Review

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A brief overview of clinical significance of blood group antibodies

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This review was derived from a presentation made on September 2, 2016 for the first Academy Day presented by the Working Party on Immunohematology at the International Society of Blood Transfusion (ISBT) Congress in Dubai. The focus of this review is to provide a brief overview of the clinical significance of blood group antibodies. Blood group antibodies can be naturally occurring (e.g., anti-A and anti-B through exposure to naturally occurring red blood cell [RBC] antigen-like substances) or can occur via exposure to foreign (donor) RBC antigens through previous transfusions, transplants, or exposure to fetal RBCs during or after pregnancy. However, not all blood group antibodies are clinically significant. Clinically significant blood group antibodies can cause adverse events after blood component transfusion or transplantation and/or can cause hemolytic disease of the fetus and newborn. ***Immunohematology* 2018;34:4–6.**

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Red blood cells (RBCs) carry numerous protein and carbohydrate antigens on their surface. In 2016, the International Society of Blood Transfusion recognized 346 RBC antigens.[1] These antigens can provoke an immune response that may lead to the development of antibodies. Such antibodies, directed at RBC antigens, can be produced through exposure to naturally occurring RBC antigen-like substances or exposure to foreign (donor) RBC antigens through previous transfusions, transplants, or exposure to fetal cells during or after pregnancy. Naturally occurring anti-A and anti-B are the only RBC antibodies normally found in human serum or plasma. All other antibodies are unexpected and can be divided into alloantibodies (an antibody to an antigen that an individual lacks) and autoantibodies (an antibody to an individual's own antigen[s]). The role of blood group antibodies in blood transfusion, transplantation, hemolytic disease of the fetus and newborn (HDFN), and, in some cases, hemolytic anemia are reviewed in previous publications and summarized here.[2–5]

Blood Component Transfusion

The presence of antibodies directed against the blood group antigens in the transfused component (major incompatibility) or antibodies in the transfused product directed against the recipient's blood group antigens (minor incompatibility) may lead to the destruction of RBCs and manifest as a hemolytic transfusion reaction (HTR). In HTRs, hemolysis may be intravascular or extravascular.

Intravascular HTR occurs rapidly, with cell destruction within a few minutes. This event is caused by IgM antibodies that activate the complement pathway, which leads to formation of a membrane-activating complex that punctures the RBC membrane and subsequently releases hemoglobin into the plasma, with severe signs and symptoms of hemolysis (described subsequently). The most common antibodies causing intravascular HTR are of the ABO blood group system (anti-A, anti-B, and anti-AB), but antibodies of other blood group systems have also been occasionally implicated.

Extravascular HTRs can be immediate (occurring within a few hours of transfusion) or delayed (occurring within a few days of transfusion) and are caused by IgG antibodies that do not bind complement (e.g., antibodies to Rh system antigens), or that bind complement at levels that do not lead to the formation of membrane activating complex (e.g., antibodies to Kidd or Duffy system antigens). RBCs coated with IgG or C3b are phagocytized by the macrophages in the spleen or sequestered by the liver macrophages. Usually, immediate extravascular HTRs occur in the presence of antibodies to ABO blood group antigens and have similar signs as intravascular HTRs but are milder.

Delayed transfusion reactions (DTRs) usually occur in patients who were previously alloimmunized to an antigen but whose antibody titers have dropped to levels not detected by serologic tests or to levels insufficient to produce immediate hemolysis. In DTRs, the presence of the antigen in the

transfused product results in an anamnestic response within a few days, resulting in the clearance of the donor's RBCs. These reactions may present with no clinical signs and may only be detected by serologic methods (delayed serologic transfusion reactions) or as delayed hemolytic transfusion reactions (DHTRs) with mild signs and few symptoms. These reactions may also result in fever, fall in hemoglobin levels, jaundice, and hemoglobinuria. In some cases, immune destruction of transfused RBCs may have no obvious pathological effects, yet these are detrimental because they reduce the efficacy of the transfusion. Severe manifestations (e.g., disseminated intravascular coagulation, renal failure) are rarely seen.

Destruction of Autologous RBCs (Autoimmune Hemolytic Anemias)

Autoimmune hemolytic anemias are a group of disorders in which the malfunction of the body's immune system leads to development of antibodies against the individual's own RBCs (autologous) and may lead to destruction of RBCs with release of hemoglobin into the plasma. These disorders can be idiopathic or secondary to a disease (e.g., systemic lupus erythematosus, lymphoma) or to drugs (e.g., alpha methyldopa, penicillin), the mechanisms of which are poorly understood and are reviewed elsewhere.[6–10] These antibodies frequently react with all RBCs tested, although in some cases, specificity to antigens of high prevalence can be determined. Certain clinical conditions may also be associated with autoantibodies (e.g., antibodies to the I antigen after viral infection or autoantibodies to the P antigen in paroxysmal cold hemoglobinuria).

Transplantation

Many blood group antigens are expressed on tissues other than RBCs. ABO antigens are expressed on most tissues and, because anti-A and anti-B occur naturally in the plasma, these antigens play a major role in transplantation. In solid organ transplantation, antibodies in the recipient directed at donor antigens result in immune reactions that may cause rejection of the transplanted organ. In hematopoietic stem cell transplantation (HSCT), hematopoietic cells can be transplanted from a donor of any blood group to a recipient of any blood group. Consequently, HSCT can result in a matched transplant from an ABO-compatible donor or a mismatched transplant from a donor with antigens to which the recipient has antibodies (major mismatch), from a donor who will produce antibodies to the recipient's RBCs (minor mismatch), or from a bidirectional mismatch in which both the donor's and recipient's RBCs produce antibodies against each other's RBCs. In a mismatched HSCT, the donor's hematopoietic cells will give rise to a new blood group in the recipient. Such mismatched HSCTs can result in immediate hemolysis at the time of graft infusion (more common with marrow transplants containing large amounts of RBCs) or delayed complications, such as hemolysis at the time of engraftment, pure RBC aplasia, delayed engraftment, or failure to engraft because of the presence of ABO antibodies or passenger lymphocytes.[11]

Hemolytic Disease of the Fetus and Newborn

HDFN is a potentially fatal alloimmune reaction caused by maternal antibodies that cross the placenta to the fetus, where they initiate immune destruction of RBCs in utero or during the neonatal period. These maternal antibodies are restricted to IgG because antibodies of other classes are not transported across the placental barrier. Maternal antibodies may have developed in response to prior exposure to paternal antigens [e.g., anti-D due to exposure of D– mother to a D+ fetus] or through previous blood transfusions [e.g., anti-K and -Jk^a in a K–, Jk(a–) woman]. Clinically, the severity of HDFN varies from mild neonatal jaundice that can be treated by phototherapy, to severe in utero anemia requiring intrauterine and/or post-delivery transfusions, to fetal or neonatal death.

Classifying RBC Antibodies

RBC antibodies can be directed at any of the more than 300 known RBC antigens, although not all of them may cause the reactions just discussed. One clinical approach is to classify these antibodies into four categories: (1) clinically significant antibodies; (2) clinically insignificant antibodies; (3) antibodies that are clinically insignificant unless they are reactive at 37°C; and (4) antibodies whose clinical significance is unknown or that have occasional case reports of being clinically significant (Table 1). For evaluation of antibodies in this last category, curated literature can be found at the Notify Library Web site (www.notifylibrary.org), an online publically accessible database of adverse outcomes collected and analyzed by editorial groups of international experts, regulators, and clinicians.[12]

Table 1. Selected RBC antibodies and their clinical significance

Group 1 Clinically significant	Group 2 Clinically insignificant	Group 3 Clinically significant when reactive at 37°C	Group 4 Unknown or variable clinical significance
ABO	Ch[a], Rg[a]	Le[a], Le[b]	Yt[a]
D, C, c, E, e	Xg[a]	M, N	Gy[a]
K, k	Cs[a]	P1	Hy
Fy[a], Fy[b]	Kn[a]	Lu[b]	Sd[a]
Jk[a], Jk[b]	McC[a], Yk[a]	A1	Ge
S, s	JMH	Bg	
Vel	Lu[a]		

Agreement does not exist in the literature for all antigens in all categories, and this list is not inclusive of all alloantibodies to blood group antigens.
RBC = red blood cell.

Incidence of RBC Alloimmunization, HTRs, and Role of Hemovigilance

It is estimated that RBC antibodies occur in less than 0.3 percent of normal blood donors,[13] although the rate of alloimmunization increases in hospitalized patients who have received a blood transfusion.[5,14] This rate is significantly higher in certain patient populations (e.g., transfusion-dependent patients with sickle cell disease or thalassemia[4,15]). Alloimmunization was shown to be the third leading cause of transfusion-associated deaths in the United States and the UK. Data are generated from ongoing hemovigilance studies reported by various national agencies such as the Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration (FDA),[16] the UK's Serious Hazards of Transfusion (SHOT) annual report,[17] and the Hemovigilance Activity Report of the French National Agency for Medicine and Health Product Safety.[18] The Notify Library has only recently begun to add cases from the literature and reporting authorities; nevertheless, it serves as a ready resource for reviewing alloimmunization related to RBC antigens resulting from transfusion, pregnancy, and transplantation.

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