Transfusion Reactions

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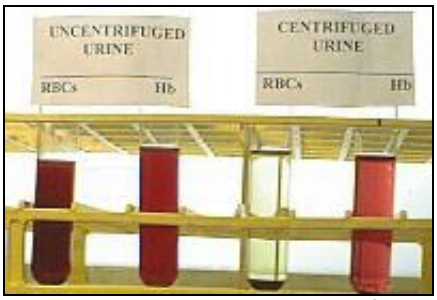
Background

Acute transfusion reactions present as adverse signs or symptoms during or within 24 hours of a blood transfusion. The most frequent reactions are fever, chills, pruritus, or urticaria, which typically resolve promptly without specific treatment or complications. Other signs occurring in temporal relationship with a blood transfusion, such as severe shortness of breath, red urine (see image below), high fever, or loss of consciousness may be the first indication of a more severe potentially fatal reaction.[1, 2, 3]



Rapid test to distinguish hematuria from hemoglobinuria. The onset of red urine during or shortly after a blood transfusion may represent hemoglobinuria (indicating an acute hemolytic reaction) or hematuria (indicating bleeding in the lower urinary tract). If freshly collected urine from a patient with hematuria is centrifuged, red blood cells settle at the bottom of the tube, leaving a clear yellow urine supernatant. If the red color is due to hemoglobinuria, the urine sample remains clear red after centrifugation.

Transfusion reactions require immediate recognition, laboratory investigation, and clinical management. If a transfusion reaction is suspected during blood administration, the safest practice is to stop the transfusion and keep the intravenous line open with 0.9% sodium chloride (normal saline). A clerical check of the information on the blood unit label and the patient's identification should be performed to ensure that the "right" blood unit was administered to the "right" patient. In most cases, the residual contents of the blood component container should be returned the blood bank, together with a freshly collected blood sample from the patient, and a transfusion reaction investigation should be initiated.

Acute transfusion reactions may present in complex clinical situations when the diagnosis requires distinguishing between a reaction to the transfused blood product and a coincidental complication of the illness being treated that occurs during or immediately after a blood transfusion.

For excellent patient education resources, visit eMedicine's Kidneys and Urinary System Center. Also, see eMedicine's patient education article Blood in the Urine.

Pathophysiology

Acute transfusion reactions are typically classified into the following entities[4] :

- Transfusion-related acute lung injury (TRALI) has 2 proposed pathophysiologic mechanisms: the antibody hypothesis and the neutrophil priming hypothesis.[5, 6]
    - The antibody hypothesis states that a human leukocyte antigen (HLA class I, HLA class II) or human neutrophil antigen (HNA) antibody in the transfused component reacts with neutrophil antigens in the recipient (ie, when antileukocyte antibodies are transfused passively in a plasma-containing blood component).[7] The recipient's neutrophils lodge in the pulmonary capillaries and release mediators that cause pulmonary capillary leakage. As a consequence, many patients with TRALI will develop transient leukopenia.[8] However, transfusions of blood components containing neutrophil antibodies may cause a wide range of reactions, including leukopenia, that do not meet the definition of TRALI.[9]
    - The neutrophil priming hypothesis does not require antigen-antibody interactions and occurs in patients with clinical conditions that predispose to neutrophil priming and endothelial activation such as infection, surgery, or inflammation. Bioactive substances in the transfused component activate the primed, sequestered neutrophils, and pulmonary endothelial damage occurs.
    - Both proposed pathophysiologic mechanisms lead to pulmonary edema in the absence of circulatory overload.
- Circulatory (volume) overload occurs when the volume of the transfused blood components and any coincidental infusions cause acute hypervolemia and, typically, acute pulmonary edema.[10, 11]
- Bacterial contamination and endotoxemia may result from inadequate sterile preparation of the phlebotomy site, opening the blood container in a nonsterile environment, or the presence of bacteria in the donor's circulation at the time of blood collection.
- Acute hemolytic transfusion reactions may be either immune-mediated or nonimmune-mediated. Immune-mediated hemolytic transfusion reactions caused by immunoglobulin M (IgM) anti-A, anti-B, or anti-A,B typically result in severe, potentially fatal complement-mediated intravascular hemolysis. Immune-mediated hemolytic reactions caused by IgG, Rh, Kell, Duffy, or other non-ABO antibodies typically result in extravascular sequestration, shortened survival of transfused red cells, and relatively mild clinical reactions.[12]
- Acute hemolytic transfusion reactions due to immune hemolysis may occur in patients who have no antibodies detectable by routine laboratory procedures.[13] Experimental evidence supports a central role for cytokines in the pathophysiology of hemolytic transfusion reactions. Tumor necrosis factor appears to be the most commonly identified mediator of intravascular coagulation and end-organ injury although other cytokines have been implicated including interleukin (IL)-8, monocyte chemoattractant protein, and IL-1 receptor antagonist.[14, 15]
- Nonimmune hemolytic transfusion reactions occur when red blood cells (RBCs) are damaged before transfusion, resulting in hemoglobinemia and hemoglobinuria without significant clinical symptoms.[16]
- Nonhemolytic febrile transfusion reactions are usually caused by cytokines from leukocytes in transfused red cell or platelet components, causing fever, chills, or rigors. In the setting of transfusion administration, a fever is defined as a temperature elevation of 1º Celsius (Centigrade) or 2º Fahrenheit. A nonhemolytic transfusion reaction is a diagnosis of exclusion, because hemolytic and septic reactions can present similarly.
- Allergic reactions typically present with rash, urticaria, or pruritus and are indistinguishable on examination from most food or drug allergies. Allergic reactions are IgE mediated. These reactions are usually attributed to hypersensitivity to soluble allergens found in the transfused blood component.[17] Anaphylactic reactions have been associated with anti-IgA in recipients who are IgA deficient.[18]
- Patients with congenital haptoglobin deficiency, typically of Northeast Asian origin, may experience anaphylactic nonhemolytic transfusion reactions when transfused with conventional blood components.[19, 20] Patients with hereditary C1-inhibitor deficiency may have recurrent attacks of angioedema when

transfused with standard plasma containing blood components.[21]

Epidemiology

Frequency

United States

- TRALI: The frequency of TRALI is estimated to occur in 0.014-0.08% of blood component transfusions or in 0.04-0.16% of patients transfused.[22, 23, 24, 25, 26, 27] In 2005, TRALI was the most frequently reported fatal complication of blood transfusion in the US.[28]
- Circulatory (volume) overload: Varies with concurrent illness
- Bacterial contamination/endotoxemia: The incidence of septic reactions may be as high as 1 case per 700 pooled random donor platelet concentrates and 1 case per 4000 single-donor (apheresis) platelet products. In a study of 1,004,206 apheresis platelet collections, 186 (1:5399) had confirmed-positive bacterial cultures.[29, 30, 31, 32] The frequency of sepsis associated with bacterially contaminated RBCs is estimated to be 1 in 250,000.[33] The frequency of contaminated RBCs based on culturing was 1 in 38,465 or 2.6/100,000 units.[34, 35]
- Acute hemolytic, immune mediated (fatal): 1 case per 250,000-600,000 population
- Acute hemolytic, immune mediated (nonfatal): 1 case per 6000-33,000 population
- Acute hemolytic, nonimmune: Infrequent
- Febrile, nonhemolytic: The frequency of febrile nonhemolytic transfusion reactions increases directly with the number of previous transfusions or pregnancies in the recipient, as well as the presence of leukocytes and/or plasma in the transfused component. Of nearly 100,000 units of whole blood and RBCs transfused, less than 1% resulted in a febrile reaction, and only 15% experienced a second reaction when subsequently transfused.[36]
- Allergic: 1 case per 333 population
- Anaphylactic: The estimated frequency is 1 in 20,000 to 1 in 47,000 blood components transfused.[37]

Mortality/Morbidity

- TRALI: Although TRALI is an uncommon event, in 2004, it was the most frequent cause of acute transfusion fatality reported to the US Food and Drug Administration (FDA). Early and intensive pulmonary support reduces the risk of a fatal outcome. No long-term morbidity has been described in survivors.
- Circulatory (volume) overload: Outcome varies with the overall clinical status of the patient. No long-term sequelae occur.
- Bacterial contamination/endotoxemia is potentially fatal and may be caused by gram-positive or gram-negative bacteria. Early diagnosis, initiation of broad-spectrum antibiotics, and other intensive supportive measures may reverse the outcome of an otherwise fatal complication of transfusion. Based on the frequency of sepsis and positive cultures of platelet units, the mortality rate is estimated to be approximately 1 in 50,000 platelet units.[33, 38]
- Acute hemolytic reactions (antibody mediated): Most severe and fatal reactions result from inadvertent transfusion of group AB or group A red cells to a group O recipient. Renal failure and disseminated intravascular coagulation (DIC) are potential complications for patients who survive the initial acute reaction. Mortality increases directly with the volume of incompatible blood that was transfused.
- Acute hemolytic reactions (non–antibody-mediated) are typically benign; these include mechanical hemolysis of serologically compatible RBCs due to freezing, pressure infusion pumps, and osmotic hemolysis.[39] Transfusion of serologically compatible but hemolyzed red cells results in acute hemoglobinemia and hemoglobinuria. Rarely, short- or long-term complications occur.
- Nonhemolytic febrile reactions are discomforting but typically benign. Occasionally, patients may have rigors, nausea, vomiting, and considerable distress. Patients who develop fever associated with a blood transfusion must be monitored carefully until the possibility of bacterial contamination of the blood product is excluded.
- Allergic reactions are typically benign but bothersome to recipients. Occasionally, allergic reactions may progress from pruritus and hives to bronchospasm and a generalized reaction, but such events are

uncommon.
- Anaphylactic reactions are potentially, but rarely, fatal. The only fatal case of anti–IgA-related anaphylaxis identified in the medical literature by the authors involved a patient with an anti – IgA/IgA reaction who died of a myocardial infarction.[40] Patients experiencing an acute attack of angioedema due to C1-inhibitor deficiency may have severe abdominal or subcutaneous attacks or laryngeal edema requiring emergency treatment.[41] The mortality rate for anaphylaxis is estimated to be approximately 1 per year.[17]
- Alloimmunization to RBC blood group antigens may be considered a complication of RBC transfusions, because such patients may be at risk of delays in the future if they require urgent transfusion of compatible RBCs.[42] Alloimmunization to RBC blood group antigens may also delay solid-organ transplantation if a significant number of serologically compatible RBCs are required.[43]

Race

In the United States, sickle cell anemia is found predominantly in the black population. Patients with sickle cell anemia require chronic red cell transfusions and, as a result, may form multiple alloantibodies to common Rh, Kell, Kidd, or other blood group antigens. The presence of such alloantibodies may increase the time required for a transfusion service to supply serologically compatible red cells. If undetected, these red cell alloantibodies may cause shortened survival of transfused red cells and extravascular hemolysis, but severe acute hemolytic reactions are uncommon.[44, 45]

Sex

- Multiparous women may form alloantibodies to leukocyte, red cell, or platelet antigens as the result of an overt or inapparent fetal-maternal hemorrhage. Women who form leukocyte antibodies following pregnancy are more likely to have febrile, nonhemolytic transfusion reactions if subsequently transfused with leukocyte-containing blood components.
- Multiparous women who form IgG red cell alloantibodies may experience delays while serologically compatible red cells are located for future transfusions. Undetected weak IgG alloantibodies are unlikely to cause acute hemolytic reactions, but they may cause shortened survival of the transfused incompatible red cells.

Age

Acute transfusion reactions may occur at any age.

- Because newborns do not form antibodies to ABO blood group antigens (anti-A, B, or AB) during the first few months of life (ie, infants do not form anti-A or anti-B until 3-4 months after birth), acute ABO-related transfusion reactions are not observed in this age group.[46] The presence of any transplacentally transferred maternal IgG anti-A, B, or AB is unlikely to cause a clinically significant reaction.
- Most blood transfusions are administered to persons aged 60 years and older; therefore, most acute transfusion reactions also occur in this age group.
- A decline in the titers of ABO antibodies after the sixth decade of life reduces the likelihood that the inadvertent transfusion of ABO-incompatible red cells will cause a severe fatal reaction.[47]

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