts of plasma. Fresh frozen plasma is no longer the treatment of choice for coagulopathies where virally inactivated or recombinant blood products exist, such as for deficiencies of factor VIII (haemophilia A) or factor IX (haemophilia B). Fears of transmitting infectious disease with plasma transfusion remain of concern, particularly for pooled products. In addition to donor screening and testing, other strategies to decrease infectious risk that have been studied include photoinactivation and solvent detergent treatment. Furthermore, in order to decrease the risk of transfusion-related acute lung injury, in the United Kingdom, only male donor plasma has been used as a source of fresh frozen plasma since 2003. A similar trend has started in

the United States of America. Cryoprecipitate is prepared by thawing fresh frozen plasma be- tween 1 and 6°C. The precipitate forms and the supernatant is removed and labelled as cryoprecipitate-reduced plasma; both products are subsequently refrozen. Each 10- to 20 ml unit of cryo- precipitate contains 100 to 350 mg fibrinogen/unit, at least 80 IU/ unit factor VIII, FXIII, fibronectin, and von Willebrand factor. Use of cryoprecipitate is generally reserved for patients with se- vere hypofibrinogenaemia (<1 g/l). Cryoprecipitate is not used to treat haemophilia or von Willebrand disease in developed countries because safer alternatives are available that avoid the risk of viral transmission. Cryoprecipitate and thrombin have been combined to make ‘fibrin glue’. This biological sealant works well but exposes the recipient to the risks of transfusion-transmitted disease because of the use of cryoprecipitate. Safer sealants have been developed that do not expose patients to cryoprecipitate. Albumin is available as a 5 or 25% solution and is used to treat hypovolaemia and hypoalbuminaemia, primarily in surgical set- tings and as a replacement fluid in plasmapheresis. Albumin is virally inactivated by heat treatment plus other viral inactivation steps, and is tested for hepatitis C virus RNA. Properly processed albumin is not considered to transmit viral disease. Readily avail- able nonplasma colloidal solutions have replaced albumin in many situations requiring volume expansion. Intravenous immuno- globulin is used to treat patients with immune thrombocytopenia, Guillain–Barré syndrome, and autoimmune haemolytic anaemias. Prompt and adequate doses of Rh (D) immunoglobulin available in intramuscular and intravenous preparations, are used to pre- vent alloimmunization in D-negative patients who are exposed to D-positive red cells through transfusion or pregnancy. Rapid ad- vances in molecular techniques led to the cloning and purification

22.8.1 Blood transfusion 5571 of recombinant clotting factors. Recombinant factors VIII, IX, and VIIa are available. Granulocytes Granulocytes are transfused primarily to neutropenic oncology patients with an absolute neutrophil count less than 500/µl and a reasonable chance of marrow recovery, who develop bacterial or fungal sepsis unresponsive to antimicrobial therapy or in patients with functional neutrophil disorder. Granulocytes collected from nonstimulated healthy donors by apheresis contain at least 1 × 1010 neutrophils/unit and can be stored for only 24 h at 20 to 24°C. Higher numbers of granulocytes can be collected when donors are stimulated by steroids and/or growth factors. The product contains a large number of red cells (20–50 ml) and must be crossmatched with the recipient’s serum. Granulocytes should be irradiated be- cause of the large number of lymphocytes present in the product. Due to their short half-life, granulocytes are usually provided daily until the patient can maintain an absolute neutrophil count above 500/µl without transfusion or until the infection resolves. Infusion of larger numbers of granulocytes allows measurable increases in recipient neutrophil counts, but the optimal dose and frequency re- main undefined. Febrile reactions to granulocytes are common, in addition to the pulmonary symptoms that are found to be more se- vere when amphotericin is administered near the time of granulo- cyte infusion. Other complications include HLA alloimmunization and transfusion-associated graft-versus-host disease, eliminated by irradiating the product. Overall, the additional benefit of granulo- cyte transfusion for neutropenic patients compared to antibiotic treatment alone remains unclear. A randomized trial, Safety and Effectiveness of Granulocyte Transfusions in Resolving Infection in People with Neutropenia (The RING Study), was initiated in 2008 and concluded in 2014. This trial attempted to assess high- dose granulocyte transfusions for the treatment of infection in neutropenia. This trial was unable to accrue sufficient numbers of patients to determine whether outcomes were improved with gran- ulocyte transfusions. To date, support for utilization of granulocyte transfusions remains anecdotal. Complications and management

of transfusion therapy See Tables 22.8.1.4 and 22.8.1.5. Acute intravascular haemolytic reactions Acute intravascular haemolytic transfusion reactions are one of the most serious transfusion complications. ABO incompatibility re- mains the most common cause of immediate intravascular haemo- lytic reactions. Donor erythrocytes carrying either A and/or B red cell antigens bind to the recipient's anti-A and/or anti-B antibodies, resulting in complement fixation, formation of the C5b-9 membrane attack complex, and subsequent haemolysis. Biological response modifiers, such as proinflammatory cytokines (interleukin (IL)-1, tumour necrosis factor α (TNFα)), chemokines (IL-8), and com- plement fragments (C3a, C5a), also play a role in the pathophysi- ology of acute transfusion reactions. The sudden onset of back pain, hypotension, tachycardia, fever, chills, diaphoresis, and dyspnoea are clinical characteristics of acute intravascular transfusion re- actions. The symptoms usually begin soon after the transfusion is started. Laboratory studies reveal an increase in unconjugated bili- rubin and a marked elevation of lactate dehydrogenase. Other evi- dence of intravascular haemolysis includes haemoglobinuria and haemoglobinaemia. The direct antiglobulin test (direct Coombs' test) becomes reactive due to the coating of donor red cells with the recipient's antibodies. Acute intravascular haemolytic transfusion reactions are usu- ally caused by transfusions of ABO-incompatible blood resulting from patient identification or clerical errors, but they can also be caused by incompatibility within other blood group (e.g. Duffy, Kidd) systems. Proper labelling of samples used by the blood bank for compatibility testing and careful identification of patients are the best ways to prevent these potentially fatal reactions. Acute haemolytic immune transfusion reactions are medical emergen- cies and treatment consists of immediately stopping the transfu- sion, close monitoring of vital signs, cardiac and airway support, and maintenance of urine output with saline diuresis with or without a loop diuretic. Dialysis should be considered in patients with renal failure. Delayed extravascular haemolytic reactions Delayed haemolytic transfusion reactions occur in patients who have a negative antibody screen on pretransfusion testing, but who then experience accelerated destruction of transfused red cells 3 to 14 days after transfusion. In most cases, red cell destruc- tion is caused by an antibody that is initially of a titre below the limits of detection on routine screening. The antibody then rap- idly forms on re-exposure to the offending antigen (Fig. 22.8.1.3). The antibodies typically fix complement to C3 and stop, thus re- sulting in extravascular haemolysis. Antibodies most commonly implicated in delayed transfusion reactions are directed against Rh (E, c), Kell, Duffy, and Kidd blood group antigens. Delayed extravascular haemolytic transfusion reactions can be diagnosed by an unexpected post-transfusion fall in haematocrit, develop- ment of unconjugated hyperbilirubinaemia, and appearance of a positive direct antiglobulin test. A delay of 3 days to 2 weeks is usually seen between transfusion and the onset of extravascular Table 22.8.1.4 Major risks of blood transfusion therapy Immune complications Nonimmune complications Acute haemolytic transfusion reactions Transfusion-associated bacterial sepsis Delayed extravascular haemolytic reaction Circulatory overload, cardiac failure Febrile transfusion reaction Viral transmission (hepatitis A, B, C, CMV, parvovirus) Allergic transfusion reaction (urticaria and anaphylaxis) Iron overload Transfusion-associated sepsis Hypocalcaemia Alloimmunization Hypothermia Transfusion-associated graft- versus-host disease Dilutional coagulopathy due to factor depletion, thrombocytopenia Transfusion-associated acute lung injury

 haemolysis. Only rarely do delayed reactions result in intravas- cular haemolysis. Febrile nonhaemolytic reactions Febrile nonhaemolytic transfusion reactions to RBC and platelet transfusion are very common. They are classically attributed to the development of antibodies in the recipient directed against HLA and/ or leucocyte-specific antigens

on donor white blood cells and plate- lets. Reactions between leucoagglutinins present in the transfused product and recipient leucocyte antigens can also occur. Subsequent formation of leucocyte antigen–antibody complexes results in com- plement binding and release of endogenous pyrogens such as IL-1, IL-6, and TNFα. Cytokines generated by leucocytes during platelet and red cell storage may also contribute to these febrile reactions to transfusion. Symptoms may occur during or several hours after the transfusion and typically include fevers (>1°C rise) accompanied by shaking chills. Rarely, vomiting, dyspnoea, hypotension, and de- creased oxygen saturation may develop. The severity of symptoms is often directly related to the number of leucocytes in the product or the rate or volume of transfusion. Leucoreduction of blood com- ponents decreases the frequency of febrile transfusion reactions. Premedication with an antipyretic can ameliorate mild febrile trans- fusion reactions. Corticosteroids can also minimize febrile trans- fusion reactions if they are administered several hours before the transfusion. Intramuscular or subcutaneous meperidine will usually resolve severe rigors within minutes. If symptoms do not resolve in less than 4 h or are especially severe, other complications such as sepsis due to contaminated blood products or a haemolytic reaction should be considered. Allergic reactions Allergic reactions to plasma, platelets, and RBCs are relatively common. They present as pruritus and/or urticaria in the absence of fever. Allergic reactions are IgE mediated and most symptoms are attributed to histamine release. It may be difficult to distinguish al- lergic and febrile transfusion reactions when urticarial symptoms are accompanied by low-grade fever. Common symptoms and signs include erythema, papular rashes, weals, and pruritus. As in other allergic responses, symptoms are not dose related and severe mani- festations can occur following small exposures. Treatment of mild allergic reactions consists of stopping the transfusion and adminis- tering antihistamines. In a mild allergic reaction with only pruritus and hives, it is acceptable to continue transfusing the same unit, pro- vided the symptoms promptly resolve and no accompanying fever or vasomotor instability is noted. Severe allergic reactions with bronchospasm and cardiovas- cular collapse are rare and should be treated like any other ana- phylactic reaction with steroids, vasopressors, and airway support. Anaphylactic transfusion reactions occur in IgA-deficient patients who have already developed anti-IgA antibodies, and then re- ceive plasma-containing blood products. While IgA deficiency is common in the general population (1 in 700 individuals), only a subset of IgA-deficient individuals are at risk since not all of them develop the antibody. Patients with IgA deficiency who have had an anaphylactic reaction or who have demonstrated anti-IgA should receive cellular products that have been saline-washed and plasma from only IgA-deficient donors. Washed RBCs may also benefit pa- tients without IgA deficiency, but who have experienced repeated moderate to severe allergic transfusion reactions. Septic reactions Blood products can become contaminated by bacteria if a donor is bacteraemic at the time of collection or if the donor’s arm is im- properly cleansed before venepuncture. Transfusing blood products contaminated by bacteria is particularly dangerous and can result in profound hypotension and shock. The risk of septic transfusion reactions is higher for platelet transfusions than other blood com- ponents because platelets are stored at room temperature. As noted previously, in an attempt to reduce the risk of transfusion-associated bacterial sepsis, blood collection facilities in the United States have implemented several strategies to detect bacterial contamination of platelet units. These include culture of the product as well as sur- rogate methods. The latter comprise (1) visual inspection for loss of swirling that occurs with a change in platelet shape associated with the fall in pH; (2) direct visualization of microorganisms using the Gram stain, Wright stain, or acridine orange; and (3) the use of
Table 22.8.1.5 Symptoms, signs, and management of transfusion reactions Reaction Symptoms and signs Management/treatment Acute intravascular haemolytic reaction Back pain, fever,

hypotension, shock, dyspnoea, haemoglobinuria, haemoglobinaemia, positive direct Coombs' test Stop transfusion, IV fluids, vasopressor support, maintain diuresis, corticosteroids, dialysis if indicated Delayed extravascular haemolytic reaction Anaemia, jaundice, fever, positive direct Coombs' test Stop transfusion, fluid support, follow lab results (haematocrit, lactate dehydrogenaase, bilirubin) Febrile reaction Fever, chills, rigors, mild dyspnoea Stop transfusion, antipyretics, consider leucoreduced product for subsequent transfusions Allergic (mild) Pruritus, urticaria Antihistamines, may continue transfusion if symptoms improve in <30 min, otherwise stop transfusion Allergic (anaphylactic) Urticaria, bronchospasm, dyspnoea, nausea, hypotension Stop transfusion, antihistamines, vasopressor support, corticosteroids, consider premedication or washed RBCs for subsequent transfusions Septic reaction Rapid onset of chills, fever, hypotension Stop transfusion, culture sample from product and patient, vasopressor support, IV fluids, broad spectrum antibiotics Transfusion-related acute lung injury Dyspnoea, tachypnoea, cyanosis, fever, hypotension Respiratory support

22.8.1 Blood transfusion 5573 dipsticks for pH and glucose readings. These surrogate methods are more rapid and less costly, but also much less sensitive than culture and are being phased out. The sensitivity of culture in detecting bac- terial contamination of blood products is affected by several factors, however, such as growth characteristics of the organism, timing of specimen collection, specimen volume, and the degree of initial bac- terial contamination. Organisms commonly implicated in septic transfusion reac- tions include Gram-positive (staphylococcus) and Gram-negative (enterobacter, yersinia, pseudomonas) bacteria. The literature demonstrates that the risk of bacterial contamination on the day of transfusion for apheresis platelets previously screened as negative by early culture is approximately 1:5000. The risk of septic trans- fusion reactions caused by contamination of platelets is approxi- mately 1:107 000. Blood cultures should be obtained from patients who develop high fevers following or during transfusion, espe- cially if they become hypotensive. A Gram stain of the suspected contaminated product may be helpful but is often negative, and the product should be cultured if possible. Other symptoms attributed to preformed endotoxin and cytokines include skin flushing, severe rigors, and rapid-onset cardiovascular collapse. The symptoms may occur during or a minute to hours after the transfusion is completed. Treatment includes fluids, cardiorespiratory support, and broad- spectrum antibiotics. Transfusion-related acute lung injury Transfusion-related acute lung injury is a serious complication of blood transfusion that presents as noncardiogenic pulmonary oe- dema. It typically occurs within 6 h of transfusion and is clinic- ally similar to the acute respiratory distress syndrome. The most common clinical findings are rapid-onset dyspnoea, tachypnoea, cyanosis, fever, and hypotension. Lung auscultation reveals diffuse crackles and decreased breath sounds. Invasive cardiac monitoring demonstrates normal cardiac pressures and function with hypox- aemia and decreased pulmonary compliance. Radiographic findings include diffuse, fluffy infiltrates typical of pulmonary oedema. In most cases, the aetiology is believed to involve an immune- mediated reaction between passively transferred donor antileucocyte antibodies present in a plasma-containing blood product with the recipient's white cells, resulting in leucocyte activation. Much less frequently, the antibodies present in the recipient may react with white cells in the transfused products. Granulocytes are first acti- vated by HLA or other antigen–antibody complexes and then mi- grate to the lungs. The activated neutrophils bind to the pulmonary capillary bed via cell adhesion molecules where they release pro- teolytic enzymes that destroy tissue, resulting in a capillary leak syndrome and pulmonary oedema. More recently, reactive lipid products released from donor cell membranes have been associated with the development of transfusion-related lung injury. Transfusion-related

acute lung injury is a clinical diagnosis and should be suspected in patients with severe, rapid-onset respira- tory distress during or soon after transfusion therapy. Definitive diagnosis requires identification of HLA and/or granulocyte anti- bodies in either the donor's or recipient's serum, as well as the cor- responding antigens on the recipient's or donor's leucocytes. This testing is performed in only a few specialized laboratories. Most patients with this syndrome will survive with supportive care, including aggressive respiratory support with supplemental oxygen, and if necessary, mechanical ventilation. Often, the hypoxia that develops during or after transfusion is attributed to fluid overload, and diuretics are empirically administered. Although not absolutely contraindicated, diuretics may be harmful and should be used with extreme caution. Corticosteroids have no proven role in the man- agement of transfusion-related acute lung injury. As discussed pre- viously, in order to reduce its incidence, plasma from female donors is no longer used as a source of fresh frozen plasma in the United Kingdom, with the United States of America beginning to follow this course as of 2007. Transfusion-associated circulatory overload Transfusions contribute to fluid overload that result in pulmonary oedema and hypertension. Transfusion-associated circulatory overload is often unrecognized and underreported; the docu- mented incidence is between 1 and 6%. The reaction should occur during or within 6 h of transfusion. Patient develops respiratory symptoms, hypoxaemia with a reduction in O2 saturation, tachy-cardia, hypertension, and pulmonary/pedal oedema. Chest radiog- raphy will show bilateral infiltrates and patient will have an elevated brain natriuretic peptide. Risk factors include extremes of age, his- tory of congestive heart failure, and renal failure. It is prevented by a slow transfusion rate and closely monitoring patient fluid status and it is managed by stopping the transfusion, respiratory support, and diuretics. Transfusion-associated dyspnoea The diagnosis of transfusion-associated dyspnoea is considered if the patient develops respiratory distress and did not meet the criteria for transfusion-related acute lung injury, transfusion-associated cir- culatory overload, or an allergic reaction and the symptoms are not explained by the patient's underlying condition. Transfusion-associated graft-versus-host disease Acute graft-versus-host disease (GVHD) is a rare complication of blood transfusion, but is fatal in approximately 90% of patients. Transfusion-associated graft-versus-host disease (TA-GVHD) oc- curs when donor immunocompetent T and NK cells attack im- munocompromised recipient cells because these recipient cells appear foreign due to differences in major or minor histocompati- bility antigens. The risk of TA-GVHD is related to the number of viable T lymphocytes transfused, the recipient's immune status, and the HLA disparity between donor and host. Therefore, multiply transfused patients who receive cells from donors who share HLA haplotypes with the recipient (i.e. blood relatives) are at greatest risk. Clinically, TA-GVHD is characterized by the acute onset of rash, ab- dominal pain, diarrhoea, liver abnormalities (elevated liver enzymes, hyperbilirubinaemia), and bone marrow suppression 2 to 30 days following transfusion. The maculopapular rash seen is similar to that observed in acute GVHD following bone marrow transplant, and biopsy of the skin may help confirm the diagnosis. Pancytopenia may be severe and is attributed to destruction of recipient marrow stem cells by donor lymphocytes. Immunosuppressive therapy with prednisone and ciclosporin has had little effect on TA-GVHD. Fortunately, the development of this condition can be prevented by irradiating cellular blood products before transfusion.

section 22 Haematological disorders 5574 Acute pain transfusion reaction This reaction occurs shortly after the initiation of transfusion, the mechanism is currently unknown. Patients complain of chest, ab- dominal, and back pain, and pain in the proximal extremities that resolves within an hour of stopping the transfusion. It can be associ- ated with other symptoms including dyspnoea,

hypertension chills, and headache. These symptoms can be manifested in other transfu- sion reactions and they should be ruled out prior to establishing a diagnosis of acute pain reaction. Hypotensive transfusion reaction Hypotensive transfusion reaction is a newly recognized complication—if not recognized early it can be life-threatening. It is characterized by the onset of clinically significant hypoten- sion (systolic <89 and 30 mmHg reduction in systolic blood pres- sure) during or within 1 h of transfusion. It can be associated with other symptoms, such as facial flushing, dyspnoea, and abdominal pain. Other transfusion reactions, such as allergic, acute haemo- lytic, and septic reactions should be ruled out. It has been asso- ciated with the use of negatively charged bedside leucoreduction filters and it is reported in patients using an angiotensin converting enzyme inhibitor, indicating that bradykinin that is produced by the activation of the contact system is a possible causative agent. Hypotensive transfusion reaction is managed with fluids, placing the patient in the Trendelenburg position and vasopressors. Patient should improve with supportive measures and after the cessation of transfusion. Post-transfusion purpura Post-transfusion purpura patients will develop thrombocyto- penia with counts decreased to at least 20% of pretransfusion count. This occurs 5 to 12 days following transfusion of platelets, RBCs, or plasma. Patient will present with purpura, mucosal bleed, epistaxis, urinary, and gastrointestinal bleeding. Post- transfusion purpura occurs due to the presence of platelet-specific alloantibodies present in patients due to previous sensitizations by transfusion or pregnancy, most commonly antihuman platelet antigen 1a (anti-HPA1a). A subsequent exposure will trigger the destruction of both the transfused and, importantly, autologous platelets, as well. Antigen negative or antigen positive platelet transfusions do not effectively increase the platelet count. Patients are managed with corticosteroids, plasmapheresis, and intravenous immunoglobulin. Transfusion-transmitted disease Despite major improvements in blood safety during the past two decades, a small risk of transfusion-transmitted disease still remains. The use of volunteer donors and predonation screening question- naires were the first steps taken to reduce the risk of transfusion-related hepatitis and HIV. These risks continue to drive mandated pretransfusion testing requirements in developed countries. The advent of enzyme immunoassays in the 1970s and more recently, nucleic acid amplification testing, have further decreased the risk of transfusion-transmitted disease (Table 22.8.1.6). Transfusion- transmitted disease is a persistent problem in parts of the world that do not have access to screening tests. At present, pretransfusion testing in the United States of America and Europe includes screening for hepatitis B (HBsAg, anti-HBc, nucleic acid amplification), hepatitis C (anti-hepatitis C virus (HCV), nucleic acid amplification), HIV (anti-HIV-1/2, nucleic acid amplification), human T-cell lymphotropic virus (anti-HTLV- I/II), and syphilis (RPR). Additionally, in the United States, donated blood is screened for West Nile virus (nucleic acid amplification) and Trypanosoma cruzi as a one-time donor testing. Nucleic acid amplification testing for HCV and HIV is typically performed on small pools of donor samples. The current estimate of the risk of transfusion-related HIV is ap- proximately 1 in 2 million units transfused. With the introduction of screening by amplification of nucleic acid templates, the 'window period', in which the virus could be transmitted by an HIV-infected Table 22.8.1.6 Organisms potentially transmitted by blood transfusion Agent/organism Estimated risk per unit transfuseda Pretransfusion testing Hepatitis B virus 1:280 000 HBsAg, anti-HBc, ALT, NAT Hepatitis C virus 1:1.9 million Anti-HCV, NAT HIV-1/2 1:2.1 million Anti-HIV-1/2, NAT HTLV-I/II virus 1:650 000 Anti-HTLV-I/II West Nile virus Unknown NAT CMV 1:10–1:20 (see text) Some units tested for anti-CMV antibodies Parvovirus B19 Unknown None Bacterial contamination 1:1500 None Treponema pallidum Rare RPR Parasites (plasmodium, ehrlichia, Babesia microti) Rare None Trypanosoma cruzi 1:25 000 (seroprevalence) Anti-Trypanosoma cruzi vCJD Unknown Deferral based on history CMV,

cytomegalovirus; NAT, nucleic acid testing; vCJD, variant Creutzfeldt–Jakob disease; a USA figures.

22.8.1 Blood transfusion 5575 but seronegative donor, has decreased to approximately 10 days. Genomic testing for HCV RNA has also been implemented in the United States and Europe to detect seronegative yet infectious units. Nucleic acid amplification testing screening has decreased the transfusion-related hepatitis C risk by decreasing the window period to 10 to 20 days. The first cases of transfusion-transmitted West Nile virus infection were documented in the United States of America in 2002; the following year, national blood donation screening for West Nile virus was initiated using nucleic acid amplification testing technology. The risk of transfusion-related transmission of this virus since instituting this screening test has not been established. Several techniques have been developed to inactivate viruses in blood products; see ‘Pathogen reduction’ for more details. Cytomegalovirus (CMV) and parvovirus B19 are common in the general donor population, and may pose a serious threat to im- munocompromised patients. Approximately 40 to 60% of blood donors have been exposed to CMV during their lifetime and sub- sequently are CMV seropositive. However, only about 2% of CMV- seropositive donors are actively infected and transfusing their blood to an immunocompromised recipient could cause acute CMV infec- tion. The actual risk of post-transfusion seroconversion of a CMV- negative recipient who receives CMV-untested blood depends on the prevalence of CMV seropositivity in the donor population. As for parvovirus B19, only a few cases of transmission by blood components have been reported in immunocompetent recipients. Thus, blood donor screening tests for parvovirus have not been recommended. Since its initial description in the United Kingdom in 1996, variant Creutzfeldt–Jakob disease (vCJD) has raised additional transfusion safety concerns. The observations from the study conducted in the United Kingdom, the Transfusion Medicine Epidemiology Review, have provided evidence that vCJD can be transmitted through blood transfusion. As of 2006, of the 66 British patients identified as having received blood from donors who went on to develop vCJD, three or four probable cases of transfusion-transmitted vCJD have been documented. These numbers may, however, be an underestimate of the overall risk of transfusion transmission of this disease. Given the long incubation period of vCJD, some surviving recipients of blood products derived from ‘vCJD donors’ may still develop the disease. Moreover, a significant number of deceased blood recipients may not have survived long enough to manifest clinical disease even if infected. The introduction of universal leucocyte depletion of the United Kingdom blood supply in 1999 may have reduced the risk to blood recipients. A number of parasitic diseases are known or suspected to be transmitted by blood transfusion. These include malaria, Chagas’ disease, babesiosis, anaplasmosis, leishmaniasis, and toxoplas- mosis. Transmission of Lyme disease (Borrelia burgdorferi) by transfusion has not been documented. Infection with babesia, if untreated, can be dangerous in at-risk populations such as asplenic patients. A screening test for babesiosis is available in the United States of America. Testing for T. cruzi was not initially mandated, however, blood centres started testing donors with an EIA test ap- proved by the FDA in 2007. In 2010, one-time screening of every donor was recommended by the FDA. At this time, blood centres maintain varying algorithms regarding the testing of T. cruzi. These algorithms range from testing first time donors only, to testing first time donors and retesting donors who report having travelled to en- demic areas of Central and South America. Use of special blood products Leucoreduction Leucocytes contained in blood components can provoke febrile nonhaemolytic reactions, induce HLA alloimmunization, and transmit CMV to at-risk recipients. Leucocytes are effectively removed from red cell and platelet concentrates by leucocyte re- duction filters. American standards require that units labelled ‘leucoreduced’ contain less than 5 × 106 white blood cells, whereas the European standard is less

than 1 × 106 white blood cells per unit. Red cells are most commonly leucoreduced shortly after blood collection (prestorage leucodepletion). Filters are similarly used to leucoreduce platelet concentrates. Apheresis devices have been designed to collect leucoreduced platelets directly (process leucoreduction). Leucoreduction has been shown to decrease the prevalence and severity of febrile transfusion reactions and the risk of HLA alloimmunization. Other generally accepted benefits of white blood cell reduction include reducing platelet refractoriness and decreasing the risk of transmitting white blood cell-related infectious agents including CMV, HTLV-I/II, ehrlichia, and anaplasma. Prestorage leucoreduced products are preferable because they contain less cyto- kines and other biological response modifiers produced by white blood cells. With the dramatic decrease in the risk of viral transmis- sion, investigators are focusing on the immunomodulatory effects of blood transfusion. These effects specifically deal with associations between allogeneic transfusion and bacterial infection, tumour pro- gression, and tumour recurrence. Universal leucoreduction of both RBCs and platelets has been required and/or is being implemented in a number of European countries and in parts of North America. Universal leucoreduction is not FDA mandated in the United States of America. Irradiation Blood components are irradiated to prevent potentially lethal TA-GVHD by interfering with the ability of donor lymphocytes to proliferate. GVHD occurs in immunocompromised recipi- ents when an immunocompetent donor is homozygous for an HLA haplotype and the recipient is heterozygous for that haplo- type. The immunocompetent donor lymphocytes will recognize the recipient as foreign and mount an immune response leading to GVHD. Irradiation of blood components is indicated for bone marrow or peripheral blood stem cell transplant recipients, pa- tients with congenital immunodeficiency states, neonates, pre- mature infants, during intrauterine exchange transfusion, when transfusing (seemingly) HLA-compatible platelet units and blood products from a blood relative. Patients with AIDS commonly re- ceive irradiated components, although no clear increased risk of TA-GVHD exists in this population. Standard guidelines recom- mend irradiating RBCs, platelets, and granulocytes with a min- imum dose of 2500 cGy. Platelets are not adversely affected by this exposure. Red cells’ shelf life, however, is shortened to 28 days after irradiation. This is due to the irradiation causing changes in the red

section 22 Haematological disorders 5576 cell membrane that induces a leak of intracellular potassium. It is not necessary to irradiate frozen noncellular blood products such as fresh frozen plasma or cryoprecipitate because they contain very few viable leucocytes. Bone marrow or peripheral blood stem cells must never be irradi- ated prior to transplant. Cytomegalovirus-safe components CMV infection is a leading cause of morbidity and mortality in marrow and solid-organ transplant patients. Most serious CMV in- fections that develop in these populations are a result of latent re- activation of recipient CMV, but CMV can also be transmitted by blood transfusion. Therefore, blood banks supply products that have a low potential of transmitting CMV. The available products include CMV-seronegative units prepared from donors who are CMV IgG antibody negative. However, seroprevalence of CMV in the popu- lation ranges from 40–80% and it is logistically difficult to provide a sufficient quantity of this product. The other available products are leucodepleted components. The latter refers to blood compo- nents leucoreduced in a blood centre or laboratory using ‘good manufacturing practice’ techniques. Studies suggest that CMV-seronegative and leucodepleted filtered products are equivalent in preventing CMV transmission. Many transfusion specialists con- sider leucodepleted units produced under conditions of good manu- facturing practice as CMV ‘safe’ in that they are unlikely to transmit CMV disease. In addition to CMV-seronegative marrow and solid- organ transplant recipients, CMV-seronegative or

safe components are generally indicated for premature infants, during intrauterine transfusions, for patients with congenital immunodeficiencies, CMV-seronegative pregnant women, and seronegative patients with HIV. The British Committee for Standards in Haematology has concluded that leucoreduced components are an ‘effective alternative’ to seronegative products for preventing CMV transmission by transfu- sion. In addition, pathogen reduction technology, recently approved by FDA for use in the United States of America, also reduces the risk of CMV transmission. Washed blood products RBCs and platelets can be washed to remove the plasma that con- tains proteins and cytokines, and replace it with saline. It is per- formed for patients with repeated severe allergic/anaphylactic reactions and in neonatal alloimmune thrombocytopenia patients receiving maternal platelets, to remove the maternal alloantibodies. Approximately 20 to 30% of the red bloods cells or platelets are lost during this process. RBCs must be transfused within 24 h and plate- lets within 4 h of washing. Considering the loss of RBCs and/or platelets during the washing process, it is important to evaluate the clinical necessity of washing. Volume reduction This process is performed by a centrifugation step and the re- moval of the supernatant to concentrate the product. Volume re- ducing of RBCs is performed to transfuse patients who are prone to volume overload and to prevent hyperkalaemia when older stored red cells are transfused to neonates or young children. Volume- reduced platelets can be resuspended in saline and should be trans- fused within 4 h. The indication for platelet volume reduction is transfusion to patients who are prone to circulatory overload, for out-of-ABO-group platelet transfusions and to reduce the incidence of febrile nonhaemolytic transfusion reactions by decreasing the cytokines that accumulate in plasma during storage. Frozen products Both RBCs and platelets can be cryopreserved and frozen. The RBC preservation process is widely used in the United States of America to store rare phenotyped red cell units and autologous blood collec- tions. RBCs are cryopreserved with glycerol to prevent dehydration and frozen at less than −65°C. This process should be performed within 6 days of collection. Once the RBC products are frozen, they can be stored for up to 10 years. Prior to transfusion the product need to be thawed at 37°C, deglycerolized-washed. Platelet cryo- preservation, using DMSO, is investigational only and not licensed for use in the United States of America. Pathogen reduction Transfusion-transmitted infections from known and emerging pathogens pose a risk to the blood supply. With donor screening and use of a donor history questionnaire, coupled with serological testing, and nucleic acid testing, the risk of transfusion-transmitted infections has decreased, but has not been completely eliminated. Newer technologies, such as pathogen reduction, will reduce this risk further by inactivating both intracellular and extracellular agents including viruses, parasites, and bacteria. Advantages of pathogen reduction include the potential to eliminate the need for future additional donor infectious disease testing, decreasing donor deferrals and extending the limited shelf life of platelets to 7 days due to the decreased risk of bacterial contamination with treated plate- lets stored at room temperature. There are several available methods of pathogen reduction which have been approved for clinical use by the FDA. Other pathogen-reduction technologies are in various stages of development for use with either whole blood plasma or cel- lular blood components. One licensed pathogen-reduction method targets cell membranes by using a solvent and a detergent to attack and damage the cell membrane of pathogens. This technology is thus applicable only to plasma products and not to cellular blood components. Methods used for pathogen reduction of plasma, besides solvent/detergent treatment, include methylene blue light treatment, and an FDA- approved psoralen–ultraviolet (UV)-A light treatment technology. In addition, plasma can be inactivated using riboflavin (vitamin B2) light treatment. Most technologies for pathogen reduction of cellular blood com- ponents target nucleic acids, preventing the

replication of pathogens and leucocytes. Several techniques have been developed to inactivate pathogens in platelets. One FDA-approved methodology, uses psor- alen and UV-A light to inactivate pathogens in units of single donor platelets. This is the same FDA-approved technology described previously for use in pathogen reduction of plasma. For platelets, riboflavin–light treatments, currently under investigation, have also been shown to inactivate many pathogens known to be transmitted by transfusion. The currently approved method in the United States of America, however, only utilizes the psoralen–UV-A technology. Methods to inactivate infectious pathogens in red cells are currently under development. A solvent/detergent approach cannot be used as it would adversely affect RBC membranes, nor can a psoralen–UV- A approach be used as the haemoglobin in red cells blocks the UV-A

22.8.1 Blood transfusion 5577 light from activating the psoralen compound drastically reducing the effectiveness of the system to inactivate pathogen nucleic acids. Albumin, immune globulin, factor concentrates, and other plasma derivatives are treated using solvent/detergent and other protocols that essentially eliminate the risk of viral transmission. Pathogen- reduction technologies are safe, nontoxic, and achieve an adequate level of pathogen inactivation while maintaining cellular quality and adequate levels of functional clotting factors. It should be noted that current technologies and most pathogen-reduction technologies currently available and under development are ineffective against spores or prions. Alternatives to blood component therapy Autologous transfusion Commonly used forms of autologous transfusion include preopera- tive blood donation, acute normovolaemic haemodilution, and autologous blood salvage. Many blood centres provide autologous preoperative blood donation services in which a patient’s blood is drawn and stored for later use, usually during a surgical procedure. The criteria for autologous donations are less stringent than those for allogeneic donors. Preoperative blood donation can be utilized in elderly patients, although there is a higher risk of anaemia and more serious cardiovascular complications associated with the do- nation. Although the use of autologous blood decreases the risk of viral infection, the risk of bacterial contamination remains. Acute normovolaemic haemodilution is performed by removing blood from a patient immediately before surgery and replacing the blood volume with crystalloid or colloid solutions to maintain haemo- dynamic stability. The withdrawn blood is then later reinfused. Autologous blood salvage is performed by collecting and then re- turning blood lost during or shortly following operative procedures using intraoperative salvage devices. This technique is primarily used in cardiac and orthopaedic surgery. Growth factors Haematopoietic growth factors used in transfusion therapy are designed to limit the exposure of patients to allogeneic blood. The isolation, characterization, and subsequent synthesis of erythropoietin by recombinant technology were important ad- vances in decreasing red cell transfusions. The use of recom- binant human erythropoietin has reduced the transfusion needs of some patients with renal failure and various anaemias. In the United States of America, use of recombinant human erythro- poietin is being restricted due to reported adverse vascular and other events. Granulocyte colony-stimulating factor has been shown to decrease infection rates in neutropenic patients under- going chemotherapy, replacing marginally effective granulocyte transfusions. Thrombopoietic growth factors, such as recombinant thrombopoietin, as well as small molecules with thrombomimetic activity, are currently being evaluated and some formulations are licensed in the United States of America. Blood substitutes For over a century, ongoing research has sought to develop haemoglobin-based oxygen-carrying compounds that can serve as an alternative to allogeneic red cell transfusion. The earliest products consisted of stroma-free haemoglobin, which was aban- doned because of its renal toxicity, and polymerized haemoglobin.

Most of these agents are not used clinically because of vasoactivity and other untoward effects; other formulations are in various phases of clinical trials. No formulation is currently licensed in the United States of America. Molecular testing in the blood bank The molecular basis of blood group antigens has been extensively studied and many of the genes that code for antigens on RBCs, platelets, and leucocytes have sequenced. Molecular-based typing in the blood bank is referred to as genotyping, as compared to the current gold standard serological typing via haemagglutination known as phenotyping. Genotyping has been more utilized in re- cent years. However, it will not soon replace serological testing because serology is inexpensive and less complex compared with genotyping. In addition, the safety of most transfusions is assured with current methods by means of ABO typing, screening, and crossmatching. Genotyping red cells has its advantages in cer- tain circumstances, for example, to resolve a typing discrepancy, in positive direct antiglobulin testing, after multiple transfusions, when typing reagents are not available for certain blood group antigens, to identify a fetus at risk of haemolytic disease of the newborn, and with patients in need of chronic transfusions with an increased risk of alloimmunizations and matching their blood is problematic. This population of patients includes sickle cell, thalassemia, and oncology patients. Genotyping assays used in the blood bank are polymerase chain reaction-based assays and many platforms have been developed in recent years. These assays have their limitations. In addition to the complexity of these assays, there are approximately 300 antigens identified and more than 1000 alleles coding them. A particular phenotype can result from multiple genetic variations and one should have a full knowledge of the different alleles present in a population prior to developing a molecular-based assay. At the current time, it is recommended that DNA testing should be used as an adjunct to serological tests especially to confirm negativity. FURTHER READING American Association of Blood Banks (AABB) (2011). Guidelines for PBM and blood utilization AABB, Bethesda, MD. American Association of Blood Banks (AABB) (2014). Technical manual, 18th edition. AABB, Bethesda, MD. Anstee DJ (2009). Red cell genotyping and the future of pretransfusion testing. Blood, 114, 248–56. Ballen KK, et al. (2004). Autologous stem-cell transplantation can be performed safely without the use of blood-product support. J Clin Oncol, 22, 4087–94. BCSH Blood Transfusion Task Force (2007). Guidelines on gamma irradiation of blood components for the prevention of transfusion- associated graft-versus-host disease. Transfus Med, 6, 261–71. Blajchman M (2006). The clinical benefits of the leukoreduction of blood products. J Trauma, 60 Suppl 6, S83–90.

 Blajchman M (2008). Platelet transfusions: an historical perspective. Hematology Am Soc Hematol Educ Program, 2008, 197. Carson JL, et al. (2017). Indications for and Adverse Effects of Red-Cell Transfusion. N Engl J Med, 377(13), 1261–72. Chou ST (2013). Transfusion therapy for sickle cell disease: a balancing act. Hematology Am Soc Hematol Educ Program, 2013, 439–46. Cohn E, et al. (1950). A system for separation of components of human blood. J Am Chem Soc, 72, 465–74. Department of Health and Human Services (2011). 2011 national blood collection and utilization survey report. Department of Health and Human Services, Washington DC. Dobroszycki J, et al. (1999). A cluster of transfusion-associated
babesiosis cases traced to a single asymptomatic donor. JAMA, 281, 927–30. Dorsey KA, et al. (2013). A comparison of human immunodeficiency virus, hepatitis C virus, hepatitis B virus, and human T-lymphotropic virus marker rates for directed versus volunteer blood donations to the American Red Cross during 2005 to 2010. Transfusion, 53, 1250–6. Dzik WH (2007). New technology for transfusion safety. Br J Haematol, 136, 181–90. Friedberg RC, Donnelly SF, Mintz PD (1994). Independent roles for platelet crossmatching and HLA in the selection of platelets for

alloimmunized patients. Transfusion, 34, 215–20. Goodnough LT (2003). Risks of blood transfusion. Crit Care Med, 31 Suppl 12, S678–86. Goodnough LT, et al. (1999). Transfusion medicine. Second of two parts–blood conservation. N Engl J Med, 340, 525–33. Goodnough LT, et al. (2009). Implementation of a two-specimen requirement for verification of ABO/Rh for blood transfusion. Transfusion, 49, 1321–8. Hébert PC, et al. (1999). A multicenter, randomized, controlled clin- ical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Eng J Med, 340, 409–17. Heddle N, Webert KE (2007). Febrile, allergic, and other noninfectious transfusion reactions. In: Hillyer CD, et al. (eds) Blood banking and transfusion medicine, 2nd edition, pp. 677−90. Churchill Livingstone, Philadelphia. Hewitt P (2006). vCJD and blood transfusion in the United Kingdom. Transfus Clin Biol, 13, 312–16. Hod E, Schwartz J (2008). Platelet transfusion refractoriness. Br J Haematol, 142, 348–60. Issitt PD, Anstee DJ (eds) (1998). Applied blood group serology, 4th edi- tion. Montgomery Scientific, Durham. Kaufman RM, et al. (2015). Platelet transfusion: a clinical practice guideline from the AABB. Transfusion, 162, 205–13. Klein HG (2006). Transfusion-associated graft-versus-host dis- ease: less fresh blood and more gray (Gy) for an aging population. Transfusion, 46, 878–80. Klein HG, Strauss RG, Schiffer CA (1996). Granulocyte transfusion therapy. Semin Hematol, 33, 359–68. Kuter DJ, Begley CG (2002). Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. Blood, 100, 3457–69. Liles WC, et al. (1997). A comparative trial of granulocyte-colony- stimulating factor and dexamethasone, separately and in combin- ation, for the mobilization of neutrophils in the peripheral blood of normal volunteers. Transfusion, 37, 182–7. Lo YM, et al. (1998). Prenatal diagnosis of fetal RhD status by mo- lecular analysis of maternal plasma. N Engl J Med, 339, 1734–8. Looney MR, Gilliss BM, Matthay MA (2010). Pathophysiology of transfusion-related acute lung injury. Curr Opin Hematol, 17, 418–23. Looney MR, Gropper MA, Matthay MA (2004). Transfusion-related acute lung injury. Chest, 126, 249–58. Marcus DM (1969). The ABO and Lewis blood-group system. Immunochemistry, genetics and relation to human disease. N Engl J Med, 280, 994–1006. Montgomery SP, et al. (2006). Transfusion-associated transmission of West Nile virus, United States 2003 through 2005. Transfusion, 46, 2038–46. Murphy MF (1999). New variant Creutzfeldt-Jakob disease (nvCJD): the risk of transmission by blood transfusion and the potential benefit of leukocyte-reduction of blood components. Transfus Med Rev, 13, 75–83. Murphy MF, Yazer MH (2013). Measuring and monitoring blood util- ization. Transfusion, 53, 3025–8. Novotny VM (2004). Prevention and management of platelet transfu- sion refractoriness. Vox Sang, 76, 1–13. Paglino JC, et al. (2004). Reduction of febrile but not allergic reac- tions to RBCs and platelets after conversion to universal prestorage leukoreduction. Transfusion, 44, 16–24. Panch SR, et al. (2019). Hemolytic Transfusion Reactions. N Engl J Med, 381(2), 150–62. Popovsky M (2012). Transfusion reactions, 4th edition. American Association of Blood Banks, Bethesda, MD. Procop GW (2013). Strategies for appropriate test utilization: the right test for the right patient at the right time. Cleveland Clinic Laboratories. https://clevelandcliniclabs.com/wp-content/assets/ pdfs/publications/2014-test-utilization.pdf. Race RR (1944). An ‘incomplete’ antibody in human serum. Nature, 153, 771–2. Reesink HW, et al. (2010). Pathogen inactivation of platelet concen- trates. Vox Sang, 99, 85–95. Reid M, Lomas-Francis C, Olsson M (2012). The blood group antigen. Elsevier, Burlington, MA. Reid ME (2009). Transfusion in the age of molecular diagnostics. Hematol Am Soc Hematol Educ Program, 2009, 171–7. Reid ME, Yazdanbakhsh K (2011). Molecular insights into blood groups and implications for blood transfusion. Curr Opin Hematol, 5, 93–102. Silliman CC (1999). Transfusion-related acute lung injury. Transfus Med Rev, 13, 177–86. Silliman CC, McLaughlin NJD (2006). Transfusion-related acute lung injury. Blood Rev, 20, 139–59. Slapak C, Fredrich N, Wagner J (2011). Transfusion safety: is this the business of blood centers? Transfusion, 51, 2767–71. Snyder

EL (2008). The role of cytokines and adhesive molecules in fe- brile non-hemolytic transfusion reactions. Immunol Invest, 24, 333–9. Snyder EL, Stramer SL, Benjamin RJ (2015). The safety of the blood supply – time to raise the bar. N Engl J Med, 372, 1882–5. Stanworth SJ, et al. (2013). A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med, 368, 1771–80. Stanworth SJ, et al. (2013). Thrombocytopenia and platelet transfusion in UK critical care: a multicenter observational study. Transfusion, 53, 1050–8. Stramer SL, Dodd RY (2013). Transfusion-transmitted emerging in- fectious diseases: 30 years of challenges and progress. Transfusion, 53, 2375–83. Utter GH, et al. (2006). Leukoreduction of blood transfusions does not diminish transfusion-associated microchimerism in trauma pa- tients. Transfusion, 46, 1863–9. Vogelsang GB, Hess AD (1994). Graft-versus-host disease: new direc- tions for a persistent problem. Blood, 84, 2061–7. Wiener AS (1943). Genetic theory of the Rh blood types. Proc Soc Exp Biol Med, 54, 316. Winslow RM (2006). Red cell substitutes. Semin Hematol, 44, 51–9.

Revision #1
Created 2026-01-22 16:42:50 UTC by Omar Ayman
Updated 2026-01-22 16:42:50 UTC by Omar Ayman