Although acute hemolytic transfusion reaction is one of the most dramatic complications of transfusion, any unfavorable consequence is considered an adverse effect of blood transfusion. The risks of transfusion should be weighed against the expected therapeutic benefits, and only when the expected benefits outweigh the potential risks should transfusion therapy be initiated.

Classification

Transfusion reactions may be divided into four broad categories as shown in Table 25-1. This chapter considers only noninfectious transfusion reactions. Chapter 26 discusses infectious risks of transfusion. Most of this Technical Manual is devoted to issues important in preventing adverse consequences. This chapter covers preventive measures in the clinical setting, as well as recognition and treatment of reactions that do occur.

All personnel involved in ordering and administering transfusions must be able to recognize a transfusion reaction so that, if one should occur, the transfusion can be stopped and corrective actions can be taken promptly. Listed below are signs and symptoms that may be associated with a transfusion reaction. If a transfusion reaction is suspected, investigation should begin promptly so that a diagnosis can be established and appropriate therapy initiated without delay.

Signs and symptoms that may occur with impending or established transfusion reactions include:

- Fever, often defined as ≥1°C or 2°F, with or without chills
- Shaking chills (rigors), with or without fever
- Pain, at infusion site, or in chest, abdomen, or flanks
- Blood pressure changes, usually acute, either hypertention or hypotension
- Respiratory distress, including dyspnea, tachypnea, or hypoxemia
- Skin changes, including flushing, urticaria, localized or generalized edema
Nausea, with or without vomiting
• Acute onset of sepsis, including fever, severe chills, hypotension, high-output cardiac failure
• Anaphylaxis

### Acute Transfusion Reactions

#### Immune-Mediated Hemolysis

**Pathophysiology**

The most severe hemolytic reactions occur when transfused red cells interact with a recipient’s antibodies; interaction of transfused antibodies with the recipient’s red cells rarely causes symptoms, although there may be accelerated red cell destruction. The interaction of antibody with antigen on the red cell membrane can initiate a sequence of neuroendocrine responses, complement activation, coagulation effects, and cytokine effects, that result in the clinical manifestations of an acute hemolytic transfusion reaction (HTR). Most severe acute HTRs result from transfusion of ABO-incompatible red cells; although antibodies other than ABO can and do cause HTRs, the results are seldom catastrophic. Symptoms of an acute HTR, sometimes misleadingly mild, may begin after the infusion of as little as 10-15 mL of incompatible blood. In anesthetized patients who cannot report symptoms, the manifestations of an acute HTR may be limited to diffuse bleeding at the surgical site, hypotension, or hemoglobinuria.

**Neuroendocrine Response**. The combination of antibody with membrane antigen forms immune complexes capable of activating Hageman factor (Factor
XIIa), which, in turn, acts on the kinin system to generate bradykinin. Bradykinin increases capillary permeability and arteriolar dilatation, causing a fall in systemic arterial pressure. Vasoactive amines induced by complement and platelet activation may also contribute to hypotension. Development of hypotension provokes sympathetic nervous system response, characterized by rising levels of noradrenaline and other catecholamines that produce vasoconstriction in organs with a vascular bed rich in alpha-adrenergic receptors, notably the renal, splanchnic, pulmonary, and cutaneous capillaries. Coronary and cerebral vessels, which have few alpha-adrenergic receptors, participate minimally in the reaction. Histamine and serotonin, vasoactive amines that mediate many clinical concomitants of the HTR, are released from granules of mast cells and platelets as immune complexes activate the complement system and platelet responses.

Complement Activation. Immune complex formation on the red cell membranes activates complement. If the enzymatic cascade proceeds to completion, intravascular hemolysis results. If complement activation terminates with C3 activation and release of anaphylatoxins (see Chapter 10), red cells coated with C3b circulate and are removed by interaction with phagocytes that have receptors for C3b. Complement activation is characteristically rapid and complete in ABO-associated reactions, and intravascular red cell destruction releases both free hemoglobin and red cell stroma into the plasma. Although free hemoglobin was, historically, considered the cause of renal failure, current thought attributes acute tubular necrosis and renal failure largely to alpha-adrenergic-mediated vasoconstriction and the presence of antibody-coated cell stroma and microthrombi in the renal vasculature. With most non-ABO blood group antibodies, complement activation is usually incomplete; hemoglobinemia and circulation of stromal fragments do not occur, but the anaphylatoxic and opsonic consequences of complement activation may have adverse effects.

Coagulation Activation. The antigen-antibody interaction may activate the intrinsic clotting cascade through Hageman factor activation, through circulation of incompatible red cell stroma, and/or by release of thromboplastic materials from white cells and platelets. If disseminated intravascular coagulopathy (DIC) occurs, it may cause some or all of the following: 1) formation of thrombi within the microvasculature and ischemic damage to tissues and organs; 2) consumption of fibrinogen, platelets, and Factors V and VIII; 3) activation of the fibrinolytic system; and 4) generation of fibrin degradation products. The outcome can be a systemic hemorrhagic state characterized by oozing or uncontrolled bleeding.

Cytokines. Leukocytes exposed to antigen-antibody complexes secrete a variety of cytokines whose combined effects include the induction of fever, hypotension, mobilization of neutrophils from bone marrow, activation of endothelial cells to express adhesion molecules and procoagulant activity, activation of T and B lymphocytes, and priming of neutrophils. Prominent among the implicated cytokines are tumor necrosis factor (TNF), interleukin-1b (IL-1b), interleukin-6 (IL-6), and interleukin-8 (IL-8). The complete role of cytokines in the consequences of immune hemolysis remains to be defined.

Renal Failure. Renal failure is the most prominent sequela of an untreated acute HTR. The combination of systemic hypotension, reactive vasoconstriction, and formation of intravascular thrombi compromises renal vascular supply. The resulting ischemia may be transient or may progress to acute tubular necrosis and renal failure.
Treatment

The treatment of an acute HTR depends on the amount of incompatible blood transfused, the specificity of the offending antibody, and the clinical severity of the reaction.

Vigorous treatment of hypotension and promotion of adequate renal blood flow are the primary concerns; if shock can be prevented or adequately treated, renal failure may be avoided. Adequacy of renal perfusion can be monitored by measurement of urine output, with a goal of maintaining urine flow rates above 100 mL/hour in adults for at least 18-24 hours. The usual first support is intravenous normal saline, but underlying cardiac and/or renal disease may complicate therapy, and it is important to avoid overhydration. Diuretics help to improve blood flow to the kidneys and increase urine output. Intravenous furosemide at a dose of 40-80 mg for an adult or 1-2 mg/kg for a child not only has a diuretic effect but also improves blood flow to the renal cortex. This dose may be repeated once, and the patient should be adequately hydrated. Mannitol has been used in the past; an osmotic diuretic, it increases blood volume and thereby may also increase renal blood flow. If no diuretic response occurs within a few hours of instituting fluid and diuretic therapy, there is a strong likelihood that acute tubular necrosis has occurred and further fluid administration and diuretic therapy may actually be harmful.

Treatment of hypotension with pressor agents that decrease renal blood flow is contraindicated. Low doses of dopamine (less than 5 µg/kg/minute) increase cardiac output and dilate the renal vasculature, but at higher doses the pressor effects of dopamine are accompanied by renal vasoconstriction.

DIC with resultant bleeding or generalized oozing may be a predominant clinical finding in some HTRs and may be the initial presentation in an anesthetized patient. Heparin has been recommended by some, both to forestall DIC when an ABO incompatibility is first discovered and to treat the established coagulopathy. Others believe the dangers outweigh potential benefits, especially because the immune event that provoked the DIC is self-limited. Administration of Platelets, Fresh Frozen Plasma (FFP), and Cryoprecipitated AHF (as a source of fibrinogen) may be necessary if bleeding due to DIC is organ- or life-threatening.

Hemolytic reactions are very rare and few clinicians have first-hand experience with them. Because medical management of an acute HTR is often complicated and may require aggressive interventions such as hemodialysis, consultation with a physician experienced in the organ systems most damaged or in intensive care medicine may be prudent when treating a patient with a severe acute HTR.

Frequency

Mistaken identity is the most common cause of ABO-incompatible transfusion, either by administration of blood to the wrong person or by administration of the wrong unit of blood or red cells to the intended recipient. The authors of a study of transfusion errors estimated that, for every 33,000 units of red cells transfused, at least one unit is ABO-incompatible with a recipient. A survey of 3601 institutions by the College of American Pathologists found 843 acute hemolytic transfusion reactions reported over a 5-year period, of which 50 (6%) were fatal. These data suggest the existence of at least 20 deaths from acute HTR every year in the United States; the 15-16 fatal acute HTRs reported per year to the Food and Drug Administration (FDA) may represent underreporting.
Prevention

Because misidentification causes the majority of immune-mediated HTRs, the best hope for prevention lies in preventing or detecting errors in every phase of the transfusion process. In each institution there should be systems designed to prevent or detect errors in patient and unit identification at the time of phlebotomy (sample acquisition), at all steps in laboratory testing, at the time of issue, and when the transfusions are given. The AABB Quality Program provides a detailed framework for instituting and assessing such systems. Active participation by physicians and management, as well as by nursing, technical, and clinical personnel, is essential.

Crucial in the prevention of transfusion mishaps are training and surveillance of transfusionists. Crucial in the prevention of harm to the patient is ensuring that all clinical staff recognize signs of acute reactions and stop the transfusion before a critical volume of blood is administered.

Non-Immune-Mediated Hemolysis

Causes

Red cells may undergo in-vitro hemolysis if the unit is exposed to improper temperatures during shipping or storage, or mishandled at the time of administration. Malfunctioning blood warmers, use of microwave ovens or hot waterbaths, or inadvertent freezing all cause temperature-related damage. Mechanical hemolysis may be caused by the use of roller pumps (such as those used in cardiac bypass surgery), pressure infusion pumps, pressure cuffs, or small-bore needles. The addition of drugs or hypotonic solutions can hemolyze cells directly, and inadequate deglycerolization may cause the cells to hemolyze after infusion. Units in which there has been bacterial multiplication may undergo hemolysis. In a patient with transfusion-associated hemolysis for which both immune and nonimmune causes have been eliminated, the possibility might be considered that the patient or donor has an intrinsic red cell defect.

Treatment

Treatment depends on the cause of nonimmune hemolysis. If the patient develops a severe reaction with hypotension, shock, and renal dysfunction, intensive clinical management is required even before the cause of the mishap is investigated. If the patient exhibits only hemoglobinemia and hemoglobinuria, supportive therapy may be sufficient.

Prevention

There should be written procedures for all aspects of procuring, processing, issuing, and administering transfusions. All staff should be trained in the proper use of equipment, intravenous solutions, and drugs used during the administration of the blood and blood components. Equipment must be properly maintained and records kept of how and when items are used. Chapter 20 discusses details of administering transfusions. Medications that can be given intravenously must never be injected into blood bags, and care must be exercised in selection and use of intravenous access devices.

Transfusion-Associated Sepsis

Bacterial contamination of transfused blood should be considered if the patient experiences severe rigors, especially if these are accompanied by cardiovascular collapse and/or fever over 40 C. Patients may, however, experience only mild symptoms despite transfusion of bacterially contaminated components. See Chapter 26 for more details.
Febrile Nonhemolytic Reactions

Pathophysiology

A febrile nonhemolytic (FNH) reaction is often defined as a temperature increase of \(\geq 1^\circ\)C associated with transfusion and without any other explanation. The 1°C definition is arbitrary; the same events might cause temperature increments of 0.5°C or 2°C without affecting physiologic significance. Febrile reactions complicate 0.5-1.5% of transfusions, and are often accompanied by chills and/or rigors. Most are benign, although some may cause significant discomfort or hemodynamic changes. The temperature rise may begin early in the transfusion or be delayed in onset for up to several hours after completion. Previous opportunities for alloimmunization, especially pregnancies and multiple transfusions, increase the frequency of FNH reactions.

Some FNH reactions are thought to result from an interaction between antibodies in a recipient’s plasma and antigens present on transfused lymphocytes, granulocytes, or platelets. Infusion of cytokines preformed in the donor component or provocation of cytokine release in the recipient probably account for many others. Because fever may be an initial manifestation of an acute HTR or septic reaction to transfusion, any observation of an unexplained transfusion-associated rise in temperature warrants prompt attention. The diagnosis of FNH reaction is made after excluding other possible explanations for the fever.

Treatment

Traditionally, occurrence of a FNH reaction has caused the transfusion to be discontinued. However, some workers believe that a FNH reaction should not routinely cause discontinuation of a transfusion, depending on whether the patient has symptoms or signs that suggest hemolysis or bacterial contamination. The fever of a FNH reaction usually responds to antipyretics. Meperidine injection may be useful in patients with severe shaking chills. Acetaminophen (650 mg for an adult) is preferred to the use of salicylates because the former drug does not affect platelet function. Antihistamines are not indicated, because most FNH reactions do not involve histamine release.

Prevention

Febrile reactions in an alloimmunized individual can often be prevented by the transfusion of blood components with a residual leukocyte content of less than \(5 \times 10^8\) leukocytes per unit. Red cell or platelet transfusions that are leukocyte-reduced to this extent frequently prevent FNH reactions, but not always. Antibodies to platelet antigens or infusion of cytokines accumulated in the stored component may cause the recipient to experience a temperature rise.

Urticaria (Hives)

Pathophysiology

The typical urticarial reaction is characterized by rash and/or hives and itching, and is usually without fever or other adverse findings. Urticaria may complicate approximately 1% of transfusions. These cutaneous reactions may result from allergy to some soluble substance in donor plasma.

Treatment

If urticaria is the only adverse event noted, the transfusion may be temporarily interrupted while an antihistamine (eg, diphenhydramine, 25-50 mg) is administered orally or parenterally. If symptoms are mild and promptly relieved, the transfusion may be resumed.
provided the interrupted infusion can be completed within the duration that institutional policy mandates for transfusion. If the patient develops extensive urticaria or a confluent total body rash during transfusion, it would be prudent to discontinue administration of the unit even if symptoms have responded to treatment.

**Prevention**

Recipients who have frequent transfusion-associated urticarial reactions may respond well to administration of antihistamine one-half hour before transfusion. If reactions are recurrent and especially severe, transfusion of washed or deglycerolized red cells may prove helpful.

**Anaphylactic Reactions**

**Pathophysiology**

Anaphylactic transfusion reactions, sometimes called immediate generalized reactions, may begin after infusion of only a few milliliters, with systemic symptoms that often are mild at first but can progress to loss of consciousness, shock, and, in rare cases, death. Symptoms may involve one or several systems, notably the respiratory tract (cough, bronchospasm, dyspnea), the gastrointestinal tract (cramps, nausea, vomiting, diarrhea), the circulatory system (arrhythmias, hypotension, syncope), or the skin (generalized flushing, urticaria). These manifestations appear to reflect generalized activity of IgE antibodies, although these may not be demonstrable in individual patients.

Generalized reactions may not begin immediately; some develop as long as an hour after transfusion is completed. Good transfusion practice calls for close observation during the first quarter hour of infusion and less intensive but nonetheless continuing surveillance throughout and after the transfusion.

**IgA Deficiency.** The classical explanation for these reactions is the presence of class-specific antibodies to IgA in persons congenitally deficient in this Ig class. IgA deficiency is the most common congenital immune deficiency, affecting 1 in 700–800 persons, of whom as many as 30% have circulating anti-IgA antibodies. Anaphylactic transfusion reactions, however, are quite rare and not everyone who has an immediate generalized reaction proves to be IgA-deficient.

**Other Conditions.** Events that can mimic generalized IgE-mediated reactions include transfusion-related lung injury (see section below) and coincidental occurrence of myocardial infarction, pulmonary embolism, or other medical catastrophes. Besides IgA/anti-IgA reactions, the differential diagnosis for anaphylaxis induced by transfusion must include reactions to other constituents, such as complement proteins, or to drugs or other soluble allergens in the transfusion component. Reactions to alloantigens on platelets or white cells may cause similar events, or hypersensitivity to other elements to which the patient is exposed, such as latex gloves or drugs.

**Treatment**

The immediate treatment of an anaphylactic transfusion reaction should be to stop the transfusion; keep the access line open with normal saline; and treat hypertension, beginning with administration of epinephrine.

In mild to moderate cases, epinephrine (1:1000) should be delivered subcutaneously or intramuscularly in a dose of 0.3–0.5 mg/kg in adults or 0.01 mg/kg in children. In severe reactions (eg, systolic blood pressure below 80 mm Hg, laryngeal edema with upper airway com-
promise, or respiratory failure), the drug should be given intravenously (1:10,000), since time is important and drug absorption is unreliable in hypertensive patients. Intravenous treatment with corticosteroids may also be necessary. Oxygen therapy should be administered, as required clinically, with endotracheal intubation if there is significant upper airway obstruction. Under no circumstances should the transfusion be restarted. Treatment will be initiated on clinical grounds; diagnosis is made retrospectively.

**Prevention**

IgA-deficient patients who have had a prior life-threatening anaphylactic reaction should receive blood components that lack IgA. Components prepared from IgA-deficient blood donors may be obtained from regional blood suppliers. An immediate need for red cells may be met by the use of deglycerolized red cells or by repeated washing of standard units. Platelets, if needed, should also be thoroughly washed. If plasma components must be given, IgA-deficient donors will be needed. It may be possible to collect and store autologous blood components from patients known to have experienced anaphylactic reactions.

**Transfusion-Related Acute Lung Injury**

**Pathophysiology**

Transfusion-related acute lung injury (TRALI) should be considered whenever a transfusion recipient experiences acute respiratory insufficiency and/or X-ray findings consistent with pulmonary edema, but without evidence of cardiac failure. The severity of the respiratory distress is usually disproportional to the volume of blood infused, which is usually too small to produce hypervolemia, and the reaction includes chills, fever, cyanosis, and hypotension. TRALI may result from multiple mechanisms. Transfused antibodies to HLA or neutrophil antigens may react with the recipient’s leukocytes, causing a sequence of events that increase the permeability of the pulmonary microcirculation, so that fluid enters the alveolar air spaces. Rarely, antibodies in the recipient’s circulation may interact with transfused granulocytes and initiate the same events. Severe pulmonary reactions, often of uncertain etiology, may occur after granulocyte transfusions, particularly in patients with known or inapparent lung infections or with conditions likely to allow prompt complement activation.

Because specific antibodies may be absent, some cases of TRALI appear to result from other mechanisms; alternative causes may include complement activation to generate the anaphylatoxins C3a and C5a; direct aggregation of granulocytes into leukoemboli that lodge in the pulmonary microvasculature; or transfusion of cytokines that have accumulated in stored blood components. If any kind of acute pulmonary reaction is suspected, the transfusion should be stopped immediately and not resumed even if symptoms abate.

**Treatment**

Oxygen therapy and ventilatory assistance are frequently required, and treatment often includes intravenous steroids. Most patients recover adequate pulmonary function within 12-24 hours.

**Prevention**

If antibody in donor plasma can be shown to have caused an acute pulmonary reaction, blood from that donor should not be used for plasma-containing components. No special precautions are needed for the patient if the problem was donor-specific and components from other donors are available.
Circulatory Overload

Pathophysiology

Transfusion therapy may cause acute pulmonary edema due to volume overload. The incidence of transfusion-induced circulatory overload is unknown. Rapid increases in blood volume are poorly tolerated by patients with compromised cardiac or pulmonary status and/or chronic anemia with expanded plasma volume. Infusion of 25% albumin, which shifts large volumes of interstitial fluid into the vascular space, may also cause circulatory overload. Hypervolemia must be considered if dyspnea, cyanosis, orthopnea, severe headache, hypertension, or congestive heart failure occur during or soon after transfusion.

Treatment

Symptoms usually improve when the infusion is stopped and the patient is placed in a sitting position. Diuretics and oxygen are often indicated and, if symptoms are not relieved, more aggressive therapy including phlebotomy may be necessary.

Prevention

Except in conditions of ongoing, rapid blood loss, anemic patients should receive blood transfusions slowly. Administration of diuretics before and during the transfusion may be helpful. For very susceptible patients, the transfusion component can be divided, allowing part to be stored in the blood bank while the remainder is infused at a suitably slow rate.

Metabolic Reactions

Among the numerous complications that may accompany massive transfusion, metabolic abnormalities and coagulopathy are particularly important. Patients who are losing blood rapidly may have preexisting or coexisting coagulopathies or develop coagulopathies during resuscitation. Left ventricular function can be depressed by some or all of the following metabolic derangements: hypothermia from refrigerated blood; citrate toxicity; lactic acidosis from systemic underperfusion; and tissue ischemia, often complicated by hyperkalemia. Hemostatic abnormalities may include dilutional coagulopathy, DIC, shock, and liver and platelet dysfunction.

Citrate Toxicity

Pathophysiology. When large volumes of FFP, whole blood, or platelet concentrates are transfused at rates exceeding 100 mL/minute, plasma citrate levels may rise and hypocalcemia may occur. Hypocalcemia is more likely to cause clinical manifestations in patients who are in shock, are hypothermic, or have liver disease. Apheresis procedures put the patient or blood donor at some risk. Exchange transfusion, especially in tiny infants who are already ill, requires careful attention to all electrolytes.

Treatment and Prevention. Intravenous administration of calcium solutions to patients with hypocalcemia could cause iatrogenic hypercalcemia and ventricular arrhythmias. Unless a patient has a predisposing condition that hinders citrate metabolism, hypocalcemia due merely to citrate overload requires no treatment other than the slowing or discontinuation of the transfusion. Massively transfused patients or those with severe liver disease may benefit from measurement of ionized calcium levels as a guide to replacement therapy. Electrocardiographic changes consistent with hypocalcemia (prolonged ST and QT segments) may require careful intravenous infusion of
small amounts of 10% calcium gluconate. Calcium should not be administered through the access line used for transfusion, and must never be added directly to the blood container, as the blood will clot.

**Hypothermia**

**Pathophysiology.** Ventricular arrhythmias may occur in patients who receive rapid infusions of large volumes of cold blood, especially if administered via central catheters positioned close to the cardiac conduction system. Hypothermia increases the cardiac toxicity of hypocalcemia or hyperkalemia and can result in serious ventricular arrhythmias and poor left ventricular performance. The use of high-volume blood warmers prevents the cardiac toxicity of rapid and massive transfusion of cold blood.

**Treatment and Prevention.** The arrhythmias may be avoided by pulling the catheter back from the cardiac atrium, by reducing the rate of infusion, by using blood warmers, or by adding warmed saline directly to the blood container. AABB Standards for Blood Banks and Transfusion Services mandates warming to no more than 42 C, and only by in-line blood warmers. Normal saline and other solutions approved by the FDA for addition to blood may be heated before intravenous infusion if the manufacturer’s instructions permit. Attention to proper protocol is critical during the use of blood warming devices or heated saline solutions, as overheating of blood can cause hemolysis and even result in fatalities.

**Hyperkalemia and Hypokalemia**

**Pathophysiology.** When red cells are stored at 1-6 C, the potassium level in the supernatant plasma or additive solution increases. This rarely causes hyperkalemic problems in the recipient because there is such rapid dilution and excretion after infusion. Hypokalemia is more of a threat, as potassium-depleted red cells may extract potassium from the recipient’s plasma and the bicarbonate metabolized from infused citrate may cause alkalosis, which causes serum potassium to drop. Hyperkalemia is most likely to occur in massively transfused patients who are persistently hypotensive, who are poorly perfused, or who have lactic acidosis. Hyperkalemia may be a problem in premature infants and newborns receiving relatively large transfusions, such as in cardiac surgery or exchange transfusion.

**Treatment and Prevention.** No treatment or preventive strategy is usually necessary, provided the patient is adequately resuscitated from whatever condition required the massive transfusion. For large-volume transfusion to sick infants, many workers prefer red cells that are no more than 7-10 days old, but for small-volume transfusions, units may be used until their expiration date.

**Air Embolism**

Air embolism can occur if blood in an open system is infused under pressure or if air enters the system while containers or blood administration sets are being changed. Symptoms include cough, dyspnea, chest pain, and shock.

If air embolism is suspected, the patient should be placed on the left side with the head down, to displace the air bubble from the pulmonic valve. Aspiration of the air is sometimes attempted.

Air embolism was more of a threat when blood came in glass bottles than it is with plastic collection and administration systems. The proper use of pumps, equipment for blood salvage or apheresis, and tubing couplers is, however, essential.
Evaluation of a Suspected Acute Transfusion Reaction

The Role of Clinical Personnel Attending to the Patient

Medical personnel attending the patient are generally the first to suspect that a transfusion reaction has occurred, and the first to take action.

1. If a transfusion reaction is suspected, the transfusion should be stopped to limit the volume of blood infused. All labels, forms, and patient identification should be checked to determine whether the transfused component being given was intended for the recipient. The transfusion service and the patient’s physician should be notified immediately.

2. An intravenous line should be maintained with normal saline (0.9% sodium chloride) or other solution approved by the FDA for administration with blood, at least until a medical evaluation of the patient has been completed.

3. A responsible physician should evaluate the patient to determine whether a transfusion reaction has occurred, what kind it is, and what actions should be undertaken. The physician should evaluate the clinical findings with the possibilities in mind of acute hemolytic reaction, anaphylaxis, transfusion-induced sepsis, and TRALI, since these are conditions that require aggressive medical management and must be reported promptly to the laboratory. If the observed events are limited to urticaria or circulatory overload, the transfusion service need not evaluate postreaction blood or urine samples. If there are signs and symptoms other than urticaria or circulatory overload, and if there is even a possibility of acute HTR, anaphylaxis, TRALI, transfusion-induced sepsis, or other serious problems, a postreaction blood sample should be sent to the laboratory for evaluation. The specimen must be carefully drawn, to avoid mechanical hemolysis, and be properly labeled. In addition, the transfusion container (with whatever contents remain), the administration set (without the needle), the attached intravenous solutions, and all related forms and labels should be sent to the laboratory. In some cases, a postreaction urine sample will be useful.

The Role of the Laboratory

The laboratory should perform three steps as soon as possible after receiving notification and the clinical material, regardless of what kind of component is thought to be implicated: check for clerical errors, check for hemolysis, and check for incompatibility.

Check for Identification Errors

The identification of each patient sample and donor blood component must be checked for errors. If an error is discovered, the patient’s physician or other responsible health-care professional must be notified immediately, and a search of appropriate records should be initiated to determine whether misidentification or incorrect issue of other specimens or components has put other patients at risk. Once the acute crisis has passed, each step of the transfusion process should be reviewed to find the source of error.

Visual Check for Hemolysis

The serum or plasma in a postreaction blood specimen must be inspected for evidence of hemolysis and compared against a prereaction sample, if avail-
able. Pink or red discoloration after, but not before, the reaction suggests destruction of red cells and release of free hemoglobin. Intravascular hemolysis of as little as 5–10 mL of red cells may produce visible hemoglobinemia. Hemolysis due to poor collection technique or other medical interventions can cause hemoglobinemia; if faulty sampling is suspected, examination of a second specimen should resolve the question. Myoglobin, released from injured muscle, may also cause pink or red plasma, and might be suspected if a patient has suffered severe trauma or muscle injury. If the sample is not drawn until 5–7 hours after an episode of acute hemolysis, hemoglobin degradation products, especially bilirubin, may be in the bloodstream and cause yellow or brown discoloration. Rising bilirubin may begin as early as 1 hour postreaction, peak at 5–7 hours, and disappear within 24 hours, if liver function is normal.

In examining a postreaction urine specimen, it is important to differentiate among hematuria (intact red cells in the urine), hemoglobinuria (free hemoglobin in the urine), and myoglobinuria (free myoglobin in the urine). In acute hemolytic reactions, free hemoglobin released from damaged cells can cross the renal glomeruli and enter the urine, but there is no stimulus for red cells to enter the urine and no source for free myoglobin molecules. Urine examination should be done on the supernatant fluid after centrifugation of a freshly collected specimen; misleading free hemoglobin may be present if previously intact red cells in a specimen undergo in-vitro hemolysis during transportation or storage.

Serologic Check for Incompatibility

A direct antiglobulin test (DAT) must be performed on a postreaction specimen, preferably one anticoagulated with a chelating agent (such as EDTA), to avoid coating of red cells by complement proteins. If the postreaction DAT is positive, a DAT should be performed on red cells from the pretransfusion specimen (unless this had already been done as part of pretransfusion testing) and used for comparison. If transfused incompatible cells have been coated with antibody but not immediately destroyed, the postreaction specimen DAT is likely to be positive, often with a mixed-field appearance. If the transfused cells have been rapidly destroyed, the postreaction DAT may be negative if the specimen is drawn several hours later. Nonimmune hemolysis, eg, from thermal damage or mechanical trauma, causes hemoglobinemia but not a positive DAT.

Additional Laboratory Evaluation

If any of the three initial tests listed above gives positive or suspicious results, the diagnosis of acute HTR should be vigorously pursued. Even if no error or apparent incompatibility is found, the possibility of acute HTR should still be considered if the patient’s clinical presentation is strongly suggestive. The tests listed below help characterize the cause of the HTR, if one has occurred, or clarify the immunologic and serologic status of patients in whom the diagnosis is unclear. Some or all may be performed, at the discretion of the physician in charge of the transfusion service.

1. Perform ABO and Rh testing on the patient’s prereaction and postreaction samples and on blood from the unit or an attached segment. If ABO and Rh typing on the prereaction and postreaction samples do not agree, there has been an error in patient or sample identification, or in testing. If sample mix-up or mislabeling has occurred, another patient's specimen may also have been incorrectly labeled; it is important to check records of all specimens re-
ceived at approximately the same time. If blood in the bag is not of the ABO type noted on the bag label, there has been an error in unit labeling.

2. Perform antibody detection tests on prereaction and postreaction samples and on the donor blood. If a previously undetected antibody is discovered, it should be identified (see Chapter 17). Once the antibody is identified, retained samples from transfused donor units should be tested for the corresponding antigen. If a previously undiscovered antibody is present in a postreaction specimen but not in a prereaction sample, the reason may be anamnestic antibody production following a recent transfusion or, less likely, passive transfer of antibody in a recently transfused component. It may be desirable to use enhancement techniques, such as increased serum-to-cell ratio, low ionic strength saline (LISS), Polybrene®, polyethylene glycol (PEG), or enzyme techniques, when retesting the pretransfusion specimen.

3. Repeat crossmatch tests, with prereaction and postreaction samples in parallel. Even if the routine procedure is an immediate-spin or computer crossmatch, the antiglobulin technique should be applied to the investigative crossmatches.

4. Perform DAT and antibody detection tests on additional specimens obtained at intervals after the transfusion reaction. A first postreaction sample may have serologically undetectable levels of a significant alloantibody, especially if all the antibody molecules have attached to the incompatible transfused cells. In this event, antibody level would rise rapidly, and antibody detection and identification would become possible within a few days.

5. Perform frequent checks of the patient’s hematocrit or hemoglobin values, to see whether the transfused cells produce the expected therapeutic rise, or whether a decline occurs after an initial increase. In patients with sickle cell anemia, survival of transfused red cells can be followed by evaluation of the levels of hemoglobin A. In any patient with phenotypic differences between autologous and transfused cells, flow cytometry, if available, can be used to follow survival.

6. Perform in-vivo red cell survival studies, if indicated, to demonstrate the rare occurrence of acute HTR in the absence of detectable alloantibody. When the patient is phenotyped in preparation for such studies, it is important that the sample be one that contains only the patient’s red cells. This may be difficult if the patient has received transfusions within the previous several weeks. Method 2.15 gives a technique for obtaining autologous red cells from a patient who has been transfused. If an antigen is present on the donor red cells and absent from those of the patient, its presence or absence in postreaction samples indicates whether the transfused cells have survived and remained in the circulation.

7. Measure haptoglobin level if results can be obtained promptly enough to help in the diagnosis. It is important to compare prereaction and postreaction levels, and to consider whether hemoglobin leakage from stored donor cells may have depressed posttransfusion haptoglobin levels.

8. Examine the blood remaining in the unit and the administration tubing for evidence of hemolysis, especially
if a nonimmune HTR is suspected. Depending on how the blood was damaged, hemolysis may be present in the container and the administration tubing, or only in the administration tubing. For example, if a hypotonic solution had been added to the container, both the blood in the container and in the administration tubing would be hemolyzed. If a faulty infusion device had been used during blood administration, hemolysis might be present in the administration tubing, but not in the container.

9. Test the patient’s serum for presence of IgA if the presentation suggests an anaphylactic reaction. If the pretransfusion specimen shows IgA deficiency, it may be worthwhile to test for anti-IgA. If IgA levels are quantitatively normal, it is unlikely to be profitable to look for antibodies to IgA isotypes.

10. Examine the returned unit for any abnormal appearance, including clots or any brownish, opaque, muddy, or purple discoloration. If the clinical presentation suggests bacterial sepsis, a Gram’s stain or other bacteriologic examination of the contents should be performed, even if the unit looks normal. A segment from the donor unit (if available) may also be examined by smear and culture. Treatment for suspected bacterial contamination should be based on clinical considerations, as a delay in therapy may result in severe morbidity or death. Treatment includes intravenous administration of antibiotics combined with therapy for shock.

11. Examine the patient’s pretransfusion sample and a sample of the donor plasma for antibodies to HLA and/or neutrophil antigens, if the clinical presentation suggests TRALI.

Delayed Consequences of Transfusion

Alloimmunization to Red Cell Antigens

Pathophysiology

Primary alloimmunization to red cell antigens becomes apparent weeks or months after transfusion. It has been estimated that alloimmunization occurs with a risk of 1-1.6% per donor unit provided that D-negative recipients receive D-negative cellular components. The cells that constitute the primary immune stimulus have usually disappeared before circulating antibody achieves a significant level.

Serologic Observations. Once alloimmunization has occurred, antibodies may diminish to undetectable levels, especially antibodies in the Kidd system (anti-Jk\textsuperscript{a} and anti-Jk\textsuperscript{b}). If red cells that express the antigen are subsequently transfused, however, an anamnestic response may cause the appearance, within hours or days, of IgG antibodies that react with the transfused red cells. If antibody attaches to the circulating donor cells, the patient’s DAT may become positive even though serum antibody has not yet become detectable. In such a case, elution and identification of the antibody become important, as it may be several hours or longer before sufficient levels of the emerging antibody allow the detection and identification of the alloantibody in the serum. Once serum antibody becomes detectable, crossmatches are likely to be incompatible, but before that point, antigen-positive cells will appear to be suitable for transfusion. If an anamnestic response is discovered by the clinical laboratory, both the transfusion service director and the patient’s clinician should be notified and the possibility of a delayed hemolytic reaction should be investigated.
Delayed Reactions. In most cases, anamnestic antibody production causes only a delayed serologic reaction, but in 20-35% of patients, hemolysis will result from the combination of high antibody levels and large numbers of transfused red cells in the circulation. The most common presenting signs of a delayed HTR (DHTR) are fever, declining hemoglobin, and mild jaundice. Some DHTRs present simply as the absence of anticipated hemoglobin or hematocrit elevation after transfusion, or as a fever of unknown origin. Other clinical problems are infrequent; there may be unexplained jaundice, and hemoglobinuria is occasionally noted, but acute renal failure is uncommon. If a DHTR is suspected, a freshly obtained blood sample may be tested for unexpected alloantibodies, both in the serum and, by DAT, on red cells. The results, if positive, should be compared with the patient’s prior test results. Discovery of a previously undetected antibody in a patient manifesting hemolysis strongly suggests a DHTR.

Treatment
Specific treatment is rarely necessary, although it may be prudent to monitor the patient’s urine output and renal function and observe for changes in coagulation functions. If transfusions are still needed, donor units should be selected that lack the antigen corresponding to the newly discovered antibody. If such units are unavailable and transfusion is necessary, the risk of overt, acute HTR should be weighed against the risk of delaying transfusion.

Prevention
Future transfusions for the patient should lack the antigen(s) responsible for the anamnestic response, even if the antibody again becomes undetectable.

Some facilities issue a medical alert card with this information for the patient to carry and present at the time of hospitalization in a different facility. It is to prevent these problems that Standards mandates permanent preservation of records of clinically significant antibodies, and review of previous records before red cells are issued for transfusion.

Alloimmunization to Leukocyte Antigens

Pathophysiology
Alloimmunization to leukocyte antigens is more frequent than to red cell antigens, ranging from 20-70% in patients who receive repeated platelet transfusions that have not been leukocyte-reduced. Many women who have had four or more pregnancies have antibodies to HLA antigens.

Prevention
Leukocyte reduction to $5 \times 10^6$ or fewer white cells per transfusion unit reduces the likelihood of HLA immunization, but does not totally eliminate it. Patients who require long-term platelet support or who may require eventual transplantation are candidates for prevention of primary HLA alloimmunization. Both red cell and platelet components should be leukocyte-reduced if this is the goal. Secondary immune responses occur after exposure to much smaller doses of transfused white cells, so use of leukocyte-reduced components may not prevent appearance of antibodies if a patient has been previously alloimmunized as a result of transfusion or pregnancy.
able dose of platelets, can result from immune or nonimmune mechanisms. Immune causes may reflect either allo- or autoimmune reactivity. Alloantibodies induced by transfusion or pregnancy may be directed against platelet alloantigens, ABO antigens, or HLA Class I antigens. Repeated transfusions of ABO-mismatched platelets seem to increase the development of platelet refractoriness. Autoimmune problems are typified by immune thrombocytopenic purpura (ITP). Nonimmune causes of platelet refractoriness include splenomegaly, infection, drug effects, and the accelerated platelet refractoriness that can occur in DIC or thrombotic thrombocytopenic purpura (TTP). Given the multiple causes of platelet refractoriness, it may not be possible to pinpoint the cause(s) for an individual patient. It has been estimated that no more than half of platelet-refractory patients have demonstrable alloantibodies.

Treatment

Several strategies may be helpful for patients with immune-mediated platelet refractoriness. Some workers advocate the use of Platelets from HLA-matched donors. Others advocate the use of cross-match-compatible Platelets without regard to HLA typing. Still others advocate determining antibody specificity, and then selecting platelet donors identified as lacking the implicated HLA alloantigen. Once alloimmunization has occurred, the use of leukocyte-reduced Platelets may avert a febrile response, but may not improve posttransfusion increments.

Posttransfusion Autoantibody

Occasionally, transfusion of allogeneic platelets stimulates production of autoantibodies; in some of these patients, hemolytic anemia or thrombocytopenia may occur. See Chapter 18 for more detail.

Transfusion-Associated Graft-vs-Host Disease

Pathophysiology

T lymphocytes present in cellular blood components may cause transfusion-associated graft-vs-host disease (GVHD), which results in some or all of the following clinical findings: fever; dermatitis or erythroderma, often starting on palms, soles, earlobes, and face, ranging from edema to full blistering; hepatitis, with elevations in alanine and aspartate aminotransferases, alkaline phosphatase, and bilirubin; enterocolitis, with 3-4 liters per day of secretory diarrhea; pancytopenia, with hypocellular bone marrow and a reduction in all marrow elements; and immunodeficiency.

Factors that determine an individual patient’s risk for transfusion-associated GVHD include whether and to what degree the recipient is immunodeficient; the degree of HLA similarity between donor and recipient; and the number of transfused T lymphocytes capable of multiplication. GVHD may occur in an immunologically normal recipient if the donor is homozygous for an HLA haplotype for which the recipient is heterozygous, and the component contains large numbers of viable T cells.

Treatment and Prevention

At present, there is no effective treatment for transfusion-associated GVHD, and over 90% of affected patients die. Gamma irradiation of cellular blood components prevents transfusion-associated GVHD. The dose mandated by AABB Standards is a minimum of 2500 cGy targeted to the midplane of the container and a minimum dose of 1500 cGy delivered to all other parts of the component. This renders T lymphocytes inca-
pable of replication without affecting the function of red cells, platelets, and granulocytes.

AABB Standards requires irradiation of cellular components in the following situations: 1) the donor unit is from a blood relative of the intended recipient, 2) the donor unit is intended for an intrauterine transfusion, 3) the recipient is suffering from a selected immunoincompetence or immunodeficiency, and 4) the recipient has received a transplant of allogeneic marrow or peripheral blood progenitor cells. Other indications for the use of gamma-irradiated blood are evolving. Many workers irradiate blood components for neonatal exchange transfusion, and for patients with Hodgkin’s disease. Patients in whom intensive chemotherapy and irradiation have caused immune deficiency may perhaps be candidates, or patients with bone marrow suppression combined with an absolute lymphocyte count less than 500/µL. Some centers have extended blood irradiation to include cellular components intended for transfusion to premature newborn recipients, to recipients of HLA-matched blood components, and to patients receiving ablative therapy in preparation for an autologous marrow transplant.

Posttransfusion Purpura

Pathophysiology

Posttransfusion purpura is a rare event, characterized by a precipitous fall in platelet count and generalized purpura occurring about a week after a blood transfusion. Affected patients, exclusively multiparous women, have been shown to manifest a platelet-specific alloantibody, usually alloanti-HPA-1a. Because HPA-1a has a prevalence of 98.3% in the population, only 1.7% of individuals are at risk of developing alloanti-HPA-1a. However, in the women with posttransfusion purpura, there is destruction of autologous HPA-1a-negative platelets as well as transfused HPA-1a-positive platelets. The mechanism for this destruction remains the subject of investigation and speculation.

Treatment

Present treatment regimens include plasma exchange and intravenous immunoglobulin therapy. Earlier workers used high-dose steroids, but with less success. Some patients manifest spontaneous recovery. The replacement fluids for plasma exchange should consist of normal saline and/or 5% albumin solutions. FFP is not recommended because its biologic contents are not required and there is the potential to transmit disease. Platelet transfusions, even if HPA-1a-negative, are usually not beneficial.

Immunomodulatory Effects of Transfusion

Transfusion has been known to modulate immune responses since observations of improved renal allograft survival in transfused patients in the 1970’s. Transfusion is thought to have other, less beneficial effects in other clinical settings, including increased rates of solid tumor recurrence and increased rates of postoperative bacterial infection. These effects are controversial but suggest that the relationship between transfusion and the immune system is more complex than previously considered.

Iron Overload

Every unit of red cells contains approximately 200 mg of iron. Chronically transfused patients, especially those with hemoglobinopathies, have progressive and continual accumulation of iron and no physiologic means of excreting it. Storage occurs initially in reticuloen-
dothelial sites, but when these are saturated, there is deposition in parenchymal cells. The threshold for clinical damage is whole-body burden of 400-1000 mg/kg body weight. Iron deposition interferes with function of the heart, liver, or endocrine glands; hepatic failure and cardiac toxicity cause most of the morbidity and mortality.

Treatment is directed at removing iron without reducing the patient’s circulating hemoglobin. Metered subcutaneous infusion of desferrioxamine, an iron-chelating agent, is valuable for reducing body iron stores in such patients, but the regimen of nightly infusion by subcutaneous pumping is both arduous and expensive.

Records of Transfusion Complications

Each transfusion service must maintain indefinitely the records of patients who have had transfusion complications or evidence of alloimmunization. Possible cases of blood contamination and transmission of disease (including, but not confined to, hepatitis B, hepatitis C, and transfusion-associated human immunodeficiency virus) must also be reported to the institution where the blood was drawn.

Records must be kept, and consulted, to prevent patients who have had a transfusion reaction from being exposed to the offending agent in subsequent transfusions. The patient with a history of anaphylactic reactions should be considered for transfusion with plasma products that lack IgA. A history of repeated or severe FNH reactions might prompt the use of leukocyte-reduced cellular blood components. Patients with red cell alloantibodies sometimes test negative in an antibody detection test, if sufficient time has passed between the stimulating event and testing. Routine checking of records for evidence of past alloimmunization can prevent some DHTRs. Routine checking of previous results of ABO and Rh testing may disclose an error in testing or in the identification of a current sample.

Records of Patients with Special Needs

In addition to records of transfusion reactions, transfusion services should maintain records of patients who need specially prepared or manipulated components. This is especially important in institutions where physicians rotate frequently, and the need for irradiated, leukocyte-reduced, or IgA-deficient components may not be known to the individual physician writing an individual order.

Reporting Transfusion Fatalities

Fatalities resulting directly from the effects of transfusion must be reported to the Director, Office of Compliance, Center for Biologics Evaluation and Research, FDA, within 24 hours and by written report within 7 days (21 CFR 606.170). Patients who are critically ill and near death often receive transfusions in close temporal proximity to death, and clinical suspicion of cause and effect may occasionally be raised. The overwhelming majority of deaths are unrelated to transfusion, but if there is a suggestion that a transfusion might have contributed to death, it may be prudent to pursue an investigation.

In the absence of such errors as administration of ABO-incompatible blood or of physiologic events clearly attributable to acute hemolysis, anaphylaxis, TRALI, or sepsis, transfusion is highly unlikely to be acutely responsible for death. The review should include all
available medical and laboratory records and results of an autopsy, if performed.

On the other hand, if investigation does reveal evidence or possibility of hemolysis, anaphylactic or pulmonary events, unexplained sepsis, or ambiguous identification records, the case may warrant more extensive inquiry.

References


