

Transfusion Reactions

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Immune Complications

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Acronyms and Abbreviations

AHTR, acute hemolytic transfusion reaction; DHTR, delayed hemolytic transfusion reaction; FFP, fresh frozen plasma; FNHTR, febrile non-hemolytic transfusion reaction; HTR, hemolytic transfusion reaction; PCV, packed cell volume; pRBCs, packed red blood cells; PTP, post-transfusion purpura; RBC, red blood cell; TA-GVHD, transfusion-associated graft-versus-host-disease; TRALI, transfusion-related acute lung injury; WB, whole blood.

Blood is a complex biologic product which, like any tissue transplant, can result in as much harm as benefit to the recipient. The term transfusion reaction denotes any adverse event associated with transfusion of blood or a blood component. The reaction may occur during or within hours to weeks after administration of a blood product. Understanding how to prevent a transfusion reaction and recognizing the potential clinical and clinicopathologic signs of an adverse reaction should one occur are key to good transfusion medicine practice.

Transfusion reactions have been classified using various terminologies in both the human and veterinary literature but are most often characterized by immunologic and non-immunologic mechanisms. There have been several reviews in the veterinary literature on blood transfusions in cats, dogs, and horses, with the incidence and type of transfusion reactions varying between institutions and species but ranging from 3–13%.^{10,11,19,20,23–26} Reports of adverse reactions underscore the need for further education on their prevention and identification.

IMMUNE COMPLICATIONS

Hemolytic Transfusion Reactions

Hemolytic transfusion reactions (HTR) jeopardize the health of an already compromised patient. A HTR is the result of naturally-occurring or induced antibodies present in the recipient plasma which can destroy donor red blood cells (RBCs) immediately upon transfusion or within hours to weeks. These reactions are classified as a type 2 hypersensitivity and are mediated by antibodies directed against antigens present on the surface of RBCs.¹ After reacting with the RBC surface antigen, IgG or IgM antibodies activate the complement system, culminating in the formation of a membrane attack complex which disrupts the lipid bilayer of the RBC membrane, causing intravascular hemolysis.¹ Also, antibody or complement fragments, primarily C3b or C4b, can adhere to the RBC surface (opsonization), enhancing RBC susceptibility to phagocytosis by leukocytes expressing receptors for these proteins.¹ Either intravascular or extravascular hemolysis can result, depending

on whether the leukocytes recognize the opsonized RBCs while in circulation or within the reticuloendothelial system. The severity of a HTR is influenced by the concentration of recipient alloantibody, the immunoglobulin type, whether the antibody is warm or cold-reacting, the amount of blood transfused, and the condition of the recipient.⁴⁶

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions (AHTRs) present within 24 hours of a RBC transfusion.^{12,36} Preformed antibodies in the recipient react with transfused donor RBCs. The recipient has previously formed an alloantibody against an antigen present on the donor's RBCs which is not present on the recipient's RBCs. Cats are similar to humans, as both have naturally-occurring alloantibodies which can result in a potentially fatal AHTR. Anti-A alloantibodies in type B cats are strong hemagglutinins and hemolysins and are present in a high concentration^{8,28} (see Chapter 92). Transfusion of type A blood to a type B cat can be fatal if not immediately recognized, with subsequent discontinuation of the transfusion and institution of supportive care.^{11,15,16} Within seconds to a few minutes of receiving as little as 1 mL of type A blood, a type B cat may exhibit restlessness, vocalization, vomiting, urination, salivation, and recumbency.^{15,16} Bradycardia, cardiac arrhythmias, decreased pulse strength, pale mucous membranes, and prolonged capillary refill time are also expected in the initial phase.¹⁶ If the reaction is recognized and the transfusion stopped, hemoglobinemia and hemoglobinuria will follow, as these reactions are IgM and complement-mediated with obvious intravascular hemolysis.^{15,16} Acute renal failure, which is seen in humans with blood type ABO transfusion reactions, has not been documented in type B cats receiving type A blood under experimental conditions.

As type B blood is not commonly stored and type B cats comprise a small percentage of cats (outside of a few breeds), inadvertent transfusion of type B blood to a type A cat is unlikely. Inaccurate blood typing results, however, could result in a type A or AB cat being mislabeled as type B with subsequent transfusion of type B blood.³³ Although type A cats generally have lower concentration of weak anti-B antibodies which are of both IgM and IgG classes, transfusion of type B blood can still cause both clinical and clinicopathologic features of a transfusion reaction including discomfort, listlessness, tachycardia and tachypnea, as well as mild hemoglobinemia, hemoglobinuria, and bilirubinuria.^{8,16,28} Direct antiglobulin tests (Coombs' test) are variably positive in both type A and type B cats receiving mismatched blood.¹⁶

A blood type AB cat could receive either type A or B pRBCs, but plasma or whole blood (WB) from a blood type A or B cat could increase the risk of a HTR reaction due to the presence of anti-B and anti-A alloantibodies, respectively. Given the generally weaker nature of anti-B alloantibodies, plasma or WB from a type A cat would be preferred: type AB WB or plasma would be

ideal, but unrealistic in most settings given the low frequency at which type AB cats are found.

Hemolytic transfusion reactions in cats can be avoided by blood typing both the donor and recipient. Crossmatching is also important, especially if the intended recipient's transfusion history is unknown or if the recipient has been previously transfused. A crossmatch test (see Chapter 139) can identify preformed alloantibodies against a blood group antigen, thus preventing an AHTR. Until recently, blood types and naturally-occurring alloantibodies outside of the AB blood group system were not recognized, but incompatible crossmatches between AB blood type compatible cats have been described, suggesting the existence of other blood groups (see Chapter 92).^{20,44} *Mik*, a newly described blood group in cats, can also result in HTRs.⁴⁵ A cat negative for the *Mik*-RBC antigen can experience an AHTR, similar to those described in type A cats receiving type B blood, after transfusion with *Mik*-positive RBCs.⁴⁵ Given that this antibody was demonstrated to be naturally-occurring, crossmatching cats prior to even a first blood transfusion may be warranted. An incompatible crossmatch test, in the face of blood-type compatibility, suggests alloantibody formation and should not be ignored.

Some dogs may have naturally-occurring RBC alloantibodies, though there is controversy regarding their clinical significance. Generally, HTRs require prior sensitization through a previous blood transfusion or, to a much lesser extent, pregnancy.⁵ A DEA 1.1 negative dog who has been sensitized by transfusion of DEA 1.1 positive blood will develop anti-DEA 1.1 antibodies. A second transfusion with DEA 1.1 positive blood will cause an AHTR. Such a reaction has been documented clinically: a DEA 1.1 negative recipient had been sensitized to the DEA 1.1 antigen through a previous transfusion, and upon inadvertently receiving DEA 1.1 positive blood 3 years later exhibited a 2°C rise in temperature within one hour of transfusion and developed hemoglobinemia and hemoglobinuria.¹⁷ Following an AHTR plasma will be red-tinged due to hemoglobine-mia (Fig. 100.1); this is most often identified when a post-transfusion PCV is measured. An AHTR is not exclusive to the DEA 1.1 antigen; alloantibody production and HTRs have been documented for other RBC antigens in dogs, including known DEA, as well as RBC antigens without DEA designation.^{4,9,31} When a compatible donor is not easily identified on a blood crossmatch, testing both siblings of the patient or potentially dogs of the same breed has been shown to be successful in identifying a compatible donor.^{4,9}

Delayed Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reactions (DHTRs) are defined as those occurring more than 24 hours following a transfusion, but the time of onset can vary to 48 hours post-transfusion depending on the reference.¹² DHTRs are often the result of an anamnestic response to a RBC antigen that the recipient lacks, with the previously produced reactive alloantibody weak or present

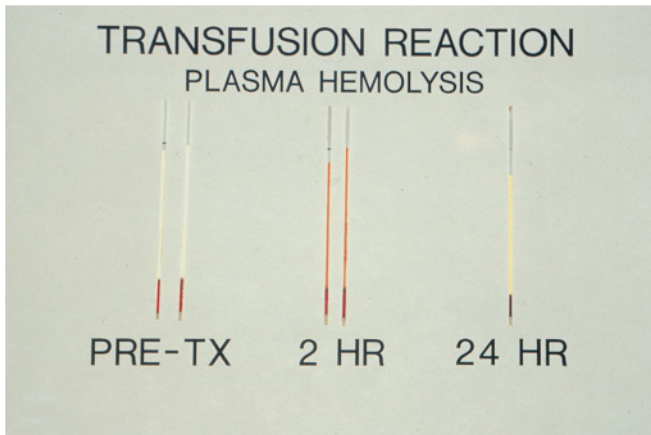


FIGURE 100.1 Serial packed cell volumes (PCVs) from a dog experiencing an acute hemolytic transfusion reaction. Note the transfusion of plasma from clear to hemolyzed to icteric over 24 hours. As a consequence of the transfusion reaction, the PCV fell following the transfusion. (Courtesy of Dr. Ann Hohenhaus.)

in very low concentrations. Pre-transfusion crossmatch testing may not identify the potential incompatibility if the test is insufficiently sensitive. Alternatively, DHTRs may be a result of primary alloimmunization to a RBC antigen, with hemolysis occurring weeks later after sufficient time for alloantibody production.¹²

A DHTR should be suspected if there is a more rapid decline than expected in PCV in the weeks following a blood transfusion, based on the patient's underlying disease. Additional clinicopathologic signs to support a diagnosis of DHTR include hyperbilirubinemia, bilirubinuria, or hemoglobinuria: fever can develop but often goes unnoticed. Diagnosis of a DHTR requires documentation of development of antibodies by the recipient against the donor(s) RBCs.

Preventing HTRs requires knowledge of blood groups present within a species, presence of naturally-occurring antibodies, prior transfusion history, and blood crossmatch testing. Regardless of the designation of acute versus delayed, the majority of HTRs can be prevented through proper blood typing and crossmatch testing.

Non-hemolytic Transfusion Reactions

Febrile and Allergic Reactions

Febrile and allergic reactions are two of the most common types of transfusion reactions reported in veterinary medicine, comprising 60–90% of reported reactions.^{20,24,25} Febrile, non-hemolytic transfusion reactions (FNHTRs) are defined in human medicine as a rise in temperature of either 2°F or 1°C during or within 4 hours post-transfusion without an obvious other cause for the rise in temperature.⁴⁶ Additional clinical signs can include vomiting and tremors: the vomiting will often resolve without treatment, but a decreased transfusion rate may help to alleviate this symptom.^{10,36}

Febrile, non-hemolytic transfusion reactions are frequently attributed to recipient alloantibodies which react with histocompatibility leukocyte antigens or other antigens present on donor lymphocytes, granulocytes, or platelets.^{6,36} Cytokines released from leukocytes and platelets within stored blood are also implicated as causes for FNHTRs and some allergic-type reactions.^{27,46} Pre-storage leukoreduction has been shown to decrease, but not eliminate, FNHTRs. Interestingly, leukoreduction of human platelet products did not significantly decrease the rate of allergic reactions, which were attributed to platelet-derived chemokines.^{6,27} Leukoreduction of canine WB does not decrease RBC viability but, for maximum reduction of leukocytes, needs to be performed on cooled blood following collection.⁷ Extrapolating from human data, leukoreduction at the time of administration would be less effective in veterinary medicine for decreasing FNHTRs; ideally, leukoreduction should be performed within a few hours of collection to minimize cytokine production and thereby prevent febrile reactions. However, routine leukoreduction of veterinary blood products is difficult to justify given the cost of the special leukoreduction filters and limited potential benefit to the majority of recipients. Platelet antigens would remain a potential source of reactivity even in leukoreduced WB or pRBCs. Recommendations for management of FNHTRs include stopping the transfusion but maintaining the intravenous line open with saline while excluding an AHTR or transfusion-related sepsis due to bacterial contamination of the unit (Fig. 100.2).

Allergic reactions are more often associated with transfusion of plasma products and are triggered by exposure to a substance, likely a protein, present in donor plasma to which the recipient has been sensitized.³⁶ Signs of an allergic reaction typically start within the first 15 minutes of a plasma transfusion but can occur during or within a few hours of administration. Clinical signs include mild to sometimes dramatic urticaria, pruritis, and erythema (Fig. 100.3). Additional signs can include vomiting, nausea, diarrhea, and/or abdominal pain.¹² Treatment of an allergic reaction to a plasma product includes stopping or, at least, decreasing the rate of transfusion, as well as administering an antihistamine such as diphenhydramine (1–2 mg/kg IM). Although pretreatment to prevent these types of immune reactions has been previously advised, administration of diphenhydramine to humans prior to leukoreduced platelet transfusions did not decrease the frequency of allergic-type urticarial reactions.⁴¹

Uncommon Immune Reactions

Post-transfusion purpura (PTP) is a relatively uncommon transfusion reaction in humans and has been described once in veterinary medicine.^{36,43} Thrombocytopenia develops 1–2 weeks post-transfusion due to recipient-produced anti-platelet antibodies. These antibodies are most often directed against a platelet specific antigen (e.g. in humans, HPA-1a) which the recipient lacks: platelets targeted for destruction are

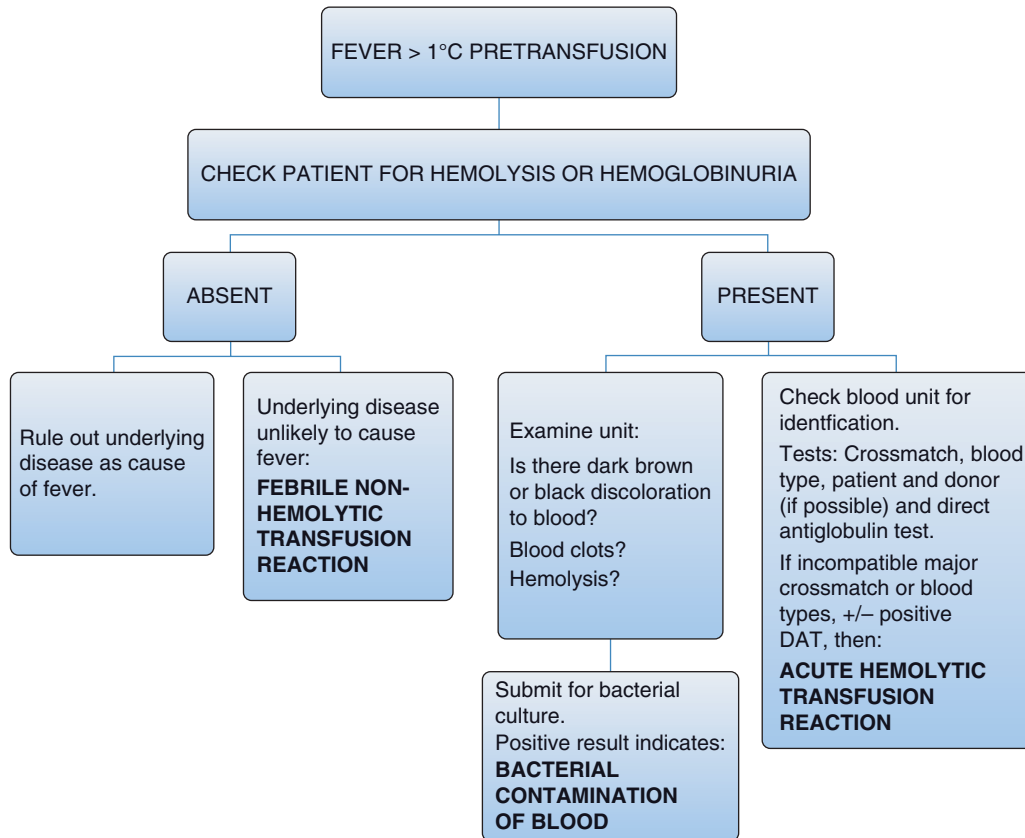


FIGURE 100.2 Algorithm for evaluation of a patient with a febrile transfusion reaction.



FIGURE 100.3 An urticarial reaction in a dog receiving plasma to treat rodenticide intoxication. Treatment with antihistamines and steroids induced resolution in 24 hours. (Courtesy of Dr. Ann Hohenhaus.)

typically those of the donor but targeting of recipient/patient platelets has also been documented.³⁶ PTP must be differentiated from worsening underlying disease or development of a concurrent disorder.

Anaphylaxis secondary to IgA deficiency has been reported in a single dog.² Anaphylaxis results from patient anti-IgA antibodies reacting to IgA antibodies in the donor plasma.² Clinical signs vary from facial

swelling, urticaria, and erythematous skin to respiratory distress, vomiting, diarrhea, and shock.¹ An IgA-deficient patient who previously demonstrated a severe anaphylactic reaction would require future transfusions that are free of IgA.

Transfusion-related acute lung injury (TRALI) is characterized by dyspnea, hypoxia, pulmonary edema, and fluffy, bilateral infiltrates on thoracic radiographs which develop during or within 6 hours of a transfusion. To date, TRALI has been described only in humans.^{35,39} Transfusion-related acute lung injury clinically mimics acute respiratory distress syndrome, circulatory overload, or cardiac failure, so it could be easily misdiagnosed. Fever may or may not be present.³⁹ Transfusion-related acute lung injury may result from several mechanisms, including both antibody-mediated pathways and non-immune causes, with neutrophil activation and subsequent leakage from capillaries (pulmonary microvasculature leakage) being the common final pathway.^{35,39} Treatment typically involves oxygen therapy and ventilation, when needed.³⁶

Transfusion-associated graft-versus-host-disease (TA-GVHD) also has yet to be reported in veterinary medicine. It results from the proliferation of viable donor T lymphocytes, which go unrecognized as foreign by the recipient's immune system; these donor T lymphocytes recognize and subsequently attack the recipient (or host).¹² In humans, certain cellular immunodeficiencies predispose the transfusion recipient to

this reaction; also, recipients of blood transfusions from close relatives place the recipient at greater risk for TA-GVHD.¹² Since leukoreduction is insufficient in preventing TA-GVHD, component irradiation is recommended in patient populations at increased risk of developing TA-GVHD (e.g. hematopoietic progenitor cell transplant recipients).¹² Clinical signs of TA-GVHD in man reportedly manifest within 2–50 days of transfusion and include a rash, diarrhea, liver dysfunction and pancytopenia. Mortality is greater than 90%.¹²

NON-IMMUNE COMPLICATIONS

Infectious Disease Transmission

Transmission of infectious agents to a blood transfusion recipient, though a relatively infrequent complication in both human and veterinary transfusion medicine, is not a true transfusion reaction but is obviously an avoidable and potentially devastating complication of transfusion. Infectious diseases documented to have been transmitted via transfusion in veterinary medicine include babesiosis, leishmaniasis, bartonellosis, and diseases caused by *Mycoplasma* sp.^{3,13,14,29,30,34,37,40} Although WB and pRBCs carry a greater risk of infectious disease transmission, plasma is not without risk; recently, herpesvirus was inadvertently transmitted to horses receiving commercially prepared plasma.³ A recent consensus statement from the American College of Veterinary Internal Medicine includes guidelines for recommended testing for both canine and feline blood donors based on the literature and known blood-borne agents (see Chapter 94).⁴² Documentation of a transfusion-acquired infection requires testing of pre-transfusion recipient blood, in addition to testing the donor; unfortunately, pre-transfusion recipient samples are not always available. Proper transfusion records will allow for easy identification of the suspected infected donor, removal of any remaining blood units from that donor, and appropriate treatment of the donor.

Transfusion-associated Sepsis

Bacterial contamination of a blood unit can result in transfusion-associated sepsis. Clinical signs associated with transfusion of a contaminated blood unit include fever, vomiting, diarrhea, hypotension, and hemolysis.¹² Contamination can occur at the time of collection from inadequate preparation of the venipuncture site or contamination of materials used in collection. Once contamination of a unit occurs, bacterial numbers tend to increase with storage time, even when the unit is refrigerated. Storage at room temperature, which is necessary to preserve the post-transfusion survival of platelets in fresh WB and platelet-rich preparations, can also lead to bacterial proliferation in contaminated units. It has been documented that units of human pRBCs stored for longer than 21 days are more likely to contain proliferating bacteria.¹⁸ The severity of a reaction will ultimately depend on the bacterial species, the number of bacteria

present, and the clinical condition of the recipient/patient.²¹

Reports of bacterial contamination of blood products and transfusion-associated sepsis are infrequent in veterinary medicine.^{2,22} Contamination of feline blood units with *Serratia marcescens* was attributed to contaminated supplies used in donor collection. Vomiting was the most common clinical sign seen in cats receiving contaminated units, and four recipients died.²² This report illustrates the importance of bacterial culture of materials other than the unit and demonstrates the steps necessary to identify the source of contamination. Contaminated WB or pRBC units are typically discolored (dark brown, purple, or black), and clots and air bubbles may also be present.^{22,36} The discoloration associated with bacterial contamination indicates deoxygenation, hemolysis, and the formation of methemoglobin. Blood units with such an abnormal appearance should not be used, and an investigation to confirm bacterial contamination and identify the source of contamination should be pursued. Lastly, administration of a blood component unit should ideally take no longer than 4 hours to reduce the potential for bacterial proliferation. Once a unit is opened, even if refrigerated, it should be used within 24 hours. If bacterial contamination is suspected after the transfusion has been started, the transfusion should be stopped immediately and the unit submitted for a Gram stain and bacterial culture. Blood culture of the recipient may also be warranted.

Uncommon Non-immune Complications

Citrate Toxicity

Citrate is the anticoagulant used in most standard blood collection systems. Plasma and WB have the greatest concentrations of citrate when compared to pRBCs. Patients most at risk for citrate toxicity include those receiving large volumes of blood products, such as in cases of massive transfusion (see Chapter 95) and, potentially, patients with severe liver disease since citrate is metabolized by the liver. Ionized hypocalcemia and hypomagnesemia result from chelation of these cations by citrate, and associated clinical signs include muscle tremors, vomiting, cardiac arrhythmias, ear twitching, hypotension and/or tetanic seizures.^{2,24} Intravenous calcium can be administered to treat clinically significant transfusion-related hypocalcemia.

Circulatory Overload

Patients with chronic anemia and a compensatory expanded plasma volume or patients with compromised pulmonary and/or cardiac function may be at risk for circulatory overload.³⁶ Expected clinical signs include respiratory distress and, in some cases, congestive heart failure; signs may be seen during or soon after transfusion. Management of fluid overload with diuretics is advised. Slowing the transfusion rate and using pRBCs rather than WB in anemic patients can help to decrease the risk of circulatory overload.

Non-immune Hemolysis Unrelated to Bacterial Contamination

Hemolysis unrelated to a blood group incompatibility or bacterial contamination may occur in vitro due to improper storage or handling of blood units, including use of a hot waterbath, inadvertent freezing, use of pumps not approved for administration of blood products, and concurrent administration of incompatible fluids, such as 5% dextrose or hypertonic saline through a shared intravenous line.^{32,36,38} Warmed blood has been demonstrated to have decreased survival in the patient which could mimic a delayed transfusion reaction.³²

PREVENTION AND RECOGNITION OF TRANSFUSION REACTIONS

Prior to blood product administration, baseline values of temperature, heart rate, and respiratory rate should be determined and pre-transfusion PCV should be recorded (see Chapters 95–99). Pre-transfusion WB and serum samples should be collected from the recipient, if not already submitted for other routine testing. These samples can be invaluable in cases of HTRs and in documentation of infectious disease transmission. Transfusion of any blood product is ideally started at a slower rate for the first 15 minutes while monitoring for signs of any adverse reactions. Clearly, in cases of severe, ongoing blood loss, rapid administration from the start may be necessary. Transfusion monitoring should be performed every 15 minutes for the first hour, with serial measurement of temperature, heart and respiratory rates. If there is any concern about an AHTR, evaluation of plasma and/or urine for the presence of hemoglobin is indicated. Lack of an expected increase in PCV post-transfusion may also be suggestive of an AHTR.

EVALUATION OF A PATIENT WITH A SUSPECTED TRANSFUSION REACTION

Investigation of hemolytic and febrile reactions should include inspection of the patient's plasma for evidence of hemolysis or icterus; evaluation of the blood product unit administered including unit labels, the administration set, Gram stain and blood culture of the transfused product; comparison of patient bilirubin both pre- and post-transfusion; retesting of patient and donor blood type, especially for reactions involving RBC-containing units; and post-transfusion crossmatch testing of recipient-donor compatibility. If a crossmatch test was performed pre-transfusion, it should be repeated in the case of a HTR; if one was not performed, a crossmatch test should be done using both pre- and post-transfusion plasma/serum, if available. In general, if a transfusion reaction is suspected, the transfusion should be stopped but the intravenous line kept open with saline until the patient and blood product can be further evaluated.

Adequately screening potential blood donors, transfusing patients only when clinically indicated, selecting the most appropriate blood component, properly administering blood products, and carefully monitoring transfusion recipients will greatly diminish the risk of a transfusion reaction.

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