Transfusion Reactions

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Synonyms and related keywords: hemolytic transfusion reactions, nonhemolytic febrile reactions, anaphylactic reactions, graft-versus-host disease, GVH disease, massive transfusion complications, transfusion-related hepatitis C, chronic hepatitis, cirrhosis

AUTHOR INFORMATION

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Disclosure

INTRODUCTION

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Background: Patients with acute blood loss or symptomatic anemia frequently require blood replacement therapy in the emergency department (ED). Although blood replacement therapy is generally safe, it should be understood that certain risks accompany the transfusion of blood and plasma components. Accordingly, emergency physicians must be familiar with and be able to manage adverse transfusion reactions, ranging from self-limited febrile responses to life-threatening intravascular hemolysis.

Pathophysiology:

Hemolytic transfusion reactions

Hemolytic transfusion reactions are the result of antibodies in the recipient's plasma directed against antigens on the donor's erythrocytes. This results in rapid intravascular hemolysis of the donor red blood cells. ABO incompatibility due to clerical error is the most frequent cause. This results in hemoglobinemia, hemoglobinuria, disseminated intravascular coagulation (DIC), renal failure, and complement-mediated cardiovascular collapse.

The recipient's antibodies to Rh or non-ABO antigens cause extravascular hemolytic reactions. These patients usually have been exposed to the antigen through previous pregnancies, transplantation, or transfusions. Antibody titers often are too low to be detected through routine antibody screening, but production of antibodies becomes amplified with reexposure. These antibodies do not activate complement; therefore, no intravascular hemolysis occurs. Instead, the RBCs are tagged for removal by splenic macrophages.

Nonhemolytic febrile reactions

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Toxic Epidermal Necrolysis
Toxicity, Ethylene Glycol
Urticaria

Nonhemolytic febrile reactions have been thought to be due to recipient antibodies formed against donor WBCs or platelets. More recently, these reactions have been postulated to stem from the formation of cytokines during the storage of the blood. These reactions seldom proceed to hypotension or respiratory distress.

Click here for patient education.

Anaphylactic reactions

Anaphylactic reactions most often are observed in those patients with a hereditary immunoglobulin A (IgA) deficiency. Some of these patients have developed complement-binding anti-IgA antibodies that cause anaphylaxis when exposed to donor IgA.

Proteins in the donor plasma can cause minor allergic reactions. This is an anaphylactoid reaction and is observed more frequently with components containing large amounts of plasma, such as whole blood, pooled platelets, and fresh frozen plasma.

Acquired diseases

Infectious diseases also may be transmitted through transfusion.

Graft-versus-host disease

Graft-versus-host (GVH) disease occurs in recipients when donor lymphocytes mount an immune response against the recipient's lymphoid tissue. Usually, the donor lymphocytes are recognized as being foreign and are destroyed. In situations when the donor is immunocompromised or when the donor is homozygous and the recipient is heterozygous for an HLA haplotype, these normal defense mechanisms may fail, resulting in GVH disease.

Transfusion-related acute lung injury

Transfusion-related acute lung injury may be caused by transfusing any plasma-containing blood product. It is caused by the interaction between the recipient's leukocytes and preexisting donor antileukocyte antibodies. This results in complement activation and increased pulmonary vascular permeability. In addition, mediators of inflammation that form while the blood is in storage are also felt to be contributory.

Massive transfusion complications

Massive transfusion is defined as the replacement of the entire blood volume within a 24-hour period or the replacement of 10 units of blood over the course of a few hours. Complications of massive transfusion include the following:

- Coagulopathy is caused by a dilutional effect on the host's clotting factors and platelets, as well as the lack of platelets and clotting factors in packed red blood cells.
- Volume overload
- Hypothermia
- Hyperkalemia may be caused by lysis of stored red cells and is increased in irradiated red blood cells.
- Metabolic acidosis and hypokalemia may be caused by the transfusion of a large amount of citrated cells.
- Hypocalcemia due to citrate toxicity may occur in those with hepatic failure, congestive heart failure (CHF), or other low-output states. It is increasingly uncommon with the use of component therapy.

Frequency:

- **In the US:** Hemolytic transfusion reactions occur in 1 per 40,000 transfused units of packed RBCs.
- Nonhemolytic febrile reactions and minor allergic reactions are the most common transfusion reactions, each occurring in 3-4% of all transfusions.
- Nonhemolytic febrile reactions and extravascular hemolysis are observed more commonly in patients who have developed antibodies from prior transfusions.
- Anaphylactic reactions occur in 1 per 20,000 transfused units.

- Due to improved preventative measures, the incidence of GVH disease is less than 0.15%
- Transfusion-related acute lung injury complicates 0.1-0.2% of all transfusions.
- Risk of transfusion-related hepatitis B is 1 per 50,000 units transfused. Risk for hepatitis C is 1 per 3000-4000 units transfused.
- Risk of transfusion-related HIV infection is 1 per 150,000 units transfused.

Mortality/Morbidity: Hemolytic transfusion reactions result in death in 1 per 100,000 units transfused.

- Transfusion-related hepatitis C causes chronic hepatitis and occurs in 50% of infected recipients.
- Cirrhosis develops in 10% of those with hepatitis.
- Transfusion-associated GVH disease is associated with an 80-90% mortality rate.
- The mortality rate of transfusion-related acute lung injury is 5%.

Sex: Nonhemolytic febrile reactions and extravascular hemolytic reactions are more common in parous females.

Age: Children have a greater risk of developing transfusion-related HIV than adults.

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History:

- In hemolytic transfusion reactions, symptoms usually occur after a small amount of blood has been transfused and almost always before the unit is transfused completely. These reactions are associated with the following:
  - Fever
  - Chills
  - Flushing
  - Nausea
  - Burning at the intravenous (IV) line site
  - Chest tightness
  - Restlessness
  - Apprehension
  - Joint pain
  - Back pain
- Nonhemolytic febrile reactions do not occur as rapidly as acute hemolytic reactions. They occur between 1 and 6 hours of transfusions and are associated with the nonspecific symptoms of fever, chills, and malaise. Some patients may complain of dyspnea. These nonspecific symptoms also occur with a hemolytic transfusion reaction.
- In anaphylactic reaction, symptoms usually occur with less than 10 mL of blood transfused and only rarely occur more insidiously. These reactions are associated with rapid development of the following:

- Chills
- Abdominal cramps
- Dyspnea
- Vomiting
- Diarrhea

- Minor allergic reactions are associated with urticaria.
- Extravascular hemolytic reactions are associated with fever and chills. Symptoms often occur after several hours and sometimes may be observed several days after transfusion.
- Symptoms of transfusion-related acute lung injury start suddenly while the blood products are being transfused or shortly thereafter. Dyspnea is the primary presenting symptom.
- GVH disease often presents within the first week following transfusion, although it may be delayed up to several weeks following transfusion. Symptoms include the following:
    - Fever
    - Abdominal pain
    - Nausea
    - Vomiting
    - Diarrhea, often copious
    - Anorexia
- Hypocalcemia from multiple transfusions may present with circumoral tingling and tremors of the skeletal muscles.

Physical:

- Hemolytic transfusion reactions are associated with the following signs, which usually occur after a small amount of blood has been transfused and almost always before the unit is transfused completely:
    - Tachycardia
    - Tachypnea
    - In severe cases, hypotension, oozing from the IV site, diffuse bleeding, hemoglobinuria, and shock
    - Oliguria may be seen in renal failure.
- In unconscious or obtunded patients, the diagnosis of hemolysis is suggested by development of the following:
    - Hypotension
    - Dark urine
    - Oozing from an IV or other puncture sites
- Nonhemolytic febrile reactions are associated with a fever.
- Anaphylactic reactions are associated with the following:

  - Anaphylactic reactions are associated with the following:
  - Tachycardia
  - Flushing
  - Urticaria
  - In more severe cases, wheezing, laryngeal edema, and hypotension
- Minor allergic reactions are associated with urticaria.
- Extravascular hemolytic reactions are associated with fever.
  - Only rarely are signs of shock and renal failure noted.
  - Clinical signs may occur several days later.
- Patients with transfusion-related acute lung injury will present with the following signs:
  - Fever
  - Tachycardia
  - Tachypnea
  - Rales
- GVH disease often presents with the following signs:
  - Erythematous, maculopapular rash, which may progress to toxic epidermal necrolysis
  - Right upper quadrant tenderness
  - Hepatomegaly

Causes:

- Transfusion-related infectious diseases caused by the presence of microorganisms in the donated blood include the following:
  - Hepatitis B
  - Hepatitis C
  - HIV-1
  - HIV-2
  - Cytomegalovirus (CMV)
  - West Nile virus
- Other diseases rarely reported to result from transfusion include the following:
  - Syphilis
  - Lyme disease
  - Malaria

  - Toxoplasmosis
  - Chagas disease
  - Jakob-Creutzfeldt disease
  - Filariasis
  - Babesiosis

- Donor blood is routinely screened for hepatitis B, hepatitis C, HIV-1, HIV-2, HTLV-1, HTLV-2, syphilis, and West Nile virus. Some, but not all donors, are screened for cytomegalovirus (CMV). Despite screening, some risk of transmission still occurs, since the donor may have been in the window where he or she is infectious but has not yet developed a detectable immunologic response at the time of donation.

- Transmission of HIV has occurred with the transfusion of only one unit, although greater risk exists with transfusion of multiple units.

DIFFERENTIALS

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Acute Respiratory Distress Syndrome
Anaphylaxis
Congestive Heart Failure and Pulmonary Edema
Disseminated Intravascular Coagulation
Hyperkalemia
Hypocalcemia
Hypokalemia
Hypothermia
Rh Incompatibility
Toxic Epidermal Necrolysis
Toxicity, Ethylene Glycol
Urticaria

Other Problems to be Considered:

Allergic reaction
Fever
Hemolysis
Sepsis

WORKUP

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Lab Studies:

- When a hemolytic transfusion reaction is suspected, send donor blood back to the blood bank to determine whether the correct unit of blood was administered to the intended recipient. In addition, the blood bank should perform a repeat type, crossmatch, antibody screen, and direct and indirect Coombs tests. Other considerations with a hemolytic transfusion reaction include the following:

  - Free serum hemoglobin appears as a pink color of the serum in a clotted centrifuged specimen. This may be observed with as little as 5-10 mL of hemolyzed blood.
  - Serum bilirubin level peaks in 3-6 hours as the free hemoglobin is metabolized.
  - Haptoglobin binds to hemoglobin and the serum hemoglobin level falls, reaching its nadir in 1-2 days.

  - Examine urine for hemoglobinuria.

- A repeat CBC fails to show the expected rise in hematocrit in patients developing intravascular or extravascular hemolysis.

- In acute transfusion-related acute lung injury, leukopenia and eosinophilia may be present.

- In GVH disease, the CBC will demonstrate pancytopenia and elevated liver enzymes levels. Electrolyte disturbances related to the diarrhea may be present.

- For the patient undergoing a massive transfusion, serially measure the following parameters:

  - Platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) should be checked after the transfusion of every 5 units of packed red cells and whenever signs or symptoms suggest a coagulopathy.

  - Potassium level

  - pH

  - Calcium level should be measured in patients developing signs, symptoms, or ECG manifestations of hypocalcemia.

- It is recommended that in the massively transfused patient, plasma and platelets be administered in response to the results of platelet count and coagulation function.

- Plasma and platelets should never be given solely in response to the number of units of packed cells transfused.

Imaging Studies:

- In transfusion-related acute lung disease, the chest radiograph is consistent with noncardiogenic pulmonary edema. The cardiac silhouette is not enlarged. Bilateral infiltrates are in an alveolar pattern.

Other Tests:

- The electrocardiogram may demonstrate prolongation of the QT interval in the massively transfused patient who develops hypocalcemia.

Procedures:

- Endotracheal intubation may be required if respiratory insufficiency complicates a severe hemolytic or anaphylactic reaction.

- Hypoxemia severe enough to require endotracheal intubation occurs in 70-75% of patients with transfusion-related acute lung injury.

- Place a Foley catheter in all patients with an intravascular hemolytic reaction to ensure continuous measurement of urinary output.

- A careful assessment will often aid in differentiating transfusion-associated volume overload from transfusion-related acute lung injury. In some cases, however, making the correct diagnosis may be very difficult. In these cases, Swan-Ganz catheterization may provide useful information.

TREATMENT

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Emergency Department Care: All patients receiving blood products should be placed on continuous cardiac monitoring and pulse oximetry.

- Hemolytic transfusion reaction

  - Stop transfusion as soon as a reaction is suspected.

  - Replace the donor blood with normal saline.

  - Examine the blood to determine if the patient was the intended recipient and then send the unit back to the blood bank.

  - Furosemide may be administered to increase renal blood flow.

    - Low-dose dopamine may be considered to improve renal blood flow.
    - Make efforts to maintain urine output at 30-100 mL/h.

- Extravascular hemolytic reactions do not require any specific treatment. However, if clinically ruling out intravascular hemolysis is difficult, follow the same treatment.
- Nonhemolytic transfusion reaction
    - Aggressive treatment of simple febrile reactions is not necessary. However, because the nonspecific symptoms are similar to those of a hemolytic transfusion reaction, differentiating this entity from a hemolytic reaction is necessary.
    - The transfusion should be terminated.
    - Evaluate the patient for evidence of hemolysis.
    - The patient's fever can be treated with acetaminophen.
- Anaphylactic reaction
    - Stop the transfusion immediately.
    - Support the airway and circulation as necessary.
    - Administer epinephrine, diphenhydramine, and corticosteroids.
    - Maintain intravascular volume.
- Minor allergic reaction
    - Administer antihistamines.
    - Although the necessity of stopping the transfusion is unclear, in more severe cases and in uncertain cases, the transfusion should be stopped.
- Transfusion-related acute lung injury
    - Monitor oxygen saturation.
    - Provide supplemental oxygen to maintain oxygen saturation greater than 92%.
    - Hypoxemia severe enough to require endotracheal intubation and positive-pressure ventilation occurs in 70-75% of patients.
    - No evidence supports the routine use of corticosteroids.
    - The blood bank should be notified.
- GVH disease
    - No effective therapies currently exist.
    - Emphasis needs to be placed on prevention.
- Massive transfusion
    - To decrease the risk of hypothermia in patients receiving massive transfusion, administer the blood through a blood warmer. Do not place blood in a microwave oven to warm, as this causes hemolysis.
    - Do not administer platelets and fresh frozen plasma routinely or by using a formula based on the number of units of packed cells transfused. Only administer with evidence of abnormal bleeding associated with thrombocytopenia or an elevated PT or aPTT.

- Treat symptomatic hypocalcemia with 5-10 mL calcium gluconate.

In hemolytic transfusion reactions, pharmacologic treatment is aimed at increasing renal blood flow and preserving urinary output. In anaphylaxis, the goals of therapy are to maintain hemodynamic stability and reverse the underlying process.

Drug Category: *Diuretics* -- These agents are used to increase renal blood flow and preserve urinary output in hemolytic transfusion reactions. They also may be used in transfusion-related volume overload.

Drug Name	Furosemide (Lasix) -- Increases excretion of water by interfering with chloride-binding cotransport system, which results in inhibition of sodium and chloride reabsorption in ascending loop of Henle and distal renal tubule. Individualize dose to patient. Depending on response, administer at increments of 20-40 mg, no sooner than 6-8 h after previous dose, until desired diuresis occurs.
Adult Dose	20-40 mg/d IV/IM
Pediatric Dose	Infants: Titrate with 1 mg/kg/dose IV increments until satisfactory effect achieved Children: 1-2 mg/kg/dose PO/IV/IM; not to exceed 6 mg/kg/dose; do not administer more frequently than q6h
Contraindications	Documented hypersensitivity; hepatic coma; anuria; severe electrolyte depletion
Interactions	Metformin decreases concentrations; interferes with hypoglycemic effect of antidiabetic agents and antagonizes muscle-relaxing effect of tubocurarine; aminoglycosides increase auditory toxicity, hearing loss of varying degrees may occur; may enhance anticoagulant activity of warfarin; may increase plasma lithium levels and toxicity
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Perform frequent serum electrolyte, carbon dioxide, glucose, creatinine, uric acid, calcium, and BUN determinations during first few months of therapy and periodically thereafter

Drug Category: *Vasopressors* -- These agents are used to increase renal blood flow and preserve urinary output in hemolytic transfusion reactions. In severe allergic reactions, epinephrine is used for its inotropic properties and ability to maintain perfusion of vital organs.

Drug Name	Dopamine (Intropin) -- Stimulates both adrenergic and dopaminergic receptors. Hemodynamic effect depends on dose. Lower doses stimulate mainly dopaminergic receptors that produce renal and mesenteric vasodilation. Cardiac stimulation and renal vasodilation produced by higher doses.
Adult Dose	1-5 mcg/kg/min IV; after initiating therapy, dose may be increased by 1-4 mcg/kg/min IV q10-30min until satisfactory response attained; maintenance doses <20 mcg/kg/min usually satisfactory for 50% of treated patients
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity, pheochromocytoma; ventricular fibrillation
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthetics, and MAOIs increase and prolong effects
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Closely monitor urine flow, cardiac output, pulmonary wedge pressure, and BP during infusion; prior to infusion, correct hypovolemia with either whole blood or plasma, as indicated; monitoring central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovolemia

Drug Name	Epinephrine (Adrenalin, Epinal, Epifrin) -- DOC for treating anaphylaxis. Stimulates alpha-, beta1, and beta2-adrenergic receptors, which in turn results in bronchodilatation, increased peripheral vascular resistance, hypertension, increased chronotropic cardiac activity, and positive inotropic effects.
Adult Dose	0.01 mL/kg of 1:1000 solution IM/SC initially; not to exceed 0.5 mL of 1:1000 solution (0.5 mg) IM/SC Severe anaphylaxis: 10 mL of 1:100,000 dilution of aqueous epinephrine IV over 10 min With no improvement, establish 1 mcg/min continuous IV infusion of 4 mcg/mL concentration; increase to 4 mcg/min prn
Pediatric Dose	0.1 mcg/kg/min SC q15min for 2 doses then q4h with increments of 0.1 mcg/kg/min prn; not to exceed 1.5 mcg/kg/min
Contraindications	Documented hypersensitivity; cardiac arrhythmias; angle-closure glaucoma; concurrent use with local anesthesia in areas such as fingers or toes because vasoconstriction may produce sloughing of tissue; do not use during labor (can delay second stage of labor)
Interactions	Increases toxicity of beta- and alpha-blocking agents and of halogenated inhalational anesthetics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution with elderly patients, prostatic hypertrophy, hypertension, cardiovascular disease, diabetes mellitus, hyperthyroidism, cerebrovascular insufficiency; rapid IV infusions may cause death from cerebrovascular hemorrhage or cardiac arrhythmias

Drug Category: *Antihistamines* -- Used to treat minor allergic reactions and anaphylaxis. Diphenhydramine may be used to pretreat patients with prior documentation of minor allergic reactions.

Drug Name	Diphenhydramine (Benadryl, Benylin, Bydramine) -- Used for symptomatic relief of allergic symptoms caused by histamine released in response to allergens.
Adult Dose	25-50 mg PO q6-8h prn; not to exceed 400 mg/d 10-50 mg IV/IM q6-8h prn; not to exceed 400 mg/d
Pediatric Dose	12.5-25 mg PO tid/qid or 5 mg/kg/d PO or 150 mg/m^2/d PO divided tid/qid; not to exceed 300 mg/d 5 mg/kg/d or 150 mg/m^2/d IV/IM divided qid; not to exceed 300 mg/d
Contraindications	Documented hypersensitivity; MAOIs
Interactions	Potentiates effect of CNS depressants; due to alcohol content, do not administer syrup dosage form to patients taking medications that can cause disulfiram reactions
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May exacerbate angle-closure glaucoma, hyperthyroidism, peptic ulcer, and urinary tract obstruction

Drug Name	Cimetidine (Tagamet) -- H2 antagonist that, when combined with H1 type, may be useful in treating itching and flushing in anaphylaxis, pruritus, urticaria, and contact dermatitis that do not respond to H1 antagonists alone. Use in addition to H1 antihistamines.
Adult Dose	300 mg IV; when clinically possible, PO q6h for 2 d or for as long as clinically indicated
Pediatric Dose	<16 years: 25-30 mg/kg/d IV in 6 divided doses; administer only if benefits outweigh risks >16 years: 25-30 mg/kg/d IV in 6 divided doses
Contraindications	Documented hypersensitivity
Interactions	Can increase blood levels of theophylline, warfarin, tricyclic antidepressants, triamterene, phenytoin, quinidine, propranolol, metronidazole, procainamide, and lidocaine
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Elderly may suffer confusional states; may cause impotence and gynecomastia in young males due to weak antiandrogen properties; may increase levels of many drugs; if changes in renal function occur during therapy, consider adjusting dose or discontinuing treatment

Drug Category: *Corticosteroids* -- These agents have limited benefit in the initial acute treatment of rapidly deteriorating anaphylactic patient. However, they may benefit patients with persistent bronchospasm or hypotension. Onset of action is approximately 4-6 h following its administration.

Drug Name	Methylprednisolone (Solu-Medrol) -- Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability. Useful in treatment of inflammatory and allergic reactions. By reversing increased capillary permeability and suppressing PMN activity, may decrease inflammation.
Adult Dose	125-250 mg IV loading dose; followed by 0.5-1 mg/kg/dose q6h for up to 5 d
Pediatric Dose	2 mg/kg IV initially; followed by 0.5-1 mg/kg/dose q6h for up to 5 d
Contraindications	Documented hypersensitivity; viral, fungal, or tubercular skin infections
Interactions	Estrogens may decrease clearance; may increase digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism (consider increasing maintenance dose); monitor patients for hypokalemia with concurrent use of diuretics
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Hyperglycemia, edema, osteonecrosis, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth suppression, myopathy, infections

FOLLOW-UP

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Further Inpatient Care:

- Continue IV fluids to maintain urine output.
- Monitor urine output.
- Continuous cardiac and blood pressure monitoring for early detection of any hemodynamic instability
- Transfusion-related acute lung injury
  - Intubated patients usually improve quickly with supportive care.
  - Once patients recover from transfusion-related acute lung injury, they can safely receive blood products as needed.

Deterrence/Prevention:

- All healthcare personnel should be familiar with the hospital's policy of checks and cross-checks to ensure that donor blood being transfused is administered to the intended patient. This best prevents hemolytic reactions.

- Administer leukocyte-poor packed RBCs in patients who have had 2 previous febrile nonhemolytic reactions and in patients who frequently receive blood products.
- If the patient has history of previous anaphylactic reactions to transfused blood, transfuse frozen deglycerolized packed RBCs or blood from IgA-deficient donors.
- Administer CMV-negative blood in patients who are immunocompromised.
- To reduce the risk of GVH disease, irradiated blood should be given to immunocompromised patients, those receiving bone marrow transplants, and those receiving blood products from a blood relative donor.
- Nonhemolytic febrile reactions recur in 15-20% of patients receiving future transfusions.

Complications:

- Intravascular hemolysis may result in the following:
    - Acute renal failure
    - DIC
    - Cardiovascular collapse
    - Death

Patient Education:

- Patients and family members of patients having any reaction to blood products must be educated about the reaction. They should be instructed to inform healthcare workers about this in order to prevent any future transfusion reactions.

MISCELLANEOUS

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Medical/Legal Pitfalls:

- Failure to carefully examine and compare patient's name and identification numbers to label on unit of blood to ensure administration to the intended recipient.
- Failure to diagnose acute intravascular hemolysis in patients who are obtunded, unconscious, or anesthetized
- Failure to suspect acute intravascular hemolysis if patient develops hypotension, dark urine, or oozing from IV or other puncture sites
- Failure to obtain informed consent, when possible, from the patient or their family or power of attorney
- Failure to inform patient of risk of transmission of infectious diseases

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