Transfusion reactions: prevention, diagnosis, and treatment

Meghan Delaney, Silvano Wendel, Rachel S Bercovitz, Joan Cid, Claudia Cohn, Nancy M Dunbar, Torunn O Apelseth, Mark Popovsky, Simon J Stanworth, Alan Tinmouth, Leo Van De Watering, Jonathan H Waters, Mark Yazer, Alyssa Ziman, for the Biomedical Excellence for Safer Transfusion (BEST) Collaborative

Blood transfusion is one of the most common procedures in patients in hospital so it is imperative that clinicians are knowledgeable about appropriate blood product administration, as well as the signs, symptoms, and management of transfusion reactions. In this Review, we, an international panel, provide a synopsis of the pathophysiology, treatment, and management of each diagnostic category of transfusion reaction using evidence-based recommendations whenever available.

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Bloodworks NW, Seattle, WA, USA (M Delaney DO); **University of Washington, Department of Laboratory Medicine, Seattle, WA, USA** (M Delaney); **Hospital Sirio Libanes Blood Bank, Sao Paulo, Brazil** (S Wendel MD); **BloodCenter of Wisconsin, Milwaukee, WI, USA** (R S Bercovitz MD); **Department of Hemotherapy and Hemostasis, CDB, IDIBAPS, Hospital Clínic, UB, Barcelona, Spain** (J Cid MD); **Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA** (C Cohn MD); **Department of Pathology and Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA** (N M Dunbar MD); **Laboratory of Clinical Biochemistry and Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway** (T O Apelseth MD); **Haemonetics Corporation, Braintree, MA, USA** (M Popovsky MD); **NHS Blood and Transplant/Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, UK** (S J Stanworth FRCP); **Radcliffe Department of Medicine, University of Oxford, Oxford, UK** (S J Stanworth); **Department of Medicine and Department of Laboratory Medicine & Pathology, University of Ottawa, Ottawa, ON, Canada** (A Tinmouth MD); **University of Ottawa Centre for Transfusion Research, Ottawa Hospital Research Institute, Ottawa, ON, Canada** (A Tinmouth); **Center for Clinical Transfusion Research, Sanquin, Netherlands** (L Van De Watering MD); **Department of Anesthesiology & Bioengineering, University of Pittsburgh & McGowan Institute for Regenerative Medicine, Pittsburgh, PA, USA** (Prof J H Waters MD); **Division of Transfusion Medicine,**

Introduction

Blood transfusions are one of the most common procedures for patients in the hospital and are associated with substantial risks and cost; therefore health-care providers need to understand the hazards related to blood product administration.[1] Although awareness is increasing of the clinical efficacy of restrictive transfusion thresholds in some settings—such that providers are being prompted to consider alternatives to transfusion and make treatment decisions to avoid unnecessary transfusions—transfusions are still an essential component of care in certain patient populations.[2] Transfusion reactions are the most frequent adverse event associated with the administration of blood products, occurring in up to one in 100 transfusions (table 1). A transfusion reaction can lead to severe discomfort for the patient and extra cost burden to the health-care system.[3–5] Although rare, reactions can be fatal, with transfusion of about one in 200 000–420 000 units associated with death.[6] Given the diversity of risks, clinicians should have accessible information about the nature, definitions, and management of transfusion-related adverse events.

Review design and methods

In this Review, we aim to provide a description of each clinical entity, as well as treatment and prevention guidelines based on published work, whenever available, and expert advice. In the appendix we offer a detailed guide for diagnostic, treatment, and management principles in a single-page format for each category to provide a more extensive and detailed description that could be used at the patient's bedside.

We derived diagnostic categories for transfusion reactions from definitions from the US National Healthcare Safety Network (NHSN) haemovigilance module.[7] We graded evidence-based recommendations using the *Chest*[8] grading system: grade 1A–2C (table 2). Since many publications on this topic are uncontrolled case reports, case series, and retrospective cohort studies, the evidence quality score reflects the quality of the literature. For example, there are few reports of transfusion reactions in the paediatric population. Therefore, although evidence-based recommendations are the goal, some clinical situations that we discuss in this Review do not have available published evidence (figure 1). In these instances, we provide recommendations and no grade is given. We provided some published haemovigilance reports as references to guide the reader to additional content, but these are not used for evidence-based recommendations. Diverse sources of data exist to define rates of specific transfusion reaction categories; however, these reactions might be under-reported, and affected by hospital factors and by the patients' underlying disease.[3] Medication doses, when provided, are noted in the appendix only. Transfusion might produce other adverse effects, such as transfusion-related immunomodulation or viral infections, which are not usually classified as transfusion reactions and, therefore, we do not include them in this Review. We also do not include studies on plasma derivatives.

General management of transfusion reactions

Transfusion reactions are usually reported to the physician by the nurse administering the blood product and often cause a change in vital signs or a new symptom.[9] The algorithm summarises the initial clinical assessment of a patient having a transfusion reaction (figure 2). Depending on the severity, the main treatment strategy for all reaction types is to stop the transfusion and keep the intravenous line open with normal isotonic saline; start supportive care to address the patient's cardiac, respiratory, and renal functions as necessary; and provide symptomatic therapy. The blood product labelling and patient identification should be rechecked to confirm that the patient received their intended product and the reaction should be reported to the blood transfusion laboratory for additional testing.[10] These universal procedures should be done in all transfusion reactions, irrespective of the type of reaction.

Search strategy and selection criteria

A reference librarian identified studies through Mesh keyword searches of the electronic databases of Cochrane Library and MEDLINE from Jan 1, 1940, to Dec 31, 2014, for the diagnostic categories, blood components and transfusions, and adverse reactions. We included only articles published in English. We excluded those focusing on plasma derivatives. Results are available on request.

Department of Pathology, University of Pittsburgh, Institute for Transfusion Medicine, Pittsburgh, PA, USA (Prof M Yazer MD)**; and Division of Transfusion Medicine, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA** (Prof A Ziman MD)

Correspondence to: Dr Meghan Delaney, Bloodworks NW, Seattle, WA 98115, USA
meghand@bloodworksnw.org

See Online for appendix

Allergic and anaphylactic transfusion reactions

Allergic transfusion reactions occur during or within 4 h of transfusion with a blood component and are most frequently associated with platelet transfusions (302 per 100 000 platelet units).[11] Symptoms are caused by mediators such as histamine, released on activation of mast cells and basophils.[12] Most allergic transfusion reactions are mild, with rash, pruritus, urticaria (hives), and localised angio-oedema.[7] The most severe reactions are anaphylactic, characterised by a life-threatening systemic reaction, typically presenting as bronchospasm, respiratory distress, and hypotension.[7,13]

In mild allergic transfusion reactions (cutaneous symptoms only), H_1 antihistamine administration (eg, diphenhydramine) should give symptomatic relief (grade 1A).[14–16] If symptoms resolve, then clinical experience suggests that transfusion can be restarted with the same unit at a reduced rate under direct observation.[14] The transfusion must be discontinued if symptoms recur or if additional symptoms appear beyond local cutaneous manifestations.

Anaphylactic reactions (incidence eight per 100 000 units) require prompt intramuscular administration of epinephrine (adrenaline; grade 1A).[13,14] In addition to supportive measures, the following second-line drugs can be considered: H_1 antihistamine (eg, chlorpheniramine, diphenhydramine; grade 1C), bronchodilators (β_2 adrenergic agonist—eg, salbutamol solution; grade 1C); glucocorticoid for intravenous administration (eg, hydrocortisone or methylprednisolone; grade 1C); and intravenous H_2 antihistamine (eg, ranitidine; grade 1C).[14]

Patients with a history of allergic transfusion reactions should be monitored closely when receiving subsequent transfusions. There is no evidence to support routine prophylaxis with antihistamines or glucocorticoids in patients with previous mild allergic transfusion reactions (grade 2C).[17] Patients with moderate to severe allergic transfusion reactions should be counselled about their diagnosis and needs for future transfusion. In these patients, premedication with antihistamines (grade 2C), minimisation of the plasma content of the unit by removal of excess supernatant (centrifugation or washing), or use of platelets stored in additive solutions reduces the incidence or decreases the severity of future reactions (grade 1C).[14,18,19] Use of corticosteroids as premedication has not been studied, but is used widely in our experience. For a patient with a history of an anaphylactic transfusion reaction, exclusion of serum protein deficiency (eg, immunoglobulin A and haptoglobin) and other allergies might be warranted (grade 1C).[14] In case of immunoglobulin A deficiency with anti-immunoglobulin A antibodies, but no history of an anaphylactic reaction, use of immunoglobulin A-deficient or washed blood components can be undertaken; however, the supporting evidence is debated.[14,20]

	Prevalence (per 100 000 units transfused)
Allergic transfusion reaction	112·2
Anaphylactic transfusion reaction	8
Acute haemolytic transfusion reaction	2·5–7·9
Delayed haemolytic transfusion reaction	40
Delayed serological transfusion reaction	48·9–75·7
Febrile non-haemolytic transfusion reaction	1000–3000
Hyperhaemolytic transfusion reaction	Unknown
Hypotensive transfusion reaction	1·8–9·0
Massive transfusion associated reactions (citrate, potassium, cold toxicity)	Unknown
Post-transfusion purpura	Unknown
Septic transfusion reaction	0·03–3·3 (product dependent)
Transfusion-associated circulatory overload	10·9
Transfusion-associated graft versus host disease	Extremely rare (near 0%) with irradiation or pathogen reduction methods
Transfusion-associated necrotising enterocolitis	Unknown
Transfusion-related acute lung injury	0·4–1·0 with mitigation (varies by component and post-implementation of risk mitigation strategies)

Table 1: **Rates of transfusion reactions**

	Description	Methodological quality of supporting evidence	Implications
1A	Strong recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low quality or very low quality evidence	Observational studies or case series	Strong recommendation but might change when higher quality evidence becomes available
2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action might differ depending on circumstances or patients' or societal values
2B	Weak recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation; best action might differ depending on circumstances or patients' or societal values
2C	Weak recommendation, low quality or very low quality evidence	Observational studies or case series	Very weak recommendations; other alternatives might be equally reasonable

Used from Guyatt et al,[8] with permission. RCT=randomised controlled trial.

Table 2: **Evidence grading system by recommendation**

Acute haemolytic transfusion reactions

Acute haemolytic transfusion reactions can be either immune or non-immune. Immune-mediated acute haemolytic transfusion reactions result from infusion of red blood cells that are incompatible with the patient's anti-A, anti-B, or other red blood cell antibodies. Immune acute haemolytic transfusion reactions are usually caused by failure of patient identification at specimen collection or transfusion, and less commonly by infusion of incompatible plasma, usually from an apheresis platelet transfusion. In either setting, the antigen–antibody interaction can lead to intravascular or extravascular haemolysis, presenting with sudden onset of fever or chills (the most common [80%], and often the only symptom), pain (from kidney capsular distension), hypotension, and dyspnoea. Other signs can include gross haemoglobinuria or haemoglobinaemia, disseminated intravascular coagulation, acute renal failure, shock, and death.[7] Since fever and chills might be the only early signs, it is important to monitor patients during transfusions and stop the transfusion immediately if there is any change in vital signs or the appearance of unexpected symptoms.[14] Health-care facilities should establish policies that define vital sign changes that should prompt evaluation of a suspected transfusion reaction.[10]

Immune acute haemolytic transfusion reactions are diagnosed on the basis of clinical findings and demonstration of serological incompatibility. Management is supportive. In severe reactions, cardiovascular, renal, and respiratory support, and treatment for disseminated intravascular coagulation with bleeding, might be necessary.[14] No evidence exists for the use of any specific intervention after an ABO-incompatible red blood cell transfusion, although case reports highlight the use of red blood cell or plasma exchange (grade 2C), intravenous immunoglobulin (grade 2C), and complement-inhibiting drugs (grade 2C).[21–24] Prevention relies on systems-based practices and comprehensive training to ensure proper patient identification at critical steps in the specimen collection and transfusion processes (grade 1A).[25,26]

Non-immune acute haemolytic transfusion reactions occur when red blood cells are haemolysed by factors other than antibodies, such as coadministration of red blood cells with an incompatible crystalloid solution (eg, 5% dextrose solution), incorrect storage of blood, or use of malfunctioning or non-validated administration systems.[27,28] Prevention requires close adherence to blood handling and administration policies.

Delayed haemolytic or delayed serological transfusion reactions

The incidence of delayed haemolytic transfusion reaction is one per 2500 transfusions, but rises to 11% in patients with sickle-cell disease.[29] Patients at risk for delayed haemolytic or serological transfusion reactions include those with a history of red blood cell antibodies (through pregnancy or transfusion exposure) in which the antibody titre subsequently decreases to levels undetectable by routine antibody detection testing. With standard laboratory techniques, 25% of red blood cell alloantibodies become undetectable over a median follow-up of 10 months after initial development, thus putting patients at risk for delayed transfusion reactions.[30]

Delayed haemolytic transfusion reactions are similar to serological reactions with regard to mechanism and timecourse. Delayed haemolytic transfusion reaction is usually due to an anamnestic immune response when the recipient is unknowingly transfused with a red blood cell unit that expresses the cognate antigen.[31] Re-exposure to the foreign antigen causes a rise in red blood cell antibody titres 24 h to 28 days after transfusion, accompanied by either a fall or failure of haemoglobin increment, rise in indirect bilirubin, or a positive direct antiglobulin (Coombs') test; subsequent laboratory testing with elution studies usually demonstrates the

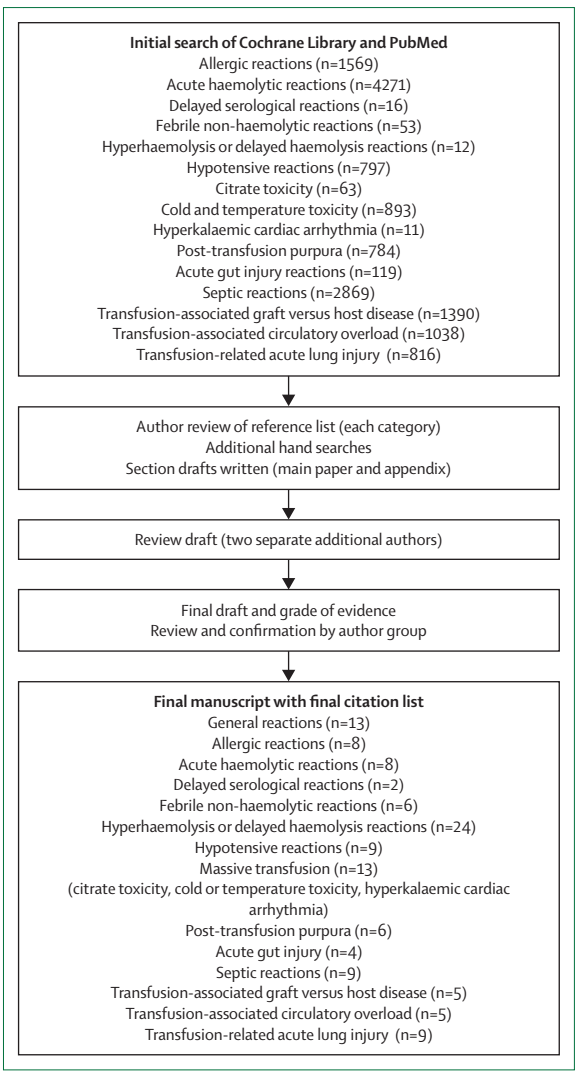

Figure 1: **Literature review and manuscript construction**

All transfusions must be stopped when a patient is experiencing a reaction and assessed by a provider
Provide supportive therapy to support vital organ function (cardiac, pulmonary, renal)
For questions regarding transfusion reaction diagnosis or management, call the transfusion service, or other appropriate physician

Reaction	Symptoms	Interventions
Increase in temperature		
Possible febrile non-haemolytic reaction	Incremental increase <1°C above baseline and no other new symptoms	• Close observation, frequent vital signs • If stable and no other new symptoms then continue with transfusion
Possible bacterial contamination Possible haemolysis	Incremental increase ≥1°C above baseline, or incremental increase <1°C with any other new symptoms (chills or rigors, hypotension, nausea or vomiting)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antipyretic drug • Consider blood cultures (patient); empirical antibiotics if neutropenic • Do not resume transfusion • Strongly consider culturing blood product if ≥2°C increase in temperature or if high clinical suspicion of sepsis • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
		For consistently febrile patient due to underlying disease or treatment, when possible: • Avoid starting transfusion if patient's temperature is increasing • Treat fever with antipyretic drug before starting transfusion • If incremental increase in temperature ≥1°C above baseline treat as per above (stop and do not resume transfusion, cultures if indicated) • Notify blood transfusion laboratory, return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
Allergic symptoms		
Urticaria	Mild hives, rash, or skin itching only	• Stop transfusion, keep intravenous line open, and assess patient • Antihistamines • Notify patient clinician and blood transfusion laboratory; sample not required • If symptoms resolve, then can resume transfusion • If symptoms do not improve or worsen or recur then discontinue transfusion; return unit (with administration set) to blood transfusion laboratory
Possible allergic reaction	Hives, rash, itching, and or any other new symptoms (throat, eye, and tongue swelling, etc)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antihistamines • Do not resume transfusion • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
Respiratory symptoms		
Possible anaphylaxis, transfusion-associated circulatory overload, septic transfusion reaction, or transfusion-related acute lung injury	Bronchospasm, dyspnoea, tachypnoea and hypoxaemia, copious frothy pink-tinged fluid (from endotrachel tube)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and patient compatibility • Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support) • Chest radiograph for presence of bilateral interstitial infiltrate, if suggestive of transfusion-related acute lung injury • Blood cultures (patient and product), if high clinical suspicion of sepsis • Do not resume transfusion • Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quaratined
All other symptoms		
Possible anaphylaxis, haemolytic transfusion reaction, fluid overload, or transfusion-related acute lung injury	Chills, rigors, hypotension, nausea or vomiting, feeling of impending doom, back or chest pain, intravenous site pain, cough, dyspnoea, hypoxia	• Stop transfusion, keep intravenous line open, assess unit, check patient ID and unit ID and patient compatibility • Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support) • Blood cultures (patient and product) if high clinical suspicion of sepsis • Do not resume transfusion • Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quaratined

***Figure 2*: Transfusion reaction decision-tree**
Algorithm to guide assessment and actions to take when a transfusion reaction is initially identified. Actions should go from left to right.

alloantibody. The most prominent clinical features of delayed haemolytic transfusion reactions include dark urine or jaundice (45–50%) followed by fever; chest, abdominal or back pain; dyspnoea; chills; and hypertension.[29,32,33] In patients with sickle-cell disease, diagnosis might be delayed when only anaemia and jaundice are present if these symptoms are attributed to veno-occlusive painful crisis.

Retrospective studies show that delayed serological transfusion reactions are more common than are haemolytic ones (0·66% *vs* 0·12%, respectively) in patients in hospital.[34,35] Both share similar serological findings, but patients with delayed serological reactions do not have clinical signs or laboratory evidence of haemolysis. The antibodies most commonly responsible for both types of reactions are from the Rh, Kell, Duffy, Kidd, MNS, and Diego blood group systems.[34] Less commonly, alloantibodies to low incidence antigens that are not detected by antibody detection screening tests can cause unrecognised haemolytic or serological transfusion reactions. When there are signs of hemolysis, retrospective crossmatching can be diagnostic.[36,37]

Most patients do not require treatment other than additional transfusions to maintain desired haemoglobin. Red blood cell exchange transfusion to remove incompatible red cells (grade 2C) or anti-CD20 in combination with methylprednisolone have been proposed for management of delayed haemolytic transfusion reaction in patients with sickle-cell disease (grade 2C).[38,39]

Prevention is based on sensitive laboratory testing, centralised medical records, and red blood cell unit selection.[40] A central repository accessible across health-care systems that includes patient red cell antibody histories can inform the transfusing facility of previously identified antibodies, even if they are no longer detectable, and thereby ensure selection of compatible units for transfusion (grade 1B).[41–43] Prospective red cell antigen matching can decrease alloimmunisation and thus the risk of subsequent delayed haemolytic transfusion reactions (grade 1A).[44,45] Non-alloimmunised patients with sickle-cell disease or thalassaemia should, at a minimum, receive red blood cells matched for Rh (D, C, c, E, e) and K antigens; more highly antigen matched units should be selected as is feasible (grade 1A).[44–47]

Febrile non-haemolytic reactions

Febrile non-haemolytic reactions are common, occurring in about 1% of transfusion episodes (1–3% per unit transfused).[48] Febrile non-haemolytic reactions are caused by pro-inflammatory cytokines or recipient antibodies encountering donor antigen in the blood product.[49] Reactions clinically present as a temperature rise of 1°C or higher, and can be accompanied by transient hypertension, chills, rigors, and discomfort. In the presence of fever, the transfusion must be stopped immediately and the patient assessed closely for signs of infection or haemolysis. Because febrile non-haemolytic reactions are a diagnosis of exclusion, other important transfusion-related aetiologies must be ruled out with post-reaction laboratory evaluation to detect haemolysis (direct antiglobulin test and visual check for grossly haemolysed plasma). For patients who do not improve after cessation of transfusion or antipyretics, have a temperature increase of 2°C or higher, or have clinical signs of new bacterial infection, clinicians should exclude a septic transfusion reaction; this is especially important after a platelet transfusion.[50] When the evaluation finds no other cause, such as an underlying febrile illness, and testing for haemolysis is negative, a diagnosis of febrile non-haemolytic reaction can be made. Antipyretic drugs and pethidine (meperidine) are appropriate, although no studies have delineated their effectiveness.[51]

Pre-storage leucocyte reduction can prevent febrile non-haemolytic reactions (grade 1A).[52] Premedication with antipyretics does not decrease rate of reactions in most patients and should be discouraged (grade 1A).[48] However, use of antipyretic drugs before transfusion for patients who are persistently febrile due to underlying disease can enable transfusion completion in our experience.[53] The use of platelet additive solutions decreases the rate of reactions from 0·5% to 0·17% (grade 1B).[18]

Hyperhaemolytic transfusion reactions

Hyperhaemolytic transfusion reactions are rare, life-threatening haemolytic transfusion reactions that typically occur in patients with haemoglobinopathies (1% to 19% of transfusions in patients with sickle-cell disease), but can be seen in those with other disorders.[54–56] Hyperhaemolytic transfusion reactions should be suspected when the post-transfusion haemoglobin concentration is lower than the pre-transfusion concentration. Signs include raised indirect bilirubin and lactate dehydrogenase and low concentrations of haptoglobin. A fall in absolute reticulocyte count (decrease from baseline concentration) during haemolysis and a rise in reticulocyte count with recovery is a common finding. Hyperhaemolytic transfusion reactions exist in acute and delayed forms. The acute form usually occurs less than 7 days after red blood cell transfusion. Serological investigation of post-transfusion samples might not show new or additional red blood cell alloantibodies and direct antiglobulin test might be negative; furthermore, transfusion of antigen-negative crossmatch compatible units might not prevent this reaction. In the delayed form, which usually occurs more than 7 days after red blood cell transfusion, the direct antiglobulin test is positive and red blood cell alloantibodies are identified in the post-transfusion sample.[57] The diagnosis of acute hyperhaemolytic transfusion is challenging, and a high index of suspicion is needed.

Avoidance of further transfusions is a treatment recommendation for mild cases because this can worsen haemolysis.[57] However, if the patient presents with rapid haemolysis and severe anaemia then transfusion might be needed. In such cases, intravenous immunoglobulin and corticosteroid (eg, methylprednisolone) are recommended (grade 2C).[58] For severe cases, additional intravenous immunoglobulin can be given, with consideration of associated risks such as renal toxicity, changes in serological testing, and thromboembolic events (grade 2C).[58] Rituximab and plasma exchange might be successful in severe cases (grade 2C).[59] Erythropoietin and eculizumab are not currently recommended due to insufficient data showing efficacy.[60] The patient should be counselled about their diagnosis and the risk associated with future transfusions.

Hypotensive transfusion reactions

Acute hypotensive transfusion reactions are uncommon and defined by an abrupt drop in systolic or diastolic blood pressure of more than 30 mm Hg within 15 min of the start of transfusion and resolving quickly (within 10 min) once transfusion is stopped.[61] Hypotension is the predominant manifestation; respiratory, gastrointestinal, or mild allergic symptoms might also be present.

These reactions are thought to occur with activation of the intrinsic contact activation pathway of the coagulation cascade and generation of bradykinin and its active metabolite des-Arg9-bradykinin.[62] Both kinins are potent vasodilators that cause facial flushing and a drop, often severe, in systolic and diastolic blood pressure, which in turn, triggers an increase in heart rate. These kinins also produce slow contraction of the intestinal smooth muscle causing abdominal pain.

Hypotensive reactions are more likely to occur in patients who have hypertension, are taking angiotensin-converting enzyme (ACE) inhibitors (since bradykinin metabolism is less efficient in the presence of an ACE inhibitor), are being transfused blood products through a negatively charged bedside leucocyte reduction filter, are undergoing apheresis, or are receiving platelets.[63–65] These reactions have also been reported during cardiopulmonary bypass and radical prostatectomy.[66–68] Transfusion must be stopped and prompt clinical assessment and supportive therapy given; no specific treatment is indicated because the hypotension typically resolves once transfusion is stopped. The same unit should not be restarted because symptoms might recur. Other transfusion reactions in which hypotension can be a sign, such as allergic, haemolytic, septic reactions, transfusion-related acute lung injury, or anaphylaxis, must be excluded. No routine preventative measures have been identified other than not using a bedside leucocyte reduction filter.[67] If the patient is being treated with an ACE inhibitor and needs continuing transfusion therapy, physicians should consider switching them to another class of antihypertensive drug (grade 2C).[69,70]

Massive transfusion-associated reactions (citrate, potassium, cold toxicity)

Massive transfusion does not have a standard definition, but can be described as a blood loss rate of 150 mL per min, transfusion of 50% of a patient's total blood volume over 3 h, or more than ten units of red blood cells in 24 h. Massive transfusion typically occurs in uncontrolled haemorrhage, such as after trauma, but can also occur during surgical procedures, organ transplantation, or in non-bleeding patient undergoing transfusion for sickle-cell disease or haemolytic disease of the newborn.

Reactions related to massive transfusion are multifactorial, caused both by patient factors (eg, hepatic injury and shock) and by factors associated with transfusion of large volumes of blood products, including sodium citrate (the anticoagulant used in stored blood products) and supernatant potassium, as well as the infusion of large volumes of refrigerated products.[71] When the patient's metabolic ability to break down citrate is exceeded, ionised calcium levels can drop, resulting in tingling, paraesthesia, and changes in cardiac function, including alterations of cardiac depolarisation (prolonged QT interval) and blunting of left ventricular response (citrate toxicity).[72,73] Management constitutes administration of supplemental calcium, usually calcium gluconate or calcium citrate (grade 1A).[74] During storage of red blood cells, potassium concentration of the unit supernatant increases. The supernatant volume is about 25–40% of the total unit volume with a potassium concentration substantially higher than that of normal human plasma.[75] Transfusion-associated hyperkalaemic cardiac arrest has been reported after administration of large volumes or rapidly transfused red blood cells, particularly in children and adolescents with hypovolaemia.[76,77] Longer storage age and irradiation of the red blood cell product, rate and volume of red blood cell transfusion, age and weight of patient, and presence of comorbidities (hyperglycaemia, hypocalcaemia, hypothermia, acidosis, and renal insufficiency) are risk factors for transfusion-associated hyperkalaemic cardiac arrest. Treatment of hyperkalaemia might include insulin, glucose, calcium gluconate, and furosemide. Given that most cases of transfusion-associated hyperkalaemic cardiac arrest have been reported in the perioperative setting, known risk factors should be considered before massive transfusion.[76] Patients with low total blood volume who might receive a large volume of red blood cells in a short period should be transfused at a maximum infusion rate of 0·5 mL/kg per min.[75] Use of red blood cells units with less supernatant (washing or plasma-reduced), or fresh units (≤7–10 days old; grade 1B), and avoidance of red blood cell units that are irradiated more than 12 h before transfusion (grade 2C), might decrease the risk of transfusion-associated hyperkalaemic cardiac arrest.[78] Findings from small studies have shown use of an inline

potassium filter before transfusion or ultrafiltration of the priming volume before initiation of extracorporeal life support to be effective (grade 1B).[79,80]

Massive transfusion can also be associated with hypothermia (cold toxicity). Red blood cell and plasma units (which are stored at refrigerated temperatures) can lead to hypothermia when given rapidly and in large volumes.[81] In severe hypothermia (<30°C), cardiac conduction slows leading to cardiac arrest. Other effects of hypothermia include slowing of temperature-dependent enzymatic reactions, resulting in impaired citrate and delayed drug metabolism, impairment of the coagulation cascade, and reduction of platelet function resulting in coagulopathy. Hypothermia can be managed with forced air warming devices (grade 1A), and, in extreme circumstances, warm peritoneal lavage or cardiopulmonary bypass (grade 1A).[82,83]

Prospective monitoring and planning can prevent these reactions; ionised calcium concentrations should be measured regularly and supplemental calcium given as needed (grade 1B). Inline blood warming devices should be used to warm blood products rapidly to normal body temperature during transfusion in the massive transfusion setting (grade 1A).[82]

Post-transfusion purpura

Post-transfusion purpura is a rare reaction defined as thrombocytopenia that develops 5–12 days after red blood cell or platelet transfusion. The clinical pattern consists of rapid onset of thrombocytopenia (platelet count can fall from normal ranges to below 10×10^9 per L within 24 h), typically in a middle-aged or elderly woman with a recent history of red blood cell or platelet transfusion.[6,84] Other findings might include widespread purpura, bleeding from mucous membranes, and, in severe cases, intracranial haemorrhage and death.[85] The transfusion precipitating the fall in platelet count causes a secondary, or anamnestic, immune response, increasing antibody titres directed against specific human platelet antigens (HPA). Post-transfusion purpura usually affects HPA-1a-negative individuals (phenotypic frequency up to 2% depending on patient ethnic origin) who have previously been alloimmunised by pregnancy; however, other HPA antigens might be implicated. In elderly patients, platelet transfusions, multiple transfusions, and the presence of comorbidities are risk factors.[86] The mechanism of destruction of the patient's own antigen-negative platelets remains unclear.

Diagnosis is confirmed by the detection of platelet-specific alloantibodies. Management should be supportive. In untreated cases, thrombocytopenia usually persists for 7–28 days, but can continue for longer. Treatment with intravenous immunoglobulin (grade 1B), steroids, or plasma exchange is indicated (grade 2C).[87] Platelet transfusion can be given, but is sometimes associated with poor increments; there is no evidence that platelet concentrates from antigen-negative donors are more effective than those from random donors in the acute thrombocytopenic phase. Prevention of recurrence of post-transfusion purpura can include use of washed red blood cell units, or use of platelet and red blood cell units from HPA compatible donors or autologous transfusion.[88] Leucocyte reduced blood components are required (grade 2A).[89] The clinical staff and patient should be advised on the risk of recurrence with future transfusions and need for antigen-negative or washed blood products (grade 2C).

Septic transfusion reactions

Septic transfusion reactions usually present during or within 4 h of transfusion. Severe septic reactions occur in about 58 000–75 000 transfusions a year, although bacterial contamination of platelets is thought to be much more common.[90–92] Fever, rigors, hypotension, and other signs associated with systemic inflammatory response syndrome are the most common presentation. Definitive diagnosis of transfusion-transmitted bacterial infection requires isolation of the same organism from the blood product and patient, but can be presumed in a culture-negative patient with clinical sepsis if bacteria are isolated from the transfused unit.[93]

In a patient with new bacterial bloodstream infection following transfusion, all units recently transfused should be evaluated for bacterial contamination with Gram stain and culture.[93] Bacterial cultures should be taken from the patient and any indwelling lines before antibiotics are started.[14] Broad-spectrum antibiotics such as β-lactams and aminoglycosides should be started empirically (grade 1A) with anti-*Pseudomonas* spp coverage if a red blood cell unit is implicated.[93]

Procedures to reduce bacterial contamination of blood products include donor screening and proper skin disinfection before collection, sequestering the first 10–50 mL of donated blood (and skin plug) in a small pouch that is diverted away from the collected blood, visual inspection of all units before issue, and pre-transfusion bacterial surveillance of platelet units (grade 1B).[91,94] Platelet units have the highest bacterial contamination rate (one in 3000–5000 units) because platelets are stored at room temperature;[95] but many do not cause infection because they are removed from the inventory due to positive surveillance, or transfused before bacterial growth has reached a clinically significant level.[94]

Pathogen reduction systems use ultraviolet light to crosslink nucleic acids (with or without amotosalen) to treat blood products and inactivate viruses, bacteria, and parasites.[94,96,97] Prospective studies of pathogen reduction systems for platelets show that their use is associated with lower septic event rates than transfusion of conventionally prepared platelets.[98] Since national implementation of pathogen reduction systems in 2011 in Switzerland, septic transfusion reactions have decreased (grade 1A).[98]

Transfusion-associated circulatory overload

Transfusion-associated circulatory overload is an under-recognised reaction, affecting about 1–8% of patients who are transfused[99–101] or occurring after about one in 9177 transfused components.[102] There is no consensus for diagnosing transfusion-associated circulatory overload; the NHSN definition requires new onset, or acute exacerbation of three or more of the following, within 6 h of transfusion: respiratory distress, raised brain natriuretic peptide (BNP or NT-pro-BNP), increased central venous pressure, left heart failure, positive fluid balance, or pulmonary oedema.[7] These criteria are similar to the UK Serious Hazards of Transfusion (SHOT) National Haemoviligance scheme for diagnosis of transfusion-associated circulatory overload, although with a shorter timeline (4 h) to development of signs and symptoms.[6] Transfusion-associated circulatory overload is caused by an excessive quantity of transfused blood components or an excessive rate of transfusion (excessive is relative to each patient). An inflammatory component might also exist.[103] Risk factors include older age, renal failure (especially if on dialysis), pre-existing fluid overload, cardiac dysfunction, administration of large volumes of blood products, and rapid administration rate. The differential diagnosis of transfusion-associated circulatory overload includes transfusion-related acute lung injury, septic transfusion reaction, and acute haemolytic transfusion reaction.

Treatment of transfusion-associated circulatory overload requires stopping transfusion and administering supplemental oxygen as needed. Administration of diuretics can be both diagnostic and therapeutic. At-risk patients should be identified (grade 2C) and given transfusions slowly over 3–4 h (grade 2C), with the smallest quantity of blood products given (ie, one unit, divided into two components) to achieve the clinical goal (grade 2C).[100] For patients with a history of transfusion-associated circulatory overload, the benefit of diuretics before or during the transfusion has not been studied, but might be logical in the haemodynamically stable patient.

Transfusion-associated graft versus host disease

Transfusion-associated graft versus host disease is an extremely rare adverse event caused by transfusion of cellular components containing viable donor lymphocytes that recognise their new host as foreign and engraft in the recipient.[104] Transfusion with whole blood, red blood cells, platelets, HLA-matched platelets, and granulocytes has been implicated.[104,105] At risk are severely immunodeficient patients such as recipients of haemopoietic stem cell transplantation (past and current) or patients with congenital immunodeficiency affecting T cells or Hodgkin's lymphoma; those in need of neonatal exchange transfusions; and patients taking high-dose chemotherapy or radiotherapy, purine-analogue drugs, alemtuzumab, or anti-thymocyte globulin for aplastic anaemia.[105] Fetuses in need of intrauterine transfusion are also at risk. Immunocompetent patients are at risk when receiving cellular components from blood relatives or if being transfused in a donor population with little HLA diversity.[106]

The signs and symptoms of transfusion-associated graft versus host disease develop 5–10 days after transfusion and usually consist of an erythematous maculopapular rash, fever, abdominal pain, diarrhoea, nausea, and vomiting. Laboratory tests show pancytopenia, abnormal liver function, and electrolyte disturbances. A skin biopsy from the affected area can help with diagnosis; although not specific, typical features include interface lymphocytic infiltrate with basil cell vacuolization.[105] Full marrow aplasia, evident on bone marrow biopsy, usually develops within 21 days of transfusion. Transfusion-associated graft versus host disease is nearly always fatal; death is usually attributable to infections.[107]

Management is supportive. Transfusion-associated graft versus host disease can be prevented by irradiating cellular blood components with gamma-rays or x-rays, or by treating blood products with pathogen reduction technology to disrupt the residual lymphocytes' ability to proliferate (grade 1B).[108] Leucocyte reduction is not sufficient for prevention; however, recent SHOT data suggest a threshold effect for the number for T cells needed to cause the reaction.[3]

Transfusion-associated necrotising enterocolitis

Necrotising enterocolitis is common in preterm and very low birthweight neonate infants. The pathogenesis of transfusion-associated necrotising enterocolitis is unknown; some investigators have postulated a connection with transfusion but the literature is dominated by retrospective case-control studies with moderate risk of bias.[109,110] Prospective studies are needed to assess the causality of any association between necrotising enterocolitis and transfusion, and the place of withholding feeds during transfusion, which could affect blood flow to the gastrointestinal tract.[111,112]

Transfusion-related acute lung injury

Transfusion-related acute lung injury is characterised by the development of non-cardiogenic pulmonary oedema after transfusion. Although understanding of the pathogenesis has increased greatly in the past few decades, it remains incompletely understood.[92,93] Cognate anti-HLA or anti-human neutrophil antigen (anti-HNA) antibodies alone are enough to cause transfusion-related acute lung injury, but most cases are postulated to occur through a two event model. The first event is a clinical disorder that causes activation of the pulmonary endothelium, leading to the sequestration and priming of neutrophils in the lung. Clinical risk factors that might function as the first event include high interleukin 8 concentrations, liver surgery, chronic alcohol abuse, shock, high peak airway pressure during

mechanical ventilation, current smoking, and positive fluid balance.[113] The second event results from the blood product transfusion, which activates the primed neutrophils causing endothelial damage and subsequently acute lung injury. This can result from either passive transfer of antibodies (immune-mediated) or pro-inflammatory mediators (non-immune mediated) in the transfused component. Since neutrophil sequestration and activation is involved in development of transfusion-related acute lung injury, recipient factors including neutrophil number and function also probably play an important role.

Risk for immune-mediated lung injury after transfusion varies by blood component. Risk has been reduced substantially by strategies targeting donor selection and blood product collection (eg, use of male donors only for plasma and plasma used for suspension of buffy coat derived platelet pools, and screening of female apheresis platelet donors for HLA/HNA antibodies with retesting after pregnancies; grade 2C).[114] Available risk estimates per component transfused (after full implementation of immune-mediated risk mitigation strategies) are based on active reporting and might underestimate risk (plasma 0·4 per 100 000 units, apheresis platelets one per 100 000 units, and red blood cells 0·5 per 100 000 units).[115]

Available risk mitigation strategies do not address non-immune-mediated injury. Novel methods for risk reduction are currently under investigation. A technique for pre-storage experimental filtration for red blood cell units,[116] which removes antibodies, lipids, white blood cells, and platelets, and prevents transfusion-related acute lung injury, is in development in an animal model.

The clinical presentation of transfusion-related acute lung injury includes dyspnoea, tachypnoea, and hypoxaemia, sometimes accompanied by rigors, tachycardia, fever, hypothermia, and hypotension or hypertension.[117] Copious frothy pink-tinged fluid might be seen in the endotracheal tube of mechanically ventilated patients, but this finding is non-specific.[114] Transient leucopenia might be noted.[117] Bilateral interstitial infiltrates are present on chest radiograph but this finding is non-specific and difficult to distinguish from overload oedema.[118] Diagnosis is made on the basis of clinical and radiographic findings in conjunction with a temporal association with transfusion (typically within 6 h, although delayed cases presenting up to 72 h after transfusion have been described).[119] Transfusion-related acute lung injury can be difficult to distinguish from oedema associated with heart failure, and other acute transfusion reactions with similar presentations (transfusion-associated circulatory overload, septic transfusion reaction, and anaphylaxis) should be excluded.[117]

Management of transfusion-related acute lung injury is supportive, with supplemental oxygen or mechanical ventilation given as needed, and application of restrictive tidal volume ventilation and a restrictive fluid strategy as in other causes of acute lung injury (grade 1A).[117] A restrictive transfusion strategy to avoid unnecessary transfusions will also be preventive.

Conclusion

In this Review we present the salient features and management of the different diagnostic categories for transfusion reactions. We recognise the highly variable pathophysiological mechanisms that underlie reactions, as well as the diverse risk factors patients might have. In acute transfusion reactions prompt recognition and cessation of transfusion is crucial, as well as communication with the transfusion service and laboratory. Correct diagnosis is essential to provide appropriate treatment and to ensure the safety of any future transfusions. Many of the evidence-based recommendations are supported by weak recommendations due to sparse publications. Prospective studies are needed in all populations; evidence is particularly sparse in children and patients who have repeat transfusion needs.

Contributors

MD conceived of the Review, gathered co-authors, guided paper development, and wrote and edited the report. SW guided the paper submission to journal, wrote and reviewed sections of the report, and graded evidence. RSB, JC, CC, NMD, TOA, SJS, JHW, and MY wrote sections of paper, reviewed sections of the report, and graded evidence. MP, AT, and LVDW guided paper development, reviewed the report, and provided expert review. AZ assisted with paper conception, guided paper development, and wrote and edited the report.

Declaration of interests

MP is an employee of Haemonetics Corporation, Braintree, MA. USA; a manufacturer of blood processing equipment. All other authors declare no competing interests.

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For the **BEST Collaborative** see http://bestcollaborative.org/

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