This chapter reviews a variety of acute, nonhemolytic, and non-infectious transfusion reactions, the most common of which are febrile, nonhemolytic transfusion reactions (FNHTRs) and allergic reactions. Other acute, nonhemolytic reactions are reported less frequently and include transfusion-related acute lung injury (TRALI) and anaphylactic or anaphylactoid reactions. Additional acute adverse effects can occur in massive transfusion because of the large volume of blood components transfused over a short period. The complications of massive transfusion include dilutional coagulopathy, hypothermia, citrate toxicity, and electrolyte disturbances, among others. Some patients cannot tolerate the acute increase in intravascular blood volume caused by transfusion and experience the complications of transfusion-associated circulatory overload (TACO). Acute reactions can be caused by the toxicity of chemicals that leach into blood components from blood storage containers or filters or by chemicals added to improve storage conditions, such as dimethyl sulfoxide (DMSO). Other reactions are caused by endogenous mediators generated in the blood during filtration, processing, or storage, such as bradykinin-mediated hypotensive reactions. It is important that these complications of transfusion be recognized by patient care teams and blood bank personnel, and that appropriate treatments and preventive measures be instituted for patient safety and well-being.

**Febrile nonhemolytic transfusion reactions**

**Description**

An FNHTR is commonly defined as an increase in body temperature of 1 °C or more that occurs during or within several hours of transfusion and is unrelated to hemolysis, sepsis, or other known causes of fever. The use of a 1 °C increase in body temperature as a threshold for defining an FNHTR avoids undue concern over small fluctuations in body temperature unrelated to transfusion that do not justify discontinuation of transfusion and follow-up investigation. Many FNHTRs begin with the patient feeling uneasy and experiencing chills. In mild reactions, the signs and symptoms do not progress. Chills with or without an increase in body temperature can be classified as an FNHTR if other possible causes of chills are unlikely and the time course of the reaction correlates with the transfusion. In the most severe reactions, patients may experience rigors (severe shaking chills) or a fever elevation of 2 °C or more over baseline. Although signs and symptoms usually are limited to chills and fever, some patients may also rarely experience more severe symptoms such as headache, nausea, and/or vomiting.

The fever of FNHTR usually persists no more than 8 to 12 hours after the start of transfusion. If fever persists 18 to 24 hours or longer, it is unlikely to be transfusion related. Generally, FNHTRs are self-limited and have no sequelae. However, elderly patients, patients with compromised cardiovascular status, or critically ill patients are at risk of cardiopulmonary complications associated with FNHTR. Because fever increases oxygen demand and consumption an estimated 13% for every 1 °C over 37 °C and shivering increases oxygen demand approximately 300%, FNHTRs can aggravate preexisting cardiac, pulmonary, and cerebrovascular insufficiency. Therefore, prompt recognition and antipyretic management of FNHTRs can be very beneficial.

An FNHTR almost always is associated with transfusion of cellular blood components, such as red cells, platelets, and granulocyte preparations and less commonly with noncellular components, such as plasma and cryoprecipitate. The incidence of FNHTR varies widely and median rates have been reported as higher for platelets (4.6%) than for red cells (0.33%).

The reaction risk of blood components, however, varies according to numerous factors, such as method of preparation of the blood component (e.g., leukocyte reduction, storage time, medications, patient and donor characteristics, monitoring practices, and many others). These factors vary among different geographic regions and medical centers. In addition, rates based on reactions reported to blood banks are lower than those based on systematic surveillance of responses to all transfusions. A recent study demonstrated that the rate of reported FNHTR were low for prestorage-leukocyte reduced pooled platelets compared to poststorage-leukocyte reduced pooled platelets.

Longer platelet storage times are also associated with higher rates of FNHTR. Reactions also are more frequent among certain recipients, such as multitransfused patients or multiparous women who have developed leukocyte or platelet alloantibodies.

**Etiology**

An FNHTR appears to be part of the systemic inflammatory response syndrome (SIRS) provoked in transfusion recipients by the immune challenge of transfusing foreign cells or infusing soluble inflammatory mediators present in stored blood components. The term *systemic inflammatory response syndrome* was coined to describe the constellation of observed body responses to various...
insults, such as infection, trauma, burns, and ischemia. It is defined as the presence of two or more of the following: body temperature more than 38°C or less than 36°C; heart rate more than 90 beats/minute; tachypnea (respiratory rate >20 breaths/minute or PaCO₂ less than 32 mm Hg); and white cell count more than 12,000/µL or less than 4 × 10⁹/L, or more than 10% immature neutrophils (band forms). Although a mild FNHTR may not completely fulfill these criteria, FNHTR is nevertheless an inflammatory response.

Exogenous pyrogens such as lipopolysaccharide (LPS) and pyro-
genic cytokines initiate a series of responses leading to hyperthermia. These responses include rapid muscle contractions that cause shivering, rigors, and an increase in heat generation. Heat conservation is achieved through cutaneous vasoconstriction, which also contributes to the sensation of a chill. Perceived chills lead to behavioral changes that can further increase body temperature. For example, the patient may cover up, and the result is inhibition of heat dissipation.

An FNHTR appears to have two possible underlying causes: (1) the more “classical” pathway of infused antigens, such as leukocytes, that stimulate the in vivo generation of cytokines in the recipient; and (2) the infusion of pyrogenic cytokines or other inflammatory response mediators (e.g., activated complement proteins, LPS, or neutrophil-priming lipids) that accumulate in the plasma portion of cellular blood components during storage.³⁻⁴ A third cause of fever, infusion of blood components contaminated with bacteria or bacterial products, will produce a febrile response, but it is not usually categorized as an FNHTR but rather as a bacterial septic reaction, if recognized. The common pathway by which these different stimuli induce posttransfusion fever has been attributed to an increase in circulating pyrogenic cytokines in the recipient, such as interleukin-1β (IL1β), IL6, and tumor necrosis factor-α (TNFα). Pyrogenic cytokines induce fever by mediating upregulation of the thermostatic set point for body temperature in the thermoregulatory center of the hypothalamus. This mechanism is supported by the association of febrile reactions with a specific cytokine polymorphism IL1RN*2.2 genotype.⁷ Severe nonhemolytic transfusion reaction have also been linked to inflammatory cytokines and chemokines generated by mononuclear cells in donor blood by HLA Class II antibody containing plasma unit.⁸ Recently, research has led investigators to a more complex model of fever generation, building on a model where cytokines principally induce fever to one where central nervous system stimulation by prosta-
glandin E2 (PGE2) is pivotal. Alternative hypotheses have resulted from the finding that a febrile response to LPS occurs even with blockade of either IL1 or TNFα and that the presence of circulating cytokines lags behind the development of fever.⁹ Research has found that LPS-induced C5a production via complement activation results in rapid peripheral PGE2 production.¹⁰ In addition, LPS binds to toll-like receptor 4 and induces cytokine production, leading to a two-phase rapid and delayed febrile response. Hyper-
thermic stimuli compete with hypothermic stimuli to achieve a central thermal balance point that may elevate or decrease based upon physiologic stimuli.¹¹ Central to the febrile response is the presence of EP3 prostaglandin receptors that bind PGE2 in the hypothalamus (Figure 58.1).¹² These newer models of the fever response provide possible explanations for why FNHTRs continue to occur despite prestorage leukocyte reduction that minimizes cytokine accumulation in storage. Clinical evidence supports the hypothesis that febrile reactions can be caused by noncytokine hyperthermic stimuli present in cellular transfusion products.¹³ More research is needed for the development of more targeted antipyretic medications that may eventually lead to the extinction of FNHTRs.

**Alloimmunization to leukocytes or platelets**

Transfusion recipients at greatest risk of an FNHTR are those with leukocyte or platelet antibodies who receive transfusions with blood components containing large numbers of passenger leukocytes or platelets.¹⁴⁻¹⁵ Less frequently, donor antibodies to leukocytes, present in the plasma portion of blood components, are associated with FNHTRs. The implicated antibodies most often have HLA specificity, although they also may be platelet- or granulocyte-specific. A minimum of approximately 1 × 10⁹ leukocytes per unit of red blood cells (RBCs) appears necessary to cause an FNHTR, although this number varies among individuals.¹⁶⁻¹⁷ The role of donor leukocytes in FNHTR is supported by the finding that decreasing the leukocyte content of blood components below this threshold reduces the incidence of FNHTRs.

A variety of mechanisms are possible by which antibody–leuko-
cyte or antibody–platelet interactions cause fever. For example, donor monocytes may be activated and secrete pyrogenic cytokines when recipient antibodies bind to them. An alternative explanation is that immune complex formation between recipient antibodies and donor leukocytes or platelets leads to generation of activated complement components such as C5a, which stimulate the production of PGE2.

**Storage-generated cytokines**

Antibodies to leukocytes or platelets do not appear to account for all FNHTRs, particularly those caused by platelet transfusions. For example, some patients with no history of transfusion or pregnancy experience an FNHTR to their first transfusion of platelets.¹⁸ It is unlikely that these reactions are mediated by recipient leukocyte or platelet antibodies because these recipients have no previous exposure to foreign cells. In addition, the rate of FNHTRs to platelet transfusion increases with increasing blood bank storage time of the transfused platelet concentrate.³⁻⁵ This indicates that time-depen-
dent change occurs in the platelet concentrate during storage that has a role in stimulating an FNHTR in some patients. Furthermore, febrile reactions still occur with the use of prestorage leukocyte reduction. In some cases, this is the result of inappropriate filter use or filter failure. However, this observation also supports the possi-
ble that a substance or substances in the plasma portion of blood components not removed by filtration may be responsible for mediating at least some FNHTRs. The discovery that pro-inflam-
matory cytokines accumulate in the plasma portion of platelet concentrates may account for many of these findings.

A variety of leukocyte-derived, pro-inflammatory cytokines, including IL1β, IL6, IL8, tumor necrosis factor-α (TNFα), macro-
phage inflammatory protein-1α (MIP1α), and growth-related onco-
gene-α (GROα), are generated and accumulate in the plasma portion of platelet concentrates during storage.¹⁹⁻²¹ Extracellular levels of these cytokines generally increase with increasing compo-
nent storage time and are roughly proportional to the passenger leukocyte content of the blood component bag. Prestorage or early-
storage leukocyte reduction (within one to two days of collection) prevents or greatly reduces generation of these cytokines. Because they have pyrogenic activity, many of these cytokines (if present in high enough concentration) can induce febrile responses in trans-
fusion recipients. Elevated levels of IL1β, IL6, and TNFα in the plasma portion of platelet concentrates correlate positively with the occurrence of an FNHTR. Some studies have shown that IL6 levels
in the plasma portion of platelet concentrates correlate best with the occurrence of FNHTR. In one study, chills, fever, or both occurred more frequently after infusion of the plasma portion of the platelet concentrates than after infusion of the cellular portion containing platelets and leukocytes.19 The plasma portions that caused an FNHTR contained higher levels of IL1β and IL6 than did those that did not cause chills or fever. These data support the role of the plasma portion of platelet concentrates as a source of inflammatory mediators and as a possible stimulus of FNHTR in some transfusion recipients. Although levels of a variety of pro-inflammatory cytokines in the plasma portion of platelet concentrates correlate with the occurrence of FNHTRs, it is unknown which, if any, of these actually mediate FNHTRs.

Platelet-derived cytokines, such as CD40L (CD154), CCL5 (RANTES), transforming growth factor β1 (TGF-β1), CXCL4 (platelet factor 4; PF4), CXCL8 (IL8), and MIP1α are present in the plasma portion of platelet concentrates and apheresis platelets. All platelet-derived cytokines accumulate during platelet storage and CD40L has been associated with clinical FNHTRs.22 These cytokines are not known to be directly pyrogenic, but they stimulate the synthesis of pro-inflammatory mediator, IL1β, IL6, IL8, and TNFα. Because RANTES can activate basophils and mast cells and stimulate histamine release, it may play a role in mediating some allergic reactions (see the "Allergic Reactions" section).23

Some pro-inflammatory cytokines, such as IL1β and IL8, have been detected in the supernatant portion of stored RBCs, although at much lower levels than in platelet concentrates.24 Because the cold storage temperature of RBC units, 1–6 °C, has an inhibitory effect on cellular metabolism, the capacity of passenger leukocytes in RBC units to synthesize and secrete cytokines is less than those in platelet concentrates. As a result, the levels of cytokines in RBC units appear to be too low to mediate significant physiologic reactions.

The stimulus for cytokine generation during storage of blood components remains unknown. Measurements of cytokine messenger RNA levels and total cytokine levels (intracellular plus extracellular) in platelet concentrates indicate that accumulation of leukocyte-derived cytokines is caused in part by new synthesis and secretion. The stimulus for synthesis and secretion of leukocyte-derived cytokines may be, for example, contact activation of monocytes after these cells interact with the plastic of the storage containers or tubing.25 Other possibilities include the direct stimulatory effects of C5a on PGE2 or the stimulatory effects of activated complement components on monocytes or other leukocytes in the blood component bag. The presence of platelet-derived cytokines (e.g., CD40L, RANTES, and TGF-β1) in the plasma portion of platelet concentrates likely results from their release from preexisting stores, because the biosynthetic activity of platelets is limited.

### Bacterial contamination of blood components

An FNHTR may result from infusion of a blood component contaminated with bacteria or bacterial products such as LPS. Unless a Gram’s stain and bacterial cultures are performed, mild septic transfusion reactions characterized by only fever and chills are likely to be classified clinically as FNHTR.26-27

Transfusion reactions caused by contaminating bacteria, whether mild or severe, are manifestations of the SIRS, described earlier. Pro-inflammatory cytokines (such as IL1β, IL6, IL8, and TNFα) are implicated in the pathogenesis of SIRS associated with sepsis.28 If bacterial contamination of blood components has occurred, the greatest source of cytokines is likely the transfusion recipient’s cells stimulated by the infused bacteria or bacterial products. However, cytokine production by leukocytes in the component bag during storage stimulated by bacteria or bacterial products also may contribute to the reaction.

### Diagnosis

As a routine part of the transfusion procedure, the vital signs of transfusion recipients (pulse, temperature, and respiratory rate and oxygen percent saturation) should be measured immediately before transfusion and at intervals during and soon after transfusion. The patient should be watched closely, particularly in the first 30–60 minutes of transfusion, for the onset of chills, shivering, or rigors, which often precede a fever.

A transfusion reaction is a possibility if chills, fever (1 °C or more over pretransfusion temperature), or both develop any time during...
transfusion or up to several hours after the transfusion has ended. A febrile response to transfusion, however, is not specific for an FNHTR. For example, a fever may be the early manifestation of a more serious acute hemolytic, septic, or TRALI transfusion reaction. When a patient has a febrile reaction to transfusion, an evaluation to rule out hemolysis and possibly bacterial contamination should be undertaken promptly. Nursing staff should stop the transfusion immediately and notify the physician caring for the patient. They should verify that the identity of the transfusion recipient, based on the patient’s identification bracelet and verbal confirmation with the recipient, if possible, matches that of the intended recipient, as indicated on the blood component tag. All containers and transfusion sets should be sent to the laboratory along with a posttransfusion blood specimen and a report that summarizes the clinical reaction. The clinical team should also have verbal communication with the blood bank staff to ensure that the postreaction blood specimen, component bag, and infusion set are received by the blood bank as soon as possible.

Investigation of a febrile reaction in the blood bank generally begins with a recheck of the records for clerical errors. The posttransfusion serum/plasma must be visually evaluated for hemolysis and should be compared with the pretransfusion specimen. A direct antiglobulin test must be performed on the posttransfusion blood specimen and ideally on a pretransfusion specimen for comparison. The ABO grouping of the patient sample and the donor unit should be repeated. When suggested by the preliminary serologic results, the crossmatch may be repeated for RBC transfusions to confirm patient–donor compatibility. The results of these tests confirm or exclude a hemolytic transfusion reaction as the basis for the fever. When a septic reaction is highly suspected, for example if the patient arrives with a high fever (2°C or more) or accompanying hypotension, the bag contents should be examined by means of a Gram’s stain and culture for bacterial contamination. Blood cultures also should be obtained from the transfusion recipient’s posttransfusion blood specimen to correlate bacteremia with the same organism that may be detected in the blood component bag. Most blood banks do not test for HLA-specific, platelet-specific, or granulocyte-specific antibodies in the recipient’s serum as possible causes of an FNHTR. Identification of these antibodies and pyrogenic cytokines is reserved for specialized laboratories and does not play a role in the immediate evaluation of most reactions.

The patient is examined by the primary team and the blood bank physician to determine whether associated symptoms or circumstances can explain the fever, such as drug reactions, sepsis, or other inflammatory conditions unrelated to transfusion. The time course of the development and resolution of fever should be examined in relation to the transfusion. In cases in which the transfusion recipient has a fever at the start of transfusion or is experiencing intermittent spiking fevers, a posttransfusion increase in body temperature can be difficult to interpret. In such cases possible FNHTR may be the most definitive diagnosis that can be made. An FNHTR is a diagnosis of exclusion, arrived at by means of eliminating the possibility of immune hemolysis, bacterial contamination of the blood component, TRALI, or other causes of fever unrelated to transfusion.

**Treatment**

The transfusion should be stopped immediately. The intravenous line should be kept open with normal saline solution to provide ready access for the possible infusion of crystalloid and intravenous medication in case the fever is a sign of a more serious hemolytic or septic reaction. Most patients, however, should be reassured that febrile transfusion reactions usually are harmless and that the fever typically responds to antipyretic therapy. The antipyretic agent of choice is acetaminophen (adults, 325 to 650 mg orally; children, 10 to 15 mg/kg orally or rectally). Aspirin and nonsteroidal anti-inflammatory drugs are contraindicated in the treatment of many transfusion recipients, such as those receiving platelets. Unless the patient has signs of an allergic reaction, such as urticaria, erythema, or pruritus, antihistamines are not indicated in the management of FNHTR. However, it is not unusual for physicians to prescribe both an antipyretic and an antihistamine in combination for mild reactions.

Patients occasionally develop rigors (severe shaking chills) after a transfusion and meperidine had been a mainstay therapy for many years. Because shivering can increase oxygen demand significantly, it is important to control the shaking chills, particularly for patients with cardiac or respiratory insufficiency. When administered to adults at doses of 25 to 50 mg intravenously, meperidine remains a very effective treatment for rigors. Meperidine is effective in rapidly arresting rigors through mechanisms not clearly understood. Unfortunately, meperidine has fallen out of favor with some hospitals because of unacceptable central nervous system toxicities and other downsides. Use of meperidine is generally contraindicated in the care of patients with renal failure because of accumulation of the proconvulsant metabolite normeperidine. Use of meperidine also is contraindicated in the care of patients who have taken monoamine oxidase inhibitors within the previous 14 days because of the risk of serotonin syndrome (excess serotonin activity). Toxicities secondary to metabolite accumulation, short half-life, and higher equianalgesic dose compared to morphine have decreased interest but was used in 36% of cases. On the basis of anecdotal evidence, morphine may be slightly less efficacious for the treatment of rigors, but its safety profile is more acceptable when given as a onetime dose of 2 to 4 mg intravenously.

After symptoms of an acute febrile reaction have been treated and the patient has been stabilized, any unused portion of the blood component should be returned to the blood bank and not transfused, even if blood bank testing rapidly rules out hemolysis. A new device that has been FDA approved for the detection of bacteria in both whole blood–derived platelets and apheresis PLT products is the Pan Genera Detection (PGD) test, which can detect 10^2 to 10^9 colony-forming units per ml and may be more sensitive than the Gram stain. The use of Gram’s stain helps detect heavily contaminated units (with detection limits not less than 10^6 organisms per ml), and lower levels of contamination may be missed. If the febrile reaction is caused by bacterial contamination of the component bag, restarting transfusion of the same component can cause a severe and even fatal septic transfusion reaction as more bacteria or bacterial products are infused. For this reason, a new blood component unit should be used if transfusion is still needed after the patient’s condition has been stabilized. Hemolysis of either donor or recipient red cells usually is not significant because of the small amount of red cells and plasma in platelet preparations. The transfusion should generally not be restarted for at least 30 minutes as a precaution to allow other possible signs or symptoms of a serious reaction to develop. High transfusion-related fevers, such as a 2°C increment or more, are more likely to be associated with septic reactions and should preclude restarting the transfusion. However, lesser fevers do not rule out bacterial contamination of the blood component. If the transfusion is restarted, the patient should be made as comfortable as possible with appropriate
antipyretic therapy, as described earlier. The transfusion should proceed slowly and the patient observed closely for further signs of a reaction or further temperature elevation throughout the transfusion, which should be stopped if symptoms recur. Restarting transfusion of a blood component that has caused an FNHTR should not be routine.

Prevention
Premedication
Premedication with acetaminophen but not diphenhydramine should be considered for patients with a history of FNHTR. Patients who have no history of FNHTR do not need premedication. Despite a number of studies showing no benefit to premedication in preventing transfusion reactions, the practice remains common in many institutions. A prospective, randomized, double-blind controlled trial of acetaminophen and diphenhydramine pretreatment showed that pretreatment mediation may decrease the risk of FNHTR to leukoreduced blood products. Premedication with the glucocorticoid hydrocortisone sodium succinate (adults, 100 mg intravenously) may be useful in the care of reaction prone patients when an antipyretic agent alone is ineffective. Glucocorticoids have anti-inflammatory effects that may help prevent or reduce the severity of FNHTRs. For example, they inhibit the enzyme phospholipid A2, thereby blocking production of arachidonic acid and its metabolites such as PGE2, a key mediator of fever. Glucocorticoids also inhibit synthesis of pyrogenic cytokines, such as IL1 and IL6. A variety of glucocorticoids other than hydrocortisone are available. However, hydrocortisone has the advantage of being a short-acting glucocorticoid (biologic half-life, 8 to 12 hours), and it induces a shorter period of immunosuppression than do many other glucocorticoid preparations. Because glucocorticoids generally act through changes in gene expression, hydrocortisone should be administered at least 4 to 6 hours before transfusion so that its anti-inflammatory action has time to take effect.

Rate of infusion
Slowing the speed of infusion of a blood component can possibly prevent or decrease the severity of FNHTR. The rate of increase in body temperature in FNHTR caused by leukocyte alloimmunization appears to be directly related to the rate of infusion of leukocytes in the blood components. A slower rate of infusion is of theoretic advantage in decreasing the severity of reactions caused by bacterial contamination or storage-generated cytokines. Slower infusion avoids a sudden bolus of bacterial toxins or cytokines that may provoke an immediate and possibly massive inflammatory response.

Leukocyte reduction
The prophylactic transfusion of leukocyte-reduced components is effective in avoiding alloimmunization to leukocytes, which is one of the major causes of FNHTR. Leukocyte-reduced blood components ideally should be transfused to such patients beginning with the first transfusion. Leukocyte reduction is effective in the care of patients already alloimmunized to leukocytes, because FNHTRs in these patients are directly related to the number and rate of infusion of passenger leukocytes. The threshold number of white cells associated with the development of an FNHTR generally ranges from 0.25 × 10^8 to 2.5 × 10^8. The removal of approximately 90% of leukocytes (10^10), which usually leaves less than 5 × 10^8 white cells per RBC unit, is sufficient to prevent most FNHTRs. For that reason, leukocyte reduction for the purpose of preventing FNHTRs often is defined as decreasing the passenger leukocytes to less than 5 × 10^8 per transfusion. Leukocyte reduction of blood components can be performed either at the time of component preparation (prestorage leukocyte reduction) or immediately before transfusion (poststorage leukocyte reduction). Poststorage leukocyte reduction by means of filtration can be performed in the blood bank before distribution of the component for transfusion or during administration of blood components. The latter often is called bedside leukocyte reduction.

Leukocyte-reduced RBC units have in the past been prepared by various poststorage techniques, including simple centrifugation with buffy coat removal, saline washing, and deglycerolization of frozen RBCs. Saline-washed and frozen deglycerolized RBCs are rendered leukocyte reduced because approximately 1 to 2 log_10 leukocytes are removed by repeated centrifugation and washing steps on automated cell washers. Filtration of RBC units through microaggregate filters designed to remove microaggregate debris more than 40 microns in diameter after an extra centrifugation step or after centrifugation and cooling (spin, cool, filter) also has been shown to reduce leukocytes in RBC units sufficiently to reduce the incidence of FNHTRs.

High-efficiency leukocyte reduction filters for red cells and platelets have been developed that are capable of removing both microaggregate debris and nonaggregated leukocytes. These leukocyte reduction filters can remove 3 or more log (99.9% or more) leukocytes, thereby decreasing the leukocyte content to approximately 1 × 10^6/unit or less. Despite their efficacy in leukocyte reduction, the use of bedside leukocyte reduction filters has had variable and sometimes disappointing results in reducing the incidence of FNHTRs to platelet concentrates. This may be the result of causes of FNHTR other than leukocyte antibodies in the transfusion recipient. For example, storage-generated, extracellular cytokines in the component bag that either are not removed or are inadequately removed by means of poststorage filtration are now believed to mediate some reactions. As a result, the practice of prestorage leukocyte reduction is increasingly replacing poststorage leukocyte reduction. Prestorage leukocyte reduction not only removes leukocytes but also removes leukocytes before they have a chance to release cytokines that can accumulate extracellularly in blood component bags during storage. Prestorage leukocyte reduction has also yielded conflicting results on the efficacy of leukocyte reduction to mitigate FNHTRs.

Prestorage leukocyte reduction of platelet concentrates or RBC units is achieved by use of blood component containers with in-line leukocyte reduction filters in a closed system between the primary collection bag and satellite containers. Prestorage leukocyte-reduced platelets also can be prepared with some automated apheresis instruments equipped with centrifugation chambers designed to minimize leukocyte collection (so-called process leukocyte reduction). Because some data indicate that only approximately 15% of patients who experience an FNHTR will have a similar reaction to the next transfusion, some blood banks provide a leukocyte-reduced component (either prestorage or bedside leukocyte reduced) only when a patient has had two or more documented febrile reactions. This practice is cost-effective but has the disadvantage of subjecting some patients to two uncomfortable reactions before a preventive measure is taken. Prestorage leukocyte reduction by means of filtration is a more efficient and cost-effective way to eliminate extracellular leukocyte-derived cytokines.
while reducing passenger leukocytes. Moreover, in evaluations of plasma removal from platelet concentrates to reduce the risk of FNHTR, this technique still is associated with FNHTR in a relatively large percentage of recipients. Neither leukocyte reduction nor poststorage plasma removal has been effective in eliminating all FNHTRs to platelet transfusions.

**Allergic reactions**

**Description**
An allergic reaction can be classified as an immediate hypersensitivity response consisting of transient localized or generalized urticaria, erythema, and pruritus. More serious allergic reactions can be complicated by hypotension and angioedema of the face and larynx. Allergic reactions can be categorized as those that have only cutaneous manifestations and usually are mild, resolving soon after administration of antihistamines. If other organ systems—cardiovascular, respiratory, or gastrointestinal—are involved beyond mild hypotension, particularly if the reaction is serious enough to necessitate treatment beyond antihistamines, the reaction would be considered anaphylactic or anaphylactoid (see the “Anaphylactic and Anaphylactoid Reactions” section). Allergic and anaphylactic reactions, however, are part of a continuum. Allergic reactions occur during or soon after transfusion of plasma-containing blood components. Atopic individuals—those with other known allergies—appear at greater risk of allergic reactions. A large retrospective review of reported transfusion reactions noted that 17% of all reactions in a nine-year period were allergic and 1% of reactions were severe.44 Other papers report allergic reaction rates of approximately 0.19% for red cells and 0.53% for platelet transfusions.42,45

**Etiology**
Allergic reactions are mediated by recipient immunoglobulin E (IgE) or non-IgE antibodies to proteins or other allergenic soluble substances in the donor plasma. The result of the hypersensitivity reaction is secretion of histamine from mast cells and basophils, which mediates cutaneous reactions by increasing vascular permeability.

Although the source of histamine in allergic reactions is believed in many cases to be the transfusion recipient’s mast cells and basophils, it has been hypothesized that histamine generated by leukocytes in stored cellular blood components may play a role. Several studies have shown that histamine accumulates in the plasma portion of platelet concentrates and RBC units with increasing storage time. However, histamine is not synthesized during storage but rather it leaks into the extracellular plasma or may be due to calcium ions (Ca²⁺) influx-inducing activity toward mast cell in patients prior to transfusion.46–48 These data are consistent with the observation that allergic transfusion reactions also are more common with increasing storage time of blood components.49 Several of the chemokines that accumulate in the plasma portion of platelet concentrates during blood bank storage, such as IL8, RANTES, and MIP1α, can recruit and activate basophils and stimulate histamine release. Therefore, it is theoretically possible that the infusion of storage generated donor cytokines during transfusion may contribute to the onset of allergic reactions among transfusion recipients. Consistent with this hypothesis, the biologic activity of RANTES is present at higher levels in apheresis platelets that cause allergic reactions.48 In a recent study that measures the concentration of allergic agonists such as C5a, brain-derived neurotrophic factor (BDNF), and CCL5 (RANTES) in apheresis platelets showed that high levels of these agonists were associated with allergic transfusion reactions.49 Therefore levels of acute inflammatory mediators and growth or chemotactic factors of basophils and mast cells do not appear to be associated with allergic transfusions reactions according to the study. However, the study only evaluated 20 platelet transfusions with associated allergic transfusion reactions.59

Allergic (and anaphylactic) reactions have been reported after infusion of antibodies in donor plasma, such as penicillin antibody infused into recipients receiving penicillin or related antibiotics, and after infusion of drugs in donor plasma, such as penicillin infused into recipients already sensitized to penicillin.

**Diagnosis**
Urticaria is readily diagnosed clinically by the presence of the cutaneous wheal-and-flare reaction. Because allergic symptoms usually are mild and are not characteristic of hemolytic transfusion reactions, serologic blood bank investigations to rule out hemolysis usually are unrevealing. Isolated, mild urticarial reactions not accompanied by other signs and symptoms necessitate minimal diagnostic evaluation. If the reaction is severe, has atypical manifestations, or is accompanied by fever (uncharacteristic of allergic reactions), a more elaborate laboratory evaluation to rule out a hemolytic or septic transfusion reaction is indicated. In the diagnosis of an allergic reaction as transfusion related, it is important to rule out, if possible, urticarial drug reactions that may be circumstantially attributed to transfusions. Careful attention to the timing of onset of urticaria relative to the transfusion may help avoid this confusion. Administration of medications should generally be discouraged in the peritransfusion period to avoid such confusion.

Even mild allergic reactions should be reported to the blood bank. Monitoring allergic reactions and correlating reactions with any newly implemented changes in blood component collection, processing, storage, or filtration are important in detecting new and unexpected causes of reactions. In the care of patients with repeated allergic reactions, notification of the blood bank allows the blood bank medical director to consult on measures to manage or prevent such reactions in the future.

**Treatment**
The patient can be treated with a first-generation, H₁-blocking antihistamine (adults, 25 to 50 mg diphenhydramine intravenously or orally). If the sedating side effects of first-generation antihistamines must be avoided, newer, less sedating antihistamines are available for oral administration (adults, cetirizine 10 mg orally, loratadine 10 mg orally, or fexofenadine 60 mg orally); however, parenteral antihistamines are preferred in the management of acute reactions because of their more rapid bioavailability. An H₂ blocker, such as cimetidine (adults, 300 mg intravenously) or ranitidine (adults, 50 mg intravenously), may be added to the H₁ blocker to speed resolution of the reaction. Combining H₁ and H₂ antagonists has given better results in treating patients with allergic reactions in nontransfusion settings than has use of an H₁ antagonist alone.51–52 For reactions characterized by only localized urticaria, such as a few hives, the transfusion can be temporarily discontinued while an antihistamine is administered. The transfusion can be resumed in approximately 30 minutes if the urticaria has cleared and if no further symptoms occur. For patients with generalized urticaria or a more serious allergic reaction accompanied by facial or laryngeal edema or hypotension, the transfusion should be discontinued and...
the infusion set with any untransfused blood returned to the blood bank. If laryngeal edema causes breathing difficulties or if hypotension is severe, epinephrine (adult dose, 0.2 to 0.5 mL of 1:1000 solution [0.2 to 0.5 mg] subcutaneously) can be administered.

Prevention

Transfusion recipients often are given routine premedication with an antihistamine such as diphenhydramine in an effort to prevent or reduce the severity of allergic transfusion reactions, even when they have had no previous reactions. The value of this approach is uncertain, because few patients have allergic reactions. At least two randomized double-blind placebo-controlled studies of premedication using diphenhydramine and acetaminophen have failed to show a benefit of premedication to reduce reactions.\(^{53–54}\) When premedication is restricted to patients who have had two or more previous allergic reactions, overall reaction rates do not increase. Accordingly, premedication with an antihistamine should probably be reserved for recipients who have had a previous allergic reaction. For patients with repeated reactions not eliminated by premedication with an H\(_1\) blocker alone, a combination of H\(_1\) and H\(_2\) blockers has been shown more effective.\(^{51–52}\)

Should premedication not prevent repeated allergic transfusion reactions, another option is to reduce the plasma content of transfused blood components. This can be achieved in RBC and platelet preparations with automated saline "washing."\(^{55–56}\) However, washing or plasma removal steps generally should be reserved for patients with two or more serious allergic reactions (e.g., those that include angioedema or hypotension) that are not prevented with premedication with both H\(_1\) and H\(_2\) blockers, because cell washing is time-consuming and can delay transfusion. Patients with two or more severe allergic reactions can undergo testing for IgA deficiency to rule out a relative deficiency of IgA, because this has been reported to cause both a severe allergic and anaphylactic reactions.\(^{57}\)

**Anaphylactic and anaphylactoid reactions**

**Description**

Anaphylactic reactions are serious and potentially life-threatening immediate hypersensitivity reactions to allergens in the plasma of transfused blood components.\(^{58}\) These reactions can have a rapid onset beginning as early as seconds to minutes after the start of the transfusion, and can occur with small transfused volumes. Anaphylactic reactions are differentiated from other allergic (urticarial) transfusion reactions by their systemic nature and severity. These reactions generally affect multiple organ systems, as evidenced by cutaneous, respiratory, cardiovascular, and gastrointestinal effects. The symptom complex often includes the rapid onset of laryngeal edema and bronchospasm with stridor, wheezing, coughing, and respiratory distress. Other symptoms include generalized urticaria, erythema, tachycardia, hypotension, nausea, vomiting, diarrhea, and cramping abdominal or pelvic pain. Severe reactions can proceed rapidly to shock, syncope, respiratory failure, and death. Fatal anaphylactic reactions are less common than are fatal hematolytic or septic reactions.

**Etiology**

Anaphylactic reactions occur when an allergen present in plasma is transfused to a patient who through previous sensitization has an IgE directed against that allergen.\(^{59}\) Immunoglobulin E is bound by means of Fc receptors to mast cells and basophils. The binding of allergen to cell-bound IgE results in cross-linking of IgE and Fc receptors. This cross-linking activates the mast cells and basophils to secrete preformed mediators, such as histamine, as well as newly synthesized mediators, such as leukotrienes, prostaglandins, cytokines, and platelet-activating factor (PAF) (Figure 58.2).\(^{60}\) PAF induces downstream production of nitric oxide (NO) through inducible and possibly constitutively expressed NO synthase.\(^{51}\)

As a potent vasodilator, NO is believed to be the principal compound causing hypotensive and cardiovascular collapse during anaphylaxis, although the exact mechanism remains under debate. Anaphylactoid reactions are acute hypersensitivity reactions that are clinically identical to anaphylaxis but are not mediated by IgE antibodies or IgE involvement cannot be established. For example, immune complexes involving antibodies other than IgE may result in complement fixation and generation of the anaphylatoxins C\(_3\)a, C\(_4\)a, and C\(_5\)a, which activate basophils and mast cells. Some cytokines secreted by monocytes as part of the inflammatory

![PRODUCTS OF MAST CELL ACTIVATION](image)

![PRODUCTS OF BASOPHIL ACTIVATION](image)

**Figure 58.2** (A) Mast cell with its activation products. (B) Basophil with its activation products. Note that currently only two products of mast cell activation (histamine and total tryptase) and one product of basophil activation (histamine) can be measured in clinical laboratories as markers of acute anaphylaxis events. Used with permission from Simons et al. (2007).\(^{60}\) IL, interleukin; GM-CSF, granulocyte macrophage colony-stimulating factor; TNF-\(\alpha\), tumor necrosis factor alpha; MIP, macrophage inflammatory protein.
cascade initiated by non-IgE immune complex formation also can directly activate basophils and mast cells and initiate anaphylactoid reactions. Moreover, IgG4 subclass antibodies can bind to Fc receptors of mast cells and basophils and, in a manner analogous to that of IgE, mediate cellular activation and degranulation after binding of allergen. The term anaphylactoid is sometimes used to describe mild or clinically atypical anaphylactic reactions. However, anaphylactoid is better used to differentiate the mechanism of the reaction, not its clinical severity or presentation.

The best documented anaphylactoid reactions have resulted from the transfusion of donor plasma containing IgA to IgA-deficient recipients who have produced a class-specific IgG anti-IgA antibody that reacts with all IgA subclasses. Less commonly, patients with normal total IgA levels have a subclass-specific IgA deficiency and may make an anti-IgA of restricted specificity. Although IgA deficiency is relatively common (approximately one case among 700 persons), anaphylactoid reactions occur only among some IgA-deficient transfusion recipients, because not all make anti-IgA. Anaphylactic or anaphylactoid reactions have been documented among patients with deficiencies of other plasma proteins, such as complement, von Willebrand factor, and haptoglobin. In an analogous manner, these patients produce an antibody to the missing factor that reacts with transfused, plasma-containing blood components. Angiotensin-converting enzyme (ACE) inhibitors are drugs commonly prescribed to treat hypertension. Patients taking ACE inhibitors have been reported to have anaphylactoid reactions during online extracorporeal apheresis such as plasma exchange.

In most anaphylactic or anaphylactoid reactions, however, the allergen is never identified, nor is evidence obtained to differentiate anaphylactic from anaphylactoid mechanisms.

**Diagnosis**

Anaphylactic and anaphylactoid reactions are diagnosed from clinical signs and symptoms. The cutaneous signs and symptoms and the often rapid onset of the reaction help differentiate anaphylactic reactions from acute hemolytic and septic transfusion reactions. Serum β-tryptase levels may be measured to confirm an anaphylactic reaction, because it is a marker for mast cell degranulation. However, no laboratory measurement is available in time to meaningfully affect recognition and management of an anaphylactic reaction.

Recipient IgA levels should be measured in a pretransfusion blood specimen to determine if the recipient is IgA deficient. Although the results of tests for IgA deficiency do not affect diagnosis or management of the reaction at hand, it is important for avoiding future reactions. Testing should be performed on a specimen drawn before transfusion, because IgA deficiency can be masked by any IgA provided by the transfusion. Recipient anti-IgA also can be measured, especially for rare cases in which the anti-IgA is subtype-specific and total IgA levels are within the reference range. Although IgA is the most commonly known allergen in anaphylactoid reactions, in most anaphylactic and anaphylactoid reactions, the offending allergen is not IgA and is never identified.

**Treatment**

Anaphylactic and anaphylactoid reactions are managed identically. Severe reactions are true medical emergencies and should be managed by experienced critical care staff, if possible. The patient should be placed in an intensive care unit as soon as it is practical without jeopardizing emergency care. Once anaphylaxis is evident clinically, 1:1000 epinephrine solution (1 mg/mL) should be administered subcutaneously in a dose of 0.2 to 0.5 mL for adults (0.01 mL/kg of body weight for children). The dose may be repeated every 15 to 30 minutes as needed. Intravenous crystalloid or colloid solution should be administered as needed to support the patient’s blood pressure. For example, 500 mL to 1 L of normal saline solution can be administered in the first 15 to 30 minutes. Further infusion should be titrated to blood pressure. If the systolic blood pressure is less than 60 mm Hg, intravenous epinephrine in a dose of 1 to 5 mL of a 1:10,000 solution (0.1 mg/mL) for adults and 0.1 mL/kg for children, is administered over 2 to 5 minutes by means of intravenous push. An epinephrine drip (1 to 4 μg/minute) may be started, and administration of other pressors, such as dopamine, can be considered. Blood pressure, pulse, and urine output should be monitored. It may be necessary to monitor the effectiveness of fluid replacement and pressor infusion through measurement of central venous pressure.

Respiratory distress is managed with supplemental oxygen. The patient’s upper airway may have to be secured with endotracheal intubation if obstruction from laryngeal edema is imminent. Stridor is a sign of laryngeal edema. Endotracheal intubation and mechanical assistance with ventilation are indicated if the PaCO2 increases to more than 65 mm Hg. When intubation is difficult or impossible because of laryngeal obstruction, cricothyrotomy or tracheostomy is an option. Wheezing caused by obstruction of small bronchi and bronchioles by increased mucus production and smooth muscle contraction can be managed with nebulized albuterol or metaproterenol and intravenous aminophylline.

Urticaria, angioedema, or gastrointestinal distress is managed with an antihistamine (adults, 50 mg diphenhydramine intravenously; children, 1 to 2 mg/kg intravenously). H2-blocking antihistamines may be added as an adjunct to H1 blockers. Glucocorticoids, such as hydrocortisone, 200 mg given intravenously every six hours, are also administered because they reduce late-phase inflammatory responses. Glucocorticoids, however, are not expected to be of benefit in the initial management of anaphylaxis because of their delayed onset of action.

**Prevention**

Patients with IgA deficiency who have already had an anaphylactic reaction or who are known to have anti-IgA should receive transfusion of RBC and platelet preparations that have been saline-washed with an automated cell washer. If plasma transfusion is necessary, only IgA-deficient donors should be used. Patients who have anaphylactic reactions to any other known plasma allergen also should be treated with transfusion of saline-washed RBCs or platelet preparations. Because anaphylactic reactions can be induced by very small amounts of allergen, washing must be extensive. Washing and saline replacement by means of automated cell washers have been shown generally successful in removing IgA sufficiently to prevent recurrences of anaphylactoid reactions.

If a patient has had one anaphylactic reaction of unknown causation, the next transfusion need not necessarily be performed with washed RBCs or platelets, because the reaction might have been donor specific. The next transfusion may be administered slowly with vigilance after premedication with both H1 and H2 blockers and a glucocorticoid. The patient care team should be prepared to respond to an anaphylactic reaction. The patient ideally should be in a critical care unit with monitoring at the time of transfusion and with a critical care physician and nurses in attendance. Some blood banks with the capability of automated cell washing, nevertheless, may choose to provide saline-washed
RBCs and platelet concentrates for future transfusions after a single anaphylactic reaction as a precautionary measure, particularly if the patient is not expected to receive many more transfusions.

**Complications of massive and rapid transfusion**

Massive transfusion is defined as the replacement of one blood volume within a 24-hour period. For practical purposes for adults of average size, this is roughly equivalent to 10 units of RBCs with any accompanying crystalloid, colloid, platelet, or plasma infusions. An infusion of greater than four units of RBCs in an hour and ongoing use anticipated could also be regarded as a massive transfusion. The possible complications include citrate toxicity, electrolyte imbalance (hyperkalemia from transfusion of older RBCs, hypocalcemia from citrate toxicity), circulatory overload, and hypothermia. Recipients of massive transfusions are at increased risk of hemolytic transfusion reactions (including ABO incompatibility), FNHTR, and allergic reactions because of the number of units they receive. Reactions can be more severe with massive transfusion because rapid infusion means the implicated unit often has been completely administered before the onset of symptoms. The large number of units transfused in a short time complicates the investigation of transfusion reactions, because each transfused component must be investigated.

The lethal triad of severe trauma consists of hypothermia, acidosis, and coagulopathy. "Damage control" resuscitation methods have been developed to directly address the coagulopathy of trauma. The coagulopathy of trauma develops because of severe injury and is already present when a patient presents for emergency medical care. Trauma coagulopathy is not caused by the resuscitation efforts of emergency medical interventions as traditionally understood. Recent advances in trauma research have shown that early application of damage control resuscitation can greatly improve survival through an application of a 1:1 plasma–red cell ratio from patient presentation. In well-coordinated trauma centers, massive transfusion protocols now provide six units of plasma, six units of RBCs, six whole blood–derived platelet concentrates (or one apheresis platelet) or four units of plasma, four units of RBCs, and one unit of apheresis platelets. Aggressive damage control transfusion has been associated with a number of risks including hyperkalemia. Despite these risks, retrospective studies have shown that the application of early, aggressive transfusion support improves overall survival in this severely injured population that would otherwise have very poor prognosis.

Rapid transfusion can also occur during therapeutic apheresis and red cell exchange apheresis (erythrocytapheresis). During apheresis procedures, as many as 10–20 units of fresh frozen plasma or 4–8 units of RBCs can be transfused over 1.5–2 hours. Although any acute transfusion reaction can occur during apheresis-associated transfusion, citrate toxicity in particular is a common but usually mild complication.

**Citrate toxicity**

Citrate infusion can induce hypocalcemia, hypomagnesemia, and other electrolyte imbalances, and these imbalances are associated with clinical symptoms. Apheresis procedures can produce a unique clinical paradox of urinary calcium excretion in the setting of hypocalcemia. Hypocalcemia is a recognized complication of liver transplantation, in which large amounts of plasma are transfused. However, the precise mechanism of hypocalcemia is not well understood and may not be caused entirely by citrated plasma.

Citrate ordinarily is rapidly metabolized to bicarbonate in mitochondria-rich tissue, such as liver, skeletal muscle, and kidney. In the routine transfusion of blood components, patients with normal liver function usually tolerate the citrate infusion without significant complications. However, patients with liver or renal failure or parathyroid dysfunction are at greater risk of citrate toxicity when they receive rapid transfusions of plasma or plasma-containing blood components. Citrate anticoagulates blood by binding divalent cations such as calcium, thus hypocalcemia is a primary symptom. Other divalent cations such as magnesium and zinc can also be bound by citrate, but the contribution of hypomagnesemia to clinical symptoms is less pronounced. During apheresis, citrate is administered as acid–citrate–dextrose formula A (ACD-A) in constant proportion to the whole blood flow rate. Healthy plateletpheresis donors receive relatively large doses of citrate, and many experience mild symptoms of the citrate effect, but the symptoms usually do not progress because of the short duration of the procedure. Donors of peripheral blood stem cells (PBSCs), however, receive smaller doses of citrate per unit of time but usually experience more severe citrate toxicity because of the longer duration of the procedure. Paresthesia caused by transient hypocalcemia is common in apheresis. It typically occurs after the initial infusion of the priming solution (if citrate is used) or later as apheresis progresses. Apheresis practitioners should be aware that peripheral paresthesia caused by hypocalcemia can be masked in patients with a preexisting neuropathy as a result of chemotherapy (vincristine) or as part of a neurologic condition.

Citrate toxicity is recognized clinically because of the signs and symptoms of hypocalcemia. It can be confirmed by measuring the plasma-ionized calcium level in the patient. Symptoms of hypocalcemia include peripheral and perioral paresthesia (Chvostek and Trousseau signs can occasionally be elicited), muscle spasm, cramping, nausea, vomiting, cardiac arrhythmia, bradycardia, hypotension, and, if severe, tetany. An electrocardiogram (ECG) can show prolongation of the QT interval with hypocalcemia, but the relation is not linear with the ionized calcium level, and ECG findings are an unreliable guide to calcium therapy.

Mild citrate toxicity during transfusion or apheresis is managed or prevented in part by means of slowing the rate of transfusion or reinfusion. When slowing the infusion rate is impossible or ineffective and the patient has signs and symptoms of hypocalcemia, calcium supplementation is indicated. The best guide to determining a need for calcium supplementation is measurement of the patient’s ionized calcium levels, if results can be obtained rapidly. Calcium replacement during apheresis should generally be given when a patient has symptoms, when the patient’s clinical condition may exacerbate citrate effects, or when prolonged large-volume leukapheresis is expected to cause citrate toxicity. Infusion of calcium itself, however, is associated with development of ventricular arrhythmia and even cardiac arrest. Therefore, intravenous calcium replacement for the management or prophylaxis of apheresis-induced citrate toxicity should be administered only by experienced apheresis staff. Under no circumstances should
calcium be added directly to a unit of blood, because it causes clots to form in the bag.

Citrate toxicity during apheresis is related to the citrate concentration of the reinfused blood or colloid solution, the infusion rate, the blood volume of the patient, and the total time over which the citrate is infused.76 It is difficult to establish a definitive safe rate of citrate infusion because of the large number of variables involved. However, citrate dosages of up to 1 mg/kg/minute given during platelethpheresis usually are well tolerated. A safe rate of calcium replacement for controlling citrate toxicity during PBSC apheresis is 0.5 to 0.6 mg of calcium ion for every 1.0 mL of infused ACD-A.77,78 These dosages have been successful for prophylaxis against citrate toxicity during large-volume leukapheresis. To avoid excessive volume during PBSC apheresis, administration of a concentrated calcium solution (calcium chloride or calcium gluconate) is appropriate. Care must be taken to coordinate the calcium infusion with whole blood flow during the apheresis procedure to avoid the potential for catheter thrombosis. Calcium administration should be halted soon after interruptions in whole blood flow.

Electrolyte disorders

Because of inhibition of sodium–potassium–adenosine triphosphatase in red cell membranes by the cold storage temperature of RBC units, extracellular potassium accumulates with increasing blood bank storage times. Extracellular potassium increases at the rate of approximately 1 mEq/day during the first three weeks of RBC storage in citrate–phosphate–dextrose–adenine-1 (CPDA-1).79 Potassium levels in additive solution-1 (Adsol) units are markedly higher on Day 7 of storage (17 mmol/L) than on Day 0 (1.6 mmol/L). The increase is even greater on Day 42 (46 mmol/L).80 Total extracellular volume in additive solution is less than half of that in CPDA-1 blood; this must be taken into account when the amount of transfused extracellular potassium is considered.

Hyperkalemia resulting from massive transfusion of older RBC units with an elevated amount of extracellular potassium can cause cardiac complications and possibly death in some patients.81 Acidosis can contribute to hyperkalemia, and severely injured patients presenting with a potassium level greater than 4 mmol/L are at increased risk. Other patients at risk of hyperkalemic complications are neonates and those with renal failure. The diagnosis of hyperkalemia is made by means of measurement of potassium in the serum and observation of ECG changes, which include peaked T waves, prolongation of the PR interval, and ventricular arrhythmia.82 In neonatal transfusions, hyperkalemia can be avoided by use of fresh RBC units (less than seven days old) or older units that have been saline-washed to remove the extracellular fraction containing the potassium.83,84 However, transfusion of older RBC units does not place neonates at risk of hyperkalemia if small-volume transfusions (10 to 15 mL/kg) are given slowly.85

Hypokalemia can also develop during massive transfusion or large-volume apheresis.70,86 As the anticoagulant citrate in blood components is metabolized to bicarbonate, the blood can become alkalotic, producing hypokalemia. The degree of hypokalemia may be sufficient to necessitate infusion of potassium if symptoms develop. However, the use of newer RBC additive solutions such as Adsol has helped to decrease the effect of hypokalemia. RBC units are plasma-reduced before the addition of additive solution, which itself contains no additional citrate. Therefore, most of the citrated plasma is removed from additive solution RBC units during production. Animal studies have shown fewer physiologic aberrations during massive transfusion with Adsol RBCs than with CPDA-1 units.87 The complications of hypokalemia, therefore, are more likely when large numbers of units of plasma rather than RBC units are transfused. Posttransfusion hypokalemia can also be due to potassium uptake by transfused old RBCs.

Hypothermia

Hypothermia, defined as a core body temperature of less than 35°C, may be caused by rapid infusion of large quantities of cold (1°C to 10°C) blood or RBC units. Hypothermia during massive transfusion has been shown to induce cardiac arrhythmia and arrest.88 Hypothermia is a known independent risk factor for early coagulopathy, multiple organ failure (MOF), development, and mortality.89 Even smaller quantities of cold blood can be cardiotoxic if transfused into central venous lines, because the newly infused cold blood can reach the heart before sufficient warming has occurred. Data published in the early 1960s showed that massive transfusion at a rate of approximately one unit every 5–10 minutes was sufficient to lower the temperature of an esophageal probe behind the right atrium to nearly 30°C.88 The resulting decrease in sinoatrial node temperature was associated with the development of ventricular fibrillation.

For most routine transfusions given at a standard rate of administration, blood does not have to be warmed.90 The patient may experience minor chills, but this is easily remedied by warming the patient, as with extra blankets. Transfusion of cold RBC units through central venous lines, however, should be avoided. Indications for warming blood include rapid transfusion, which are generally considered to be more than 50 mL/kg/hour for an adult and more than 15 mL/kg per hour for a child, and exchange transfusion for infants. Because blood warming during certain massive transfusions sometimes delays infusion and impedes resuscitation, it is not always practical. Warming blood for transfusion in the treatment of patients with cold agglutinin disease has a theoretic basis but is debatable because supportive outcome data are lacking.

If blood has to be warmed, an approved warming device should be used and the temperature must be kept below a point where hemolysis occurs.90 Care must be taken when warming up blood because warming to a temperature above 42°C may cause hemolysis.91 Infusion of thermally injured cells can induce disseminated intravascular coagulation and shock. Heating blood with a device other than an approved blood warming device, such as a commercial microwave oven, is unacceptable. Blood that has been warmed but not used should not be reissued for another patient because of the increased risk of bacterial proliferation at warmer temperatures.

The maximum flow rate that can be achieved with commercially available blood warmers is 850 mL/minute; however, most can provide a rate of only 150 mL/minute. Most recent research has focused on comparisons between commercial warming devices and the comparison studies usually evaluate warming capability in the rapid transfusion setting.92 Most of the available federally approved blood warming devices safely warm blood and other intravenous fluids across a range of flow rates. However, although little recent data exist correlating the clinical benefits of warming blood, many emergency centers and trauma services use such devices routinely without incident.

An alternative to using mechanical blood warmers that circumvents such flow limitations is rapid admixture with warm or hot saline solution immediately before transfusion.90,92 This technique immediately warms a unit of RBCs, yet does not cause significant hemolysis. However, it necessitates that warmed saline solution be
available at all times in trauma care and requires attention to technique to avoid the direct infusion of hot saline solution into the patient.

**Reactions attributed to microaggregate debris**

Microaggregate debris ranges in diameter from 20 to 120 microns and consists of nonviable platelets, white cells, and strands of fibrin that form in blood during storage. Because of their size, microaggregates are not removed from transfused blood with the standard 170- to 260-micron screen filters. A variety of adverse events have been attributed to the presence of microaggregate debris after large-volume and massive transfusion.

Studies in the 1960s showed that patients undergoing open heart surgery with cardiopulmonary bypass experienced postperfusion syndrome during the postoperative period. This symptom complex consisted of cerebral and renal dysfunction attributed in part to occlusion of end-organ capillaries with microaggregate debris. Cotton wool (Swank) microaggregate blood filters capable of retaining particles or debris with a size of 40 microns or more appeared to eliminate many of these reactions. During the Vietnam War, some soldiers who underwent massive transfusion experienced respiratory distress syndrome (shock lung). At autopsy, the cause was presumed to be the material found in soldiers’ lungs that was positive on a periodic acid–Schiff (PAS) test. Because microaggregate debris stains PAS-positive, this was taken at the time as positive on a periodic acid–Schiff (PAS) test. Between 1970 and 1980, some blood centers undertook to determine whether removal of microaggregate debris from blood was clinically significant. Several studies showed that microaggregate filtration of up to 6 units of blood during either hip or cardiac surgery provided no benefit. Collins et al. concluded that the underlying clinical condition rather than the infusion of the microaggregate debris in blood led to the development of the respiratory distress syndrome reported earlier among patients undergoing massive transfusions. Microaggregate blood filters today are used mostly in conjunction with cardiopulmonary bypass pumps and reinfusion of shed autologous blood collected during or after surgery. With the widespread adoption of leukocyte reduction filtration, routine leukocyte-reduced red cell transfusions are no longer complicated by microaggregate debris because these filters can remove not only leukocytes, but also the larger microaggregate particles. Current studies are investigating the utility of washing stored blood to remove microaggregate debris that accumulates during storage.

**Circulatory overload**

Hypervolemia, termed TACO, is a possible consequence of transfusion in the care of patients with cardiac insufficiency, renal impairment, or already expanded blood volumes, such as patients with chronic anemia. Moreover, patients with restricted blood volumes (e.g., infants and small children) are at risk of TACO if transfused blood is not reduced to an amount proportional to body mass and intravascular blood volume. The reported incidence of TACO varies widely depending on the method of data collection used. The risk of TACO increases with rapid infusion. The 2011 US Food and Drug Administration report on transfusion-related mortality indicated that TACO was the second most commonly reported cause of death next to TRALI, accounting for an average of 15% of reported deaths between 2007 and 2011.

Circulatory overload increases central venous pressure, causes congestion of the pulmonary vasculature, and decreases lung compliance, manifesting as dyspnea, tachycardia, acute hypertension, and in the extreme, pulmonary edema and left- or right-sided heart failure. Other signs and symptoms of circulatory overload include tachypnea, dry cough, chest or throat tightness, jugular venous distention, and pulmonary rales. Laboratory measurements of circulatory overload include PaO₂, atrial natriuretic peptide and B-type natriuretic peptide (BNP). B-type natriuretic peptide (BNP), and N-terminal pro-BNP (NT-pro-BNP) are cardiac neurohormones specifically secreted from the ventricles in response to volume expansion and pressure overload. BNP has a reported 81% sensitivity for detecting circulatory overload in the appropriate clinical setting. However, BNP and NT-pro-BNP testing did not reliably distinguish TACO from TRALI and possible TRALI in a cohort of transfused critically ill patients. Diagnosing TACO can be difficult and confounded by other concomitant pathology. There is no accepted clinical definition of TACO and the symptoms of TACO can overlap significantly with other transfusion reactions such as TRALI (Table 58.1). Some rapid methods of differentiating the overlapping symptoms include blood pressure, response to diuretic therapy, white cell count, and heart auscultation for an S3 (third heart sound).

If symptoms of overload appear, the transfusion should be stopped, and intravascular volume reduction through diuresis should be instituted as needed (e.g., administration of 40 mg furosemide intravenously). The patient should be placed in an upright (reverse Trendelenburg) position, if possible, with supplemental oxygen as necessary.

Rapid transfusion of any blood component into a patient who is not actively hemorrhaging produces no benefit and can cause harm.

### Table 58.1 Features in TRALI and TACO

<table>
<thead>
<tr>
<th>Feature</th>
<th>TRALI</th>
<th>TACO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>Fever can be present</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Hypotension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Acute dyspnea</td>
<td>Acute dyspnea</td>
</tr>
<tr>
<td>Neck veins</td>
<td>Unchanged</td>
<td>Can be distered</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Rales</td>
<td>Rales, S3 may be present</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Diffuse, bilateral infilrates</td>
<td>Diffuse, bilateral infilrates</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Normal, decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>PA occlusion pressure</td>
<td>18 mmHg or less</td>
<td>Greater than 18 mmHg</td>
</tr>
<tr>
<td>Pulmonary edema fluid</td>
<td>Exudate</td>
<td>Transudate</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Positive, even, negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Response to diuretic</td>
<td>Minimal</td>
<td>Significant</td>
</tr>
<tr>
<td>White count BNP</td>
<td>Transient leukopenia &lt;200 pg/mL</td>
<td>Unchanged &gt;1200 pg/mL</td>
</tr>
<tr>
<td>Leukocyte antibodies</td>
<td>Donor leukocyte antibodies</td>
<td>Donor leukocyte antibodies may or may not be present, positive results can suggest TRALI even with true TACO cases</td>
</tr>
</tbody>
</table>

The typical patterns that would be expected for cases of transfusion-related acute lung injury (TRALI) or transfusion-associated circulatory overload (TACO) are represented. A given case of TRALI or TACO may lack some of the typical features. Also, a case of TRALI may have some features suggesting TACO or vice versa, and TRALI and TACO can be present together. The best strategy is to develop a full clinical profile of the case using the feature list above, and determine which diagnosis is most supported: BNP, brain natriuretic peptide; PA, pulmonary artery.
As a general guide, infusion should be at a rate not to exceed 2 to 4 mL/kg/hour, and the rate should be lower (~1 mL/kg/hour) for patients at high risk of circulatory overload.105 In neonates, a slower blood infusion rate increases the hematocrit and decreases cardiac demand without affecting pulmonary artery pressure. More rapid infusion rates are associated with decreased lung compliance and increased pulmonary airflow resistance.106,107

For patients with volume overload caused by medical reasons existing before transfusion, furosemide can be given prophylactically, and transfusion should proceed slowly. The rate of transfusion can be even further slowed, if necessary, by dividing a unit of RBCs or another component into smaller aliquots and transfusing a portion at a time over as much as four hours, the maximum allowable time a blood component should be kept outside blood-bank-monitored storage. For RBCs and thawed plasma, the unused portion can be stored in the blood bank at 1 °C to 6 °C for up to 24 hours while the initial aliquot is administered. Platelet aliquots can be sampled from a single apheresis platelet unit, and with this practice, donor exposures can be minimized. It is important that transfusion of all or part of a blood component be completed within four hours and that any unused portion be stored under regulated blood bank conditions because of concerns about increased risk of bacterial contamination during improper storage. RBC units, apheresis platelets, and whole blood–derived platelet pools can be further concentrated by means of centrifugation and plasma removal, if other measures to prevent volume overload are inadequate.

**Toxic reactions resulting from blood manufacture or processing**

**Hypotensive reactions**

Hypotension may accompany various transfusion reactions including hemolytic and allergic reactions, sepsisemia, and TRALI, but isolated hypotension as a primary manifestation has not been considered a unique type of transfusion reaction. In the past several years, there have been several reports of transfusion reactions characterized primarily by hypotension, and it now appears that such reactions do require a separate category of transfusion reactions.108 Hypotension has been reported among patients receiving bedside, leukocyte-reduced platelets who are also medicated with ACE inhibitors.109 These reactions appear to be caused by generation of bradykinin in transfused blood just as it is being passed through negatively charged leukocyte reduction filters. The mechanism is believed to involve the formation of activated factor XIIa when factor XII, a contact factor, is exposed to the negatively charged filter surface. The filter surface can mimic exposed, negatively charged subendothelium, which is the natural activating stimulus for the contact factors of the intrinsic coagulation pathway after blood vessel damage in vivo. Factor XIIa converts prekallikrein to kallikrein, which cleaves high-molecular-weight kininogen to form bradykinin. The biologic activity of the infused bradykinin is prolonged in transfusion recipients who are also receiving ACE inhibitors (e.g., captopril and enalapril), which inhibit kininase II, the enzyme that breaks down bradykinin. The combination of bradykinin generation just as the blood is being infused with inhibition of the transfusion recipient’s ability to break down bradykinin produces prolonged bradykinin activity conducive to hypotensive reactions. These reactions are less likely with use of prestorage leukocyte-reduced blood components, because the bradykinin is broken down rapidly in the component bag during storage before transfusion. Although hypotensive reactions have been reported more frequently with negatively charged bedside leukocyte reduction filters, they also have been rarely reported with positively charged filters. This can be explained in part by the possibility that patients taking ACE inhibitors may be more prone to hypotensive reactions in general because of their relative inability to rapidly break down bradykinin generated in vivo by any allergic mechanism. Hypotensive reactions to bedside leukocyte reduction among patients taking ACE inhibitors can be prevented by use of prestorage leukocyte-reduced blood components or by means of temporary discontinuation of ACE inhibitor treatment.

Apheresis procedures are also associated with hypotensive reactions and the literature has described hypotensive reactions in both adult and pediatric apheresis patients.110,111 Apheresis may contribute to hypotensive reactions through several mechanisms including the potentiation of bradykinin-mediated effects by albumin and secondary to hypocalcemia.111,112 Data suggest that calcium infusions can mitigate some atypical apheresis reactions, while withholding ACE inhibitor medications 24 to 48 hours before apheresis may also contribute to lessening reactions.

**Ocular reaction to leukocyte-reduced blood components: red eye syndrome**

Some patients receiving transfusions of RBCs prestorage leukocyte reduced with a specific filtration system (LeukoNet Prestorage Leukocyte Reduction Filtration System, HemaSure, Marlborough, MA) sustained bilateral conjunctival erythema (red eye syndrome).113 The conjunctival erythema occurred within 24 hours of transfusion. Resolution occurred spontaneously within 2 to 21 days with a median duration of five days. The implicated prestorage leukocyte reduction system has been discontinued, and red eye syndrome has not been reported with other leukocyte reduction filters.114 The red eye symptoms are hypothesized to be an allergic or toxic reaction to cellulose acetate derivatives that leached from the filter membrane.

**Plasticizer toxicity**

Plasticizers are chemicals used to make rigid polyvinyl chloride plastics more malleable. The traditional plasticizer for blood storage bags is di(2-ethylhexyl)phthalate (DEHP), which leaches over time from the plastic into the blood and blood components with increasing exposure. The DEHP metabolite, mono(2-ethylhexyl)phthalate (MEHP), also accumulates during storage.115 Infusion of blood that contains DEHP results in deposition of DEHP in various tissues; the greatest accumulation is in body fat. Results of some studies with animals have suggested that DEHP is toxic and may even be carcinogenic in large quantities.116 Other studies with animals have shown that MEHP is associated with formation of peroxisomes, indicating tissue alteration and toxicity. Although there have been no reports of transfusion-related plasticizer toxicity among humans, results of some in vitro experiments suggest that high concentrations of MEHP have a negative inotropic effect and can cause irregular contractions in isolated human myocardial cells. Some clinical data have described the production of antiplasticizer IgE in transfusion recipients and the incorporation of plasticizer into red cells during storage.117 Despite the possible adverse effects of DEHP plasticizers, other data indicate that these substances stabilize red cell membranes and improve the morphologic features of platelets during storage.118,119 No good evidence exists, however, of actual improvement in posttransfusion outcomes as the result of these effects.
Formulations for plastic blood bags are being developed with plasticizers other than DEHP that have a decreased capacity to leach into plasma. For example, one polyvinyl chloride–based material is made with plasticizer butyl tri-n-hexyl citrate (BTHC). Although BTHC also leaches into blood components, it does so at a significantly slower rate than does DEHP. It also provides an antihemolytic effect similar to that of DEHP. Studies have shown this citrate-based plasticizer is suitable for storage of both RBCs and platelets.

**Dimethyl sulfoxide toxicity during infusion of cryopreserved progenitor cells**

DMSO is a versatile solvent that has been used as the principal cryopreservative for mononuclear cells since the 1950s. It is widely used as a cryopreservative for marrow and PBSCs used in human hematopoietic progenitor cell transplantation. Despite this, DMSO is not approved by the FDA as a pharmacologic agent for intravenous administration, and guidelines for intravenous administration are obscure. Toxicologic studies, however, have established the general safety of intravenous DMSO infusion. The metabolism of DMSO yields a characteristic harmless odor, described as a malodorous garlic or sulfur-like smell. Because of the exceptional solvent properties of the compound, DMSO is distributed throughout all tissues after administration. The two metabolites of DMSO are dimethyl sulfide and dimethyl sulfide (DMS). Dimethyl sulfide is an odorless compound excreted by the kidney, and DMS is excreted through the lungs and through other tissues and contributes to the characteristic odor.

The clinical toxicity of DMSO in marrow transplantation has been studied. Anaphylactoid symptoms attributable to the release of histamine and other mediators are common. Other toxic clinical signs and symptoms include hemolysis with hemoglobinuria, hyperosmolarity, increased serum transaminase values, nausea, vomiting, abdominal cramping, fever, chills, tachypnea, cough, diarrhea, flushing, and headache. Patients who have been conditioned with chemotherapy or who have smaller body mass (<70 kg), seem more likely to experience nausea and vomiting after infusion of DMSO-preserved cells. Cardiovascular toxicities include decreased heart rate and bradycardia, occasionally increased heart rate and tachycardia, ectopic heartbeat, heart block, hypotension, hypertension, and other lesser blood pressure changes. Some studies, however, raise the question whether there is any significant cardiovascular toxicity of DMSO. It is possible that some adverse effects attributed to DMSO may be caused by the cellular infusion itself.

The mechanism of the clinical toxicities associated with DMSO infusion has not been well established. Histamine receptor binding of DMSO, histamine release, direct vagal tonic effects, cold thermal vagal responses, and renal failure secondary to hemolysis explain many of the symptoms observed during cryopreserved cellular infusions. Increases in thrombin-antithrombin complex, β-thromboglobulin, platelet factor 4, and von Willebrand factor caused by DMSO have been described.

Several measures can be taken to prevent or reduce DMSO toxicity. Antihistamine prophylaxis is recommended routinely before any administration of DMSO. Intravenous DMSO should be given at a 10% to 40% solution to avoid local irritation. The recommended maximum daily dose of DMSO is 1 g/kg/day. Slowing an infusion containing DMSO or increasing the time between infusions of multiple aliquots greatly diminishes DMSO-related toxicity, which appears to be a dose-dependent but short-lived response. However, because DMSO is toxic to thawed mononuclear cells, hematopoietic progenitor cells can tolerate exposure to 10% DMSO for only as long as 1 hour. This limits how much the infusion rate can be slowed. Antiemetics and sedatives can help to ameliorate symptoms, and cellular products can be carefully washed before infusion to remove DMSO and other substances.

**Reactions in special transfusion settings**

**Granulocyte transfusion reactions**

Granulocyte transfusions remain in use as a treatment option for neutropenic patients because of improved granulocyte collection yields after donor treatment with steroids and granulocyte colony-stimulating factor (G-CSF). Febrile nonhemolytic transfusion reactions after granulocyte transfusion are common. Severe reactions can be accompanied by pulmonary complications (e.g., TRALI, dyspnea, pulmonary infiltrates, and hypoxia), hypotension, and even cardiovascular collapse. In a recent study of dexamethasone- and G-CSF-stimulated granulocyte transfusions, 37% of patients (7% of transfusions) experienced chills, 32% of patients (7% of transfusions) experienced a fever, and 11% of patients (2% of transfusions) experienced hives or itching during a course of therapy. Oxygen desaturation of greater than 3% occurred in 7% of transfusions, and severe desaturation of greater than 6% occurred in three of 11 patients experiencing oxygen desaturation. In addition, granulocyte transfusions carry further risk of leukocyte alloimmunization and cytomegalovirus infection.

Concurrent administration of amphotericin B and granulocytes has been linked to severe pulmonary reactions, although the association has not been confirmed and remains in doubt. In a study that examines one hundred and ninety-five series of granulocyte transfusions in 144 patients demonstrated no severe pulmonary toxicity from concomitant administration of granulocytes and amphotericin B. Dyspnea as a side effect of granulocyte transfusion was equally common among patients receiving amphotericin B and those in a matched control group not receiving amphotericin B. It is safe to administer granulocyte transfusion and amphotericin B simultaneously without pulmonary toxicity.

Nevertheless, it is prudent to separate amphotericin B administration and granulocyte therapy by at least 6 hours to avoid confusion about the cause of a severe reaction, which can occur with either of these reaction-prone treatments. Because of the relatively high rate and severity of febrile, pulmonary, and allergic reactions, it is prudent to give premedication with acetaminophen and diphenhydramine to recipients of granulocyte transfusions. Hydrocortisone may be added as premedication in the treatment of patients with severe reactions who otherwise cannot tolerate granulocyte transfusion, although the immunosuppressive effects of this agent are unwelcome among patients who need granulocyte transfusions to fight serious and life-threatening infections. Granulocyte concentrates should be transfused slowly.

**Autologous transfusion reactions**

A variety of reactions to autologous blood occur despite the complete compatibility. In a study involving 596 hospitals, the rate of reported FNHTRs to autologous blood was 0.12% and the rate of allergic reactions was 0.01% per transfused unit. Such rates are approximately fivefold to 10-fold lower than those reported for allogeneic units. The cause of autologous transfusion reactions has not been clearly established. Mechanisms in many
### Table 58.2 Transfusion Reaction Summary

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Signs and Symptoms</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile, nonhemolytic frequency of FNHTRs before leukocyte-reduction 0.33–0.37% in (red cells), 0.45 to 2.18% in (platelets) after leukocyte reduction 0.15–0.19% (red cells), 0.11 to 0.15% (platelets)</td>
<td>Recipient antibodies against leukocytes or platelets antigens in donor blood components; cytokines in plasma or supernatant portion of stored components; undetected bacteria contamination of blood component</td>
<td>Chills, fever (&gt;1 °C increase in body temperature); rigors in severe reactions</td>
<td>Stop transfusion, notify physician and blood bank, maintain IV line, monitor vital signs; physician may order acetaminophen</td>
<td>Premedicate with aceterminophen (or glucocorticoid for refractory cases); give leukocyte-reduced RBCs</td>
</tr>
<tr>
<td>Allergic overall frequency of 0.11%</td>
<td>Allergen is a soluble substance in donor plasma</td>
<td>Localized or generalized urticaria, erythema and pruritus; if severe, may have laryngeal or facial angioedema, and hypotension</td>
<td>Hold transfusion, notify physician, monitor vital signs; physician may order antihistamines or restart of transfusion if mild urticaria clears and no other symptoms in 30 minutes</td>
<td>Premedicate with H1 blocking antihistamine; add H2 blocker or glucocorticoid for refractory cases; consider washed RBCs and platelets for repeated or severe reactions</td>
</tr>
<tr>
<td>Anaphylactic or anaphylactoid</td>
<td>Recipient antibodies to a soluble substance in donor plasma; infusion of plasma with IgA into IgA-deficient recipient with IgG anti-IgA antibodies</td>
<td>Urticaria, flushing, angioedema, stridor, wheezing, lachycardia, hypotension, shock, abdominal pain, diarrhea, pelvic pain</td>
<td>Stop transfusion; maintain IV line; notify physician and blood bank; monitor vital signs; physician may order antihistamines, epinephrine, oxygen, IV crystalloid, or glucocorticoids</td>
<td>Premedicate with antihistamines and glucocorticoid; transfuse washed RBCs and platelets for recurrent reactions; use IgA deficient donors or washed RBCs and platelets for sensitized patients with IgA deficiency</td>
</tr>
<tr>
<td>Transfusion-associated circulatory overload (TACO)</td>
<td>Blood volume too large or infusion too fast for compromised cardiovascular system</td>
<td>Dyspnea, orthopnea, systolic hypertension, headache, peripheral edema, coughing, cyanosis</td>
<td>Slow or stop transfusion; keep IV line open; notify physician; monitor vital signs and input and output; physician may order diuretics and oxygen</td>
<td>Transfuse slowly; use split units; consider premedication with diuretics; carefully monitor aged, debilitated, cardiac or pediatric patients</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Core body temperature &lt;35 °C caused by rapid infusion of cold blood products, such as RBCs, FFP, cryoprecipitate</td>
<td>Decreased body temperature, chills, cardiac arrhythmia (ventricular fibrillation)</td>
<td>Slow or stop transfusion; use an approved blood warmer, blankets, and other patient warming techniques (warm lavages, lamps)</td>
<td>Transfuse slowly, use an approved blood warmer</td>
</tr>
<tr>
<td>Citrate toxicity</td>
<td>Excessive infusion of citrate during apheresis procedure or massive or rapid transfusion; patients with liver failure are at increased risk</td>
<td>Perioral or peripheral paresthesia, tingling, buzzing, teeth chattering, bed or chair moving, cramps, nausea, vomiting, arrhythmia, bradycardia, hypotension, prolongation of QT interval, tetany</td>
<td>Slow or stop transfusion; slow or stop apheresis procedure; give IV calcium chloride or gluconate (for FFP, citrate-A: 0.5 mg Ca²⁺ +1.0 mL ACD-A), or check ionized Ca²⁺ and dose per results; monitor relief of symptoms</td>
<td>More likely in pediatric and lightweight patients (&lt;70 kg) and patients with liver dysfunction, renal failure, or less skeletal muscle; observe patients closely for any symptoms, give IV calcium (for PBSC apheresis: 0.5 mg Ca²⁺ /1.0 mL ACD-A), hyperkalemia: give fresh products (&lt;7 days old), or washed products</td>
</tr>
<tr>
<td>Electrolyte disorder</td>
<td>Hyperkalemia: transfusion of older blood components or massive transfusion of RBCs</td>
<td>Hyperkalemia: cardiac arrhythmia, ECG changes—peaked T waves, prolongation of PR interval (if severe, flat or lost P wave), widened QRS, ventricular arrhythmia</td>
<td>Hyperkalemia: give calcium to protect against cardiac effect, alkalize blood, D50 plus insulin, sodium polystyrene sulfonate; dialysis</td>
<td>Hypokalemia: give potassium</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Bradykinin generation with use of negatively charged bedside leukocyte reduction filters in patients taking angiotensin-converting enzyme (ACE) inhibitors; apheresis procedures using albumin, especially in patient’s taking ACE inhibitors; see also citrate toxicity</td>
<td>Perioral or peripheral paresthesia, tingling, buzzing, teeth chattering, bed or chair moving, cramps, nausea, vomiting, arrhythmia, bradycardia, hypotension, prolongation of QT interval, tetany</td>
<td>Hypokalemia: give potassium</td>
<td>Hypokalemia: give Adsol-preserved RBCs (not Nutricel)</td>
</tr>
<tr>
<td>Citrate toxicity</td>
<td>Hyperkalemia: massive or rapid transfusion of citrate and metabolic alkalosis</td>
<td>Hyperkalemia: cardiac arrhythmia, ECG changes—ST depression, U waves</td>
<td>Hypokalemia: give potassium</td>
<td>Hypokalemia: give Adsol-preserved RBCs (not Nutricel)</td>
</tr>
<tr>
<td>Hypotensive</td>
<td>Bradykinin generation with use of negatively charged bedside leukocyte reduction filters in patients taking angiotensin-converting enzyme (ACE) inhibitors; apheresis procedures using albumin, especially in patient’s taking ACE inhibitors; see also citrate toxicity</td>
<td>Bradykinin generation with use of negatively charged bedside leukocyte reduction filters in patients taking angiotensin-converting enzyme (ACE) inhibitors; apheresis procedures using albumin, especially in patient’s taking ACE inhibitors; see also citrate toxicity</td>
<td>Avoid use of bedside leukocyte reduction filters in patients taking ACE inhibitors; use prestorage leukocyte-reduced components or discontinue ACE inhibitor before transfusion or apheresis procedure; if during apheresis, correct electrolyte disorder such as hypocalcemia</td>
<td>Avoid use of bedside leukocyte reduction filters in patients taking ACE inhibitors; use prestorage leukocyte-reduced components or discontinue ACE inhibitor before transfusion or apheresis procedure; if during apheresis, correct electrolyte disorder such as hypocalcemia</td>
</tr>
<tr>
<td>DMSO toxicity</td>
<td>Cryopreservative for bone marrow, PBSCs, Cord blood, donor lymphocyte infusions, or any frozen cellular component; toxicity with DMSO &gt;1.0 g/kg day</td>
<td>Flushing, nausea, vomiting, abdominal cramping, throat tightness and cough, hypotension, hypertension, arrhythmia, fever, chills, headache, hemoglobinuria, hyperosmolality, increased liver enzymes</td>
<td>Antihistamines; antiemetics; slow or stop the infusion; supportive care; wait between infusions for symptoms to clear</td>
<td>Antihistamines; washed or plasma or volume depleted cellular infusions; antiemetics</td>
</tr>
</tbody>
</table>

IV, intravenous; RBCs, red blood cells; FFP, fresh frozen plasma; PBSC, peripheral blood stem cell; ACD-A, acid-citrate-dextrose-adenine; D50, dextrose 50% in water; ECG, electrocardiogram; DMSO, dimethyl sulfoxide.
themselves at increased risk of bacteremia.\footnote{Granulocytes would very likely cause febrile reactions and dyspnea. However, granulocytes are not listed in the table because they are infrequently transfused compared to other blood components.} Allergic reactions may be provoked by histamine from blood storage containers or by chemicals leaching from blood storage containers or filters. Moreover, autologous transfusions may contribute to volume overload and hypervolemic reactions through mechanisms identical to allogeneic transfusions.

Summary

A variety of acute, nonhemolytic, and noninfectious reactions are reported after transfusion (Table 58.2). Many of these reactions have an immune basis and represent inflammatory or allergic responses to infused cells (e.g., many FNHTRs) or plasma (e.g., some FNHTRs, allergic, and anaphylactic reactions). Although urgent transfusion can be lifesaving, it is important to recognize that a large volume of blood components given too quickly can itself have adverse chemical or physical effects, such as hypothermia, hyperkalemia, hypokalemia, hypocalcemia, and circulatory overload. Some reactions also are caused by unintended consequences of blood storage conditions or processing, such as generation of bradykinin by the contact of blood with some filter surfaces, leaching of toxic chemicals from filters or containers, and use of the chemical DMSO during hematopoietic progenitor cell preservation. It is important that these reactions and toxicities be recognized rapidly by the patient care team and blood bank personnel so that appropriate treatment and preventive measures can be instituted quickly. Care providers who administer transfusions must recognize that some symptoms of transfusion reactions, such as fever, are nonspecific and may be early manifestations of potentially life-threatening reactions, such as hemolysis or sepsis (Table 58.3). For that reason, the guiding rule regarding most transfusion reactions is to err on the side of conservatism and stop the transfusion immediately. Transfusion of a blood component that causes a reaction before complete infusion should not be restarted, with the possible exception of mild urticarial reactions. Several strategies are available to prevent repeated reactions among patients who are reaction-prone. These include leukocyte reduction for the prevention of FNHTRs, cell washing for the prevention of allergic and anaphylactic reactions and possibly some FNHTRs, and various premedication regimens.

Disclaimer

The authors have disclosed no conflicts of interest.

Key References

A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion


